Evidence Summary: relationship ABO group, SARS-CoV-2, and COVID-19

Evidence Evaluation Center for Decision Making-CEEDS

Global Institute of Clinical Excellence

Health and Innovation Presidency

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Contents

Title	Evidence summary about the relationship between ABO blood group type, the SARS-CoV-2 infection, and COVID-19 severity
Id	14072022IH
Requestor area	
Request Date	14072022
Answer Date	29072022

1. Questions:

a. Is there an association between ABO blood group type and SARS-CoV-2 infection?

b. Is there a relation ABO type to the severity of the SARS-CoV-2 infection?

1.1. PICOTS

For the first question:

Population	Any population exposed to COVID
Intervention	ABO group
Comparator(s)	adjusted for sex, comorbidities, ethnicity or age, and other factors when possible
Outcomes	COVID-19 infection
Settings	✓ Outpatient ✓ Inpatient ✓ Institutionalized

For the second question:

Population	Any population diagnosed with COVID-19
Intervention	ABO group
Comparator(s)	adjusted for sex, comorbidities, ethnicity or age, and other factors when possible
Outcomes	• Hospitalization • Admission to the intensive care unit (ICU) • Need for mechanical ventilation • Mortality
Settings	✓ Outpatient ✓ Inpatient ✓ Institutionalized

2. Description About blood groups

First, we follow the International Society of Blood Transfusion (ISBT) definitions in this summary. So, the term 'blood group' refers to an individual's combination of Red Blood Cell (RBC) surface antigens. Antigens are specific sites on different proteins, glycoproteins, or glycolipids that form parts of the RBC membrane that the immune system can interact with. (ISBT, 2022)

There are 43 blood group systems containing 345 red cell antigens. Forty-eight genes genetically determine the 43 systems. (ISBT, 2022).

ABO, Rh, Duffy, Kell, Lewis, MNS, and Kidd are the most widely mentioned blood groups. But it is necessary to remember that some antigens are not linked to a blood group; ISBT has classified them into three categories:

1. Collections (the 200 series):
2. the 700 Series contains antigens that do not fit into any system or collection which have an incidence of <1% across all human ethnic populations,
3. and the 901 Series includes antigens with a frequency >99% across people of different ethnic ancestry.

ABO system

ABO is the blood system used most because of its clinical significance for transfusion purposes.

Phenotype and genotype of blood types	
Phenotype	**Genotype**
A	AA or AI
B	BB or BI
AB	AB
O	II

The worldwide distribution of the blood groups in the ABO system varies in the table taken from the systematic review of Goel et al.

Table of ABO Geographic Distributions for the native and contemporary populations

Region		Native population		Current population			
		Type A %	Type O %	Type B %	Type A %	Type O %	Type B %
North America	Canada	Up to 40	80–100	0–5	40+	40+	9
	United States	0–15*	80–100	0–5	40+	40+	˜10
Central and South America		Absent	90–100	0–5	10–30	50–80	˜10
Greenland		Up to 40+					
Australia		Up to 40+ †	60–80 (North)	0–5	38	49	˜10
Africa		15–20	60–80	10–20	˜20–25 ¥	Up to 60	West > 20
Middle East		15–20	60–80	5–15	˜25	>40	>20
Europe	Scandinavia	25–40 ‡	50–70	0–10	40+	˜40	10
	Western Europe	25–30	60–70	5–10	30–40	30–40	˜10
	Eastern Europe	25–30	50–60	10–20	30–40	30–40	˜10
Russia		15–20	50–60	15–30	˜35	˜35	˜10
Asia	China	20–25	60–70	15–25	˜30	˜50	˜20
	Japan	15–25	50–70	10–15	40	30	20
	Pacific	15–20	60–70	15–25	25–30	>40	˜30
	India	15–20	56–60	Up to 30	22	29	38

*Blackfoot of Montana: 30–35%.

† Aboriginal Australians: 40–53%.

‡ Lapp: 50–90%.

¥ Cameroon 38, Uganda 39, South Africa 32%.

From an evolutionary perspective, it is widely accepted that blood type A is ancient, and all the other groups are mutations from the A blood type (Calaffell, F. 2008). Franchini & Bonfanti, among other authors, have tried to connect blood type evolution with resistance to diseases (Franchini, M., & Bonfanti, C. 2015). Still, there are critical undefined aspects before concluding.

As we have seen, the blood types are far from straightforward, so any conclusion from them must take care of the complexity and uncertainties related.

3. Methodology

We carried out a Rapid Systematic Review (Manual of Rapid Systematic Reviews. Global Institute for Clinical Excellence. 2021)

3.1. Eligibility Criteria

3.1.1. Sources

We searched systematic reviews with or without meta-analysis in PubMed.

3.1.2. Information Search

We ran a search on July 17, 2022, for studies meeting the following inclusion criteria:

- Population, intervention, comparison, and outcomes according to the PICOT question.
- Types of studies: RCTs with published and publicly available data.
- Publication format: complete reports or reports with interim analyses.
- Publication status: results of studies published in indexed journals and gray literature.
- Outcome reporting: studies reporting outcomes of interest attributable to the comparison of interest.

The search included the following terms "ABO blood type" AND "COVID-19" AND “Severity” present in the title or abstract of the article. The search syntaxes used can be found in Appendix 1. Specific filters were used for systematic reviews, with no restriction on the search period. The number of references identified in the literature search is summarized using the PRISMA flow chart, Annex 2.

3.1.3. Screening, selection, and extraction

A reviewer screened the total number of references identified in the search examining the titles and abstracts against the predefined eligibility criteria. Table attached. From the group of pre-selected references, the reviewer verified that each study met the eligibility criteria by reading each publication in full text. We summarized the findings in narrative form.

3.2. Search outcomes, Screening, and selection

We show the search results, Screening, and selection of evidence for this rapid review. Through the PubMed database search and additional searches, we detected 460 titles; from these, we included three published systematic reviews.

4. Evidence Synthesis

4.1 Potential mechanisms

Through the literature search, we have found different mechanisms to explain the association between ABO blood groups and SARS-CoV- 2 infections and establish the connection to the disease's severity. Still, none of the mechanisms are entirely supported by empirical evidence. First, we describe the mechanisms that are biologically plausible in explaining the association between ABO blood groups and SARS-CoV- 2 infections, but without undisputable evidence:

1. “anti-A and/or anti-B antibodies serve as viral neutralizing antibodies by binding to A and/or B antigens expressed on the viral envelope, thereby preventing the interaction of the virus and ACE2 receptor, lastly limiting the entry of the virus into the lung epithelium and infection of target cells.” (Gutiérrez-Valencia, M., et al. 2022)

2. “The SARS-CoV-2 virus and SARS-CoV spike (S) proteins may be bound by anti-A isoagglutinins (e.g., present in group O and group B individuals), which may block interactions between virus and angiotensin-converting-enzyme-2-receptor, thereby preventing entry into lung epithelial cells” (Goel, R. et al. 2021)

Second, we describe the mechanisms that are biologically plausible in explaining the association between ABO blood groups and COVID-19’s severity, but still without clear empirical evidence:

a. “The increased ACE1 activity in group A individuals could predispose to cardiovascular complications, accounting for severe COVID-19” (Gutiérrez-Valencia, M. et al. 2022)
b. “Variation of von Willebrand factor and Factor VIII levels by ABO type, with higher levels in group A individuals, could contribute to the risk of thromboembolic disease and severe COVID-19.” (Gutiérrez-Valencia, M. et al., 2022)
c. “ABO blood group influences the glycosyltransferase activity and the risk of venous thromboembolism, which is frequent in severe COVID-19 cases.” (Gutiérrez-Valencia, M. et al., 2022)

After checking into the mechanisms that could potentially explain the relationship between ABO blood type and COVID-19 is worth noticing that translation of these mechanisms into clinical significance is complicated and sometimes impossible with the existing data.

4.2 Hospitalization

No significant differences were found in any of the comparisons between ABO blood groups when analyzing the risk of hospitalization.

4.3 Admission to Intensive Care Unit

None of the blood groups showed a different risk of ICU admission than the others.

4.4 Mechanical ventilation

No significant differences in any of the comparisons in the requirement of mechanical ventilation

4.5 Mortality

Data seem conflicting about the mortality, but interestingly in some studies, mortality was higher in group O than in B blood type.

In most studies, the A blood group showed a higher risk of mortality when compared to the non-A group and B group.

5. Summary Table with the Systematic reviews included

Authors/Year	Type	number of studies included (only for SR)	geography of the studies included (only for SR)	number of participants	participants for outcomes: Infection. Finding	participants for outcomes: hospitalization	participants for outcomes: ICU admission	participants for outcomes: mechanical ventilation	participants for outcomes: mortality	participants Blood group: A	participants Blood group: B	participants Blood group: AB	participants Blood group: O	Quality of Evidence
Gutiérrez-Valencia et al. (2022)	systematic review (SR)	63	Europe (47,6%) America (28,6%) Asia or Africa (23,8%)	6.470.438	1564162 heterogeneity persisted after the sensitivity analyses	34154 No significant differences were found in any of the comparisons between ABO blood groups when analyzing the risk of hospitalization.	32690 None of the blood groups showed a different risk of ICU admission compared to the others.	10210 No significant differences were found in any of the comparisons in the requirement of mechanical ventilation.	39542 A blood group < NON - A and B Participants with B blood group showed a lower mortality risk than participants in non-B blood group	38,30%	12,10%	4,20%	45,40%	The quality of the evidence for COVID-19 infection results was rated as “very low” for all the comparisons. Results for hospitalization, admission to ICU, and mortality were qualified as “low” or “very low.”

Authors/Year	Type	number of studies included (only for SR)	geography of the studies included (only for SR)	number of participants	participants for outcomes: Infection. Finding	participants for outcomes: hospitalization	participants for outcomes: ICU admission	participants for outcomes: mechanical ventilation	participants for outcomes: mortality	participants Blood group: A	participants Blood group: B	participants Blood group: AB	participants Blood group: O	Quality of Evidence
Gheshlagh, R. G., Ansari, M., Dalvand, P., Shabani, F., & Albatineh, A. N. (2022).	systematic review (SR)	27	non stated by the authors.	23,285 COVID-19 case subjects and 590,593 control subjects	the results indicated that the pooled estimates of OR (95% confidence interval) for blood groups A, O, B, and AB were 1.26 (1.13-1.40), 0.77 (0.71-0.82), 1.05 (0.99-1.12), and 1.11 (0.99-1.25), respectively. Therefore, individuals infected with COVID-19 have higher odds of having blood group A and lower odds of having blood group O..	NA	NA	NA	NA	NA	NA	NA	NA	Very low

Authors/Year	Type	number of studies included (only for SR)	geography of the studies included (only for SR)	number of participants	participants for outcomes: Infection. Finding	participants for outcomes: hospitalization	participants for outcomes: ICU admission	participants for outcomes: mechanical ventilation	participants for outcomes: mortality	participants Blood group: A	participants Blood group: B	participants Blood group: AB	participants Blood group: O	Quality of Evidence
Banchelli, F., Negro, P., Guido, M., D'Amico, R., Fittipaldo, V. A., Grima, P., & Zizza, A. (2022).	a systematic review (SR)	22	non stated by the authors.	more than 1,200,000 individuals of whom 74,563 resulted positive to SARS-CoV-2 and 1,166,717 resulted negative, were included in the meta-analysis	487,985 subjects had blood group A, 151,879 had group B, 52,621 had group AB, and 548,795 had group O. Group O was slightly less associated with infection as compared to the other three blood groups (OR = 0.91, 95% CI = 0.85–0.99, p = 0.02). Conversely, group A was slightly more associated with infection, as compared to the other three groups	NA	NA	NA	NA	487985 (40,7%)	151879 (12,7%)	52261 (4,3%)	548795 (45,8%)	Low

6. Conclusions

- ✓ Regarding the association between ABO blood groups and SARS-CoV-2 infection, the odds favor a "maybe" answer, but there are important caveats, as the biological mechanisms need to be proved. Furthermore, statistics are inconclusive because of the studies' heterogeneity.
- ✓ When trying to establish a nexus between ABO blood groups and COVID-19 severity, the best guess is a no, because there are unproven plausible biological hypotheses, and the data don't favor all the studies that possibility. However, in a potential scenario where these hypotheses are valid, there would still be a higher chance that the clinical significance of the finding in the real world is worthless.
- ✓ Genotypes and phenotypes of the ABO blood system are potential confounders.
- ✓ We cannot exclude influence of mendelian inheritance involved in susceptibility to SARS-CoV-2 infection and COVID-19 severity, but maybe the chosen feature of ABO blood type is not the right one.

7. References

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2. Goel, R., Bloch, E. M., Pirenne, F., Al-Riyami, A. Z., Crowe, E., Dau, L., Land, K., Townsend, M., Jecko, T., Rahimi-Levene, N., Patidar, G., Josephson, C. D., Arora, S., Vermeulen, M., Vrielink, H., Montemayor, C., Oreh, A., Hindawi, S., van den Berg, K.,

Serrano, K., … ISBT COVID-19 Working Group (2021). ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 Working Group. *Vox sanguinis*, *116*(8), 849–861. https://doi.org/10.1111/vox.13076

3. Calafell, F., Roubinet, F., Ramírez-Soriano, A., Saitou, N., Bertranpetit, J., & Blancher, A. (2008). Evolutionary dynamics of the human ABO gene. *Human genetics*, *124*(2), 123–135. https://doi.org/10.1007/s00439-008-0530-8

4. International Society of Blood Transfusion (ISBT). 2022. Red Cell Immunogenetics and Blood Group Terminology. Retrieved on July 28, 2022, from https://www.isbtweb.org/isbt-working-parties/rcibgt.html

5. Franchini, M., & Bonfanti, C. (2015). Evolutionary aspects of ABO blood group in humans. *Clinica Chimica Acta; international journal of clinical chemistry*, *444*, 66–71. https://doi.org/10.1016/j.cca.2015.02.016
6. Banchelli, F., Negro, P., Guido, M., D'Amico, R., Fittipaldo, V. A., Grima, P., & Zizza, A. (2022). The Role of ABO Blood Type in Patients with SARS-CoV-2 Infection: A Systematic Review. Journal of clinical medicine, 11(11), 3029. https://doi.org/10.3390/jcm11113029
7. Gheshlagh, R. G., Ansari, M., Dalvand, P., Shabani, F., & Albatineh, A. N. (2022). Association between ABO blood group and COVID-19 infection: an updated systematic review and meta-analysis. Immunohematology, 38(1), 5–12. https://doi.org/10.21307/immunohematology-2022-034
8.

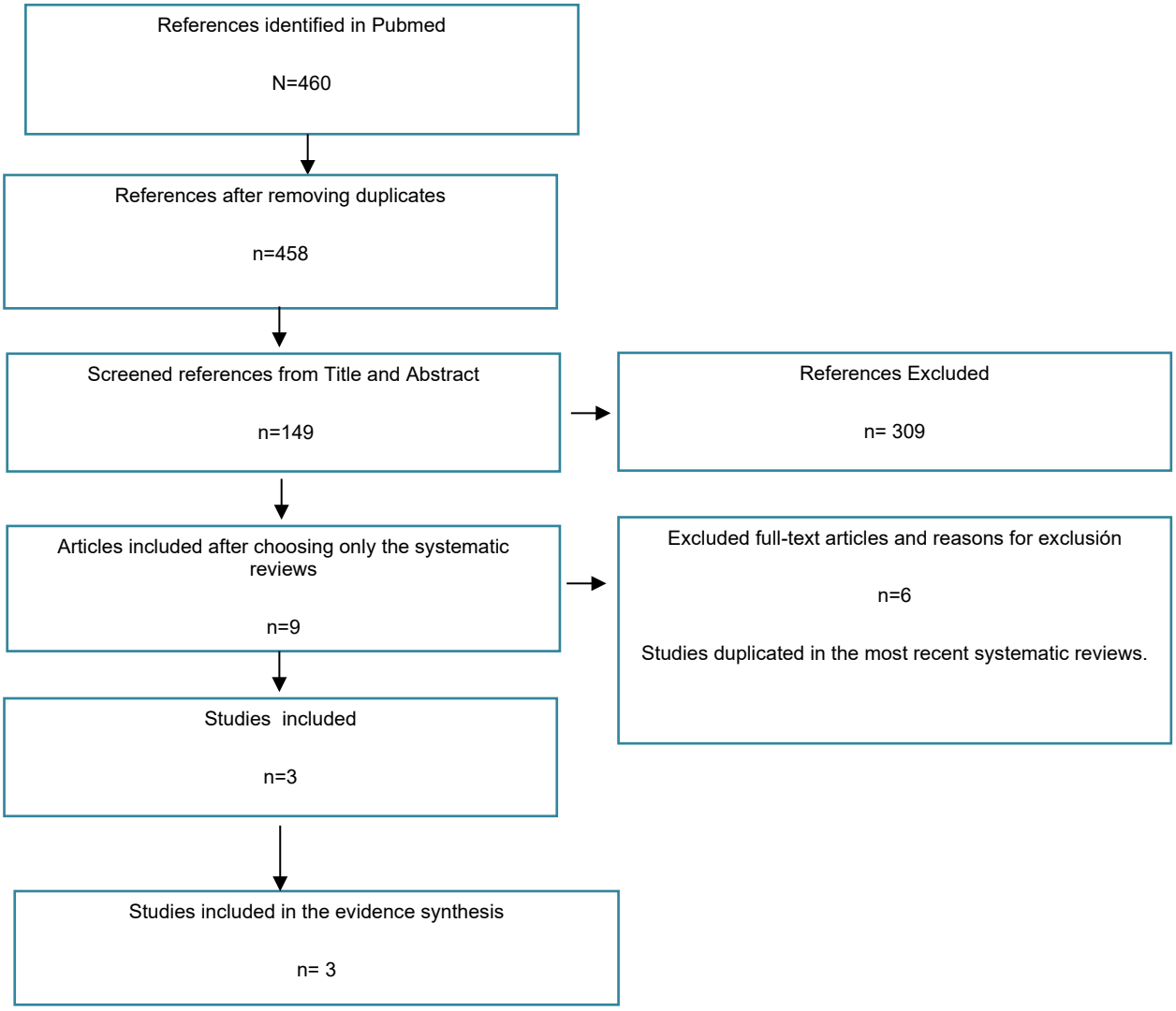
8. Annexes

Annex 1. Evidence search reports in electronic databases.

Search	Electronic
Database	**PubMed**
Search Date	14/06/2022
Range	unrestricted
Language	Unrestricted
Additional Restrictions	**None**
Equation used	(("blood group antigens"[MeSH Terms] OR ("blood"[All Fields] AND "group"[All Fields] AND "antigens"[All Fields]) OR "blood group antigens"[All Fields] OR ("blood"[All Fields] AND "type"[All Fields]) OR "blood type"[All Fields]) AND ("sars cov 2"[MeSHTerms] OR "sars cov 2"[All Fields] OR "covid"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19"[All Fields]) AND ("sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields])) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter])

	Translations **blood type:** "blood group antigens"[MeSH Terms] OR ("blood"[All Fields] AND "group"[All Fields] AND "antigens"[All Fields]) OR "blood group antigens"[All Fields] OR ("blood"[All Fields] AND "type"[All Fields]) OR "blood type"[All Fields] **covid:** "sars-cov-2"[MeSH Terms] OR "sars-cov-2"[All Fields] OR "covid"[All Fields] OR "covid-19"[MeSH Terms] OR "covid-19"[All Fields] **severity:** "sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields]

Annex 2. PRISMA Diagram: search flowchart, Screening, and studies selection.



Annex 3. Article`s abstract and validation before including into the literature.

year	Title	Abstract	Meets objective after reading title +abstract
2022	Correlation of SARS-CoV-2 infection severity with ABO blood groups and RhD antigen: a case-control study.	The role of ABO types and RhD antigen in coronavirus disease 2019 (COVID-19) severity has been investigated in several recent studies. Thus, the objective of this study was to identify the relationship of ABO and RhD types with symptomatic COVID-19 disease and determine the groups associated with an increased risk of hospitalization. This observational case-control study was performed in 530 Iraqi-Kurdish patients with COVID-19. Among them, 184 were severe cases that required hospitalization, while 346 were mild to moderate cases that were treated at home. ABO and RhD antigen groups were compared between cases and 1698 control records from 1 year before the pandemic. The diagnosis of COVID-19 was based on real-time polymerase chain reaction tests and high-resolution chest computed tomography scans with the typical clinical presentation. There were no significant differences in ABO and RhD antigen distributions between the COVID-19 cases and non-COVID controls. No ABO group was associated with the risk of hospitalization as a marker of the severity of infection. There was no significant association between symptomatic COVID-19 disease and any ABO group or RhD antigen type. No impact of ABO groups on hospitalization was documented.	yes
2022	Stress hyperglycemia ratio, rather than admission blood glucose, predicts in-hospital mortality and adverse outcomes in moderate-to severe COVID-19 patients, irrespective of pre-existing glycemic status.	To compare admission-blood-glucose (ABG) or stress-hyperglycemia-ratio (SHR) performs better in predicting mortality and worse outcomes in COVID-19 patients with (DM) and without known Type 2 Diabetes Mellitus (UDM). ABG and SHR were tested for 451 patients with moderate-severe COVID-19 infection [DM = 216,47.9%; pre-diabetes = 48,10.6%, UDM = 187,41.4%],who were followed-up to look for in-hospital-mortality (primary outcome) and secondary outcomes (ICU stay or mechanical ventilation, hospital-acquired-sepsis and multiple organ dysfunction syndrome [MODS]). Those with and without SHR ≥ 1.14 were compared; logistic regression was done to identify predictors of outcomes, with subgroup analysis based on pre-existing DM status and COVID-19 severity. Those who died (n = 131) or developed ≥ 1 secondary outcomes (n = 218) had higher prevalence of SHR ≥ 1.14, ABG ≥ 180 mg/dl and higher median SHR (p all < 0.01). Those with SHR ≥ 1.14 had higher mortality (53.7%), higher incidence of ≥ 1 secondary outcomes (71.3%) irrespective of pre-existing diabetes status. SHR ≥ 1.14, but not ABG ≥ 180 was an independent predictor of mortality in the whole group (OR: 7.81,4.07-14.98), as also the DM (OR:10.51,4.34-25.45) and UDM (5.40 (1.57-18.55) subgroups. SHR ≥ 1.14 [OR: 4.41 (2.49-7.84)] but not ABG ≥ 180 could independently predict secondary outcomes AUROC of SHR in predicting mortality was significantly higher than ABG in all subgroups. SHR better predicts mortality and adverse outcomes than ABG in patients with COVID-19, irrespective of pre-existing chronic glycemic status.	no

2022	Diabetic Covid-19 severity: Impaired glucose tolerance and pathologic bone loss.	Diabetes mellitus (DM), hypertension, and cardiovascular diseases (CVDs) are the leading chronic comorbidities that enhance the severity and mortality of COVID-19 cases. However, SARS-CoV-2 mediated deregulation of diabetes pathophysiology and comorbidity that links the skeletal bone loss remain unclear. We used both streptozocin-induced type 2 diabetes (T2DM) mouse and hACE2 transgenic mouse to enable SARS-CoV-2-receptor binding domain (RBD) mediated abnormal glucose metabolism and bone loss phenotype in mice. The data demonstrate that SARS-CoV-2-RBD treatment in pre-existing diabetes conditions in hACE2 (T2DM + RBD) mice results in the aggravated osteoblast inflammation and downregulation of Glucose transporter 4 (Glut4) expression via upregulation of miR-294-3p expression. The data also found increased fasting blood glucose and reduced insulin sensitivity in the T2DM + RBD condition compared to the T2DM condition. Femoral trabecular bone mass loss and bone mechanical quality were further reduced in T2DM + RBD mice. Mechanistically, silencing of miR-294 function improved Glut4 expression, glucose metabolism, and bone formation in T2DM + RBD + anti-miR-294 mice. These data uncover the previously undefined role of SARS-CoV-2-RBD treatment mediated complex pathological symptoms of diabetic COVID-19 mice with abnormal bone metabolism via a miRNA-294/Glut4 axis. Therefore, this work would provide a better understanding of the interplay between diabetes and SARS-CoV-2 infection.	no
2022	Usefulness of monocyte distribution width and presepsin for early assessment of disease severity in COVID-19 patients.	Early predictors of severe coronavirus disease 2019 (COVID-19) would identify patients requiring intensive care. Recently, the monocyte distribution width (MDW) and presepsin level have been used for the early diagnosis of sepsis. Here, we assessed the utility of MDW and presepsin for the early assessment of COVID-19 severity. Eighty-seven inpatients with confirmed COVID-19 were enrolled and divided into 3 groups by the type of respiratory support: (1) mechanical ventilation or high-flow nasal cannula oxygen therapy (MVHF-OT), (2) conventional oxygen therapy, and (3) no oxygen therapy. We measured the complete blood count; MDW; erythrocyte sedimentation rate; and the levels of presepsin, C-reactive protein, procalcitonin, lactate dehydrogenase, ferritin, Krebs von den Lungen-6 (KL-6), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralizing antibody. Thirteen (14.9%) patients on MVHF-OT exhibited a significantly higher mortality and a longer hospital stay than did the others. The MDW and presepsin levels were significantly elevated on admission, and correlated with COVID-19 severity (both $P < .001$). Notably, only the MDW correlated significantly with symptoms in the no oxygen therapy group ($P < .012$). In the first week after admission, the MDW fell and no longer differed among the groups. The KL-6 level did not differ by disease severity at any time. Neutralizing antibodies were detected in 74 patients (91.4%) and the level of neutralization correlated significantly with COVID-19 severity ($P < .001$). The MDW and presepsin are useful indicators for early assessment of disease severity in COVID-19 patients.	no

2022	Associations of Clinical Factors and Blood Groups With the Severity of COVID-19 Infection in Makkah City, Saudi Arabia.	The possible associations between the different blood groups and clinical factors with COVID-19 infection among patients in Makkah city. To investigate the relationship between ABO blood groups and COVID-19 infection in patients who were tested positive and to elucidate the most common ABO blood groups with a higher infectivity of COVID-19 and disease association. This was an observational cross-sectional study that included COVID-19 patients diagnosed with PCR and who were hospitalized in Al-Noor Specialist Hospital (Makkah) during the period between March to November 2020. The ABO and Rhesus blood groups alongside the clinical characteristics were determined and retrieved from medical records and HESN of the Ministry of Health of the Kingdom of Saudi Arabia (KSA). The overall confirmed COVID-19 cases included in this study were 1,583 patients who underwent positive PCR testing between March and November 2020. The frequencies of blood groups were as follows: group O + (37%), group A + (29.2%), group B + (22.6%), group AB + (5.1%), group O - (2.8%), group B - (1.8%), group A - (1.1%), and group AB - (0.4%). However, no significant correlations were observed for ABO groups and Rh types with the severity of COVID-19 illness. Conversely, signs and symptoms of respiratory distress syndrome (RDS), pneumonia, and respiratory failure symptoms, alongside a history of diabetes mellitus, hypertension, chronic kidney diseases, and congestive heart failure significantly increased the risk of death from COVID-19 infection. Moreover, the rates of fever, cough, and asthma were markedly lower in the deceased group compared with the recovered group of patients. The association between the different blood groups with the prevalence and mortality of COVID-19 among infected patients has yet to be elucidated as we found no significant differences in the observed versus expected distribution of ABO phenotypes among the included cases. The prevalence of RDS, pneumonia, and respiratory failure was found higher among hospitalized COVID-19 patients in the deceased group. However, other factors such as fever, cough, and asthma appeared to be more significantly lower than in the recovered group.	yes
2022	A Cross-Sectional Study of the Association of ABO Blood Group and Rh Type With Severity of COVID-19 Infection in a Tertiary Care Center of South India.	Background The novel coronavirus disease 2019 (COVID-19) was declared a pandemic that had affected 224 countries, causing >2.1 million deaths worldwide. The association of the different ABO blood groups with the risk and severity of COVID-19 infections has been speculated in many studies. This study aims to determine the incidence of COVID-19 infections among various blood groups and the association of ABO blood groups and Rh type with the severity of COVID-19 infection as well as with other outcome predictors of COVID-19 infection including neutrophil-to-lymphocyte ratio, D-dimer, ferritin, lactate dehydrogenase, and C-reactive protein. Methodology This was a retrospective study conducted among 150 serologically positive patients >18 years of age who underwent treatment in a district government hospital over two months. Patients were categorized into severity groups, and laboratory data were divided into those corresponding to severe disease and otherwise, in accordance with national guidelines. Appropriate statistical analysis was performed. Results The frequency of blood groups A, B, AB, and O was 30.7%, 29.4%, 13.7%, and 39%, respectively. There was a statistically significant number of patients belonging to non-O blood groups who developed a severe COVID-19 infection (group C) ($p = 0.005$). There was an increased risk of multiorgan failure ($p = 0.035$), non-invasive ventilation ($p = 0.005$), intubation, and mortality among non-O blood	yes

		groups, and was the maximum for A blood group even after adjusting for age and pre-existing comorbidities. Increased D-dimer levels were noted in non-O blood groups (p = 0.037). No statistically significant association was found between Rh typing and the severity of COVID-19 infection. Conclusions Our findings provide evidence that individuals with non-O blood groups are susceptible to developing more severe COVID-19 infections and should take active preventive measures. Moreover, they should be cautiously monitored and treated once infected.	
2022	ABO blood group and link to COVID-19: A comprehensive review of the reported associations and their possible underlying mechanisms.	ABO blood group is long known to be an influencing factor for the susceptibility to infectious diseases, and many studies have been describing associations between ABO blood types and COVID-19 infection and severity, with conflicting findings. This narrative review aims to summarize the literature regarding associations between the ABO blood group and COVID-19. Blood type O is mostly associated with lower rates of SARS-CoV-2 infection, while blood type A is frequently described as a risk factor. Although results regarding the risk of severe outcomes are more variable, blood type A is the most associated with COVID-19 severity and mortality, while many studies describe O blood type as a protective factor for the disease progression. Furthermore, genetic associations with both the risk of infection and disease severity have been reported for the ABO locus. Some underlying mechanisms have been hypothesized to explain the reported associations, with incipient experimental data. Three major hypotheses emerge: SARS-CoV-2 could carry ABO(H)-like structures in its envelope glycoproteins and would be asymmetrically transmitted due to a protective effect of the ABO antibodies, ABH antigens could facilitate SARS-CoV-2 interaction with the host' cells, and the association of non-O blood types with higher risks of thromboembolic events could confer COVID-19 patients with blood type O a lower risk of severe outcomes. The hypothesized mechanisms would affect distinct aspects of the COVID-19 natural history, with distinct potential implications to the disease transmission and its management.	yes

2022	[Value of red blood cell distribution width in evaluating the severity of illness of novel coronavirus Delta variant].	To explore the value of red blood cell distribution width (RDW) in evaluating the severity of patients infected with novel coronavirus Delta variant. A total of 28 patients infected with novel coronavirus Delta variant in designated hospital treated by the First Affiliated Hospital of Xi'an Jiaotong University medical team from December 2021 to January 2022 were enrolled (23 cases of common type, 4 severe and 1 critical cases). The detailed clinical data of patients was collected. Then, Pearson's correlation analysis was used to identify the blood examination indexes which affected the arterial partial pressure of oxygen (PaO 2) and arterial partial pressure of carbon dioxide (PaCO 2). According to the median standard deviation of red blood cell distribution width (RDW-SD, 42.5 fL), 28 patients were divided into low RDW-SD group (≤ 42.5 fL, 16 cases) and high RDW-SD group (> 42.5 fL, 12 cases), and the immune related indexes of the two groups were compared. Receiver operator characteristic curve (ROC) was drawn to evaluate the predictive value of RDW-SD on the severity of illness of coronavirus disease 2019 (COVID-19). Correlation analysis showed that RDW-SD was the only index related to PaO 2 and PaCO 2 on the first day of admission, which was negative correlation with PaO 2 (r = -0.379, P = 0.047) and positive correlation with PaCO 2 (r = 0.509, P = 0.006). The results of effects of different clinical characteristics on RDW-SD level showed that there was no statistically significant difference in RDW-SD between groups with different clinical characteristics (including male/female, ≥ 65 years old/< 65 years old, having/without hypertension, having/without diabetes, smoking/not smoking, having/without hyperpyrexia, with/without fever for 3 days, with/without respiratory symptoms, with/without digestive symptoms). It was suggested that RDW-SD be relatively stable and not affected by the patient's baseline level. The percentage of B cells in low RDW-SD group was higher than that in high RDW-SD group (23.01±3.01 vs. 15.34±5.34, P < 0.05), immunoglobulin G (IgG) level in low RDW-SD group was lower than that in high RDW-SD group (g/L: 11.43±3.20 vs. 15.42±1.54, P < 0.05). The area under ROC curve (AUC) of RDW-SD in evaluating severe cases was 0.83 [95% confidence interval (95%CI) was 0.59-1.06], which was close to multilobularinltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hyper-tension and age (MuL BSTA score; AUC = 0.82, 95%CI was 0.51-1.12) and better than British Thoracic Society's modified pneumonia score (CURB-65 score; AUC = 0.70, 95%CI was 0.50-0.91). RDW-SD has significant evaluative effect on the severity of COVID-19 patients with Delta variants.	yes

2022	Role of ABO Blood Groups in Susceptibility and Severity of COVID-19 in the Georgian Population.	The establishment of the potential role of the infected people's ABO blood type in the virus infectivity and aggressivity could clarify the aspects of the various susceptibility to virus and play a key role in assessing its spreading potential in the future. We studied the possible association of risk of coronavirus disease-2019 (COVID-19) infection and severe outcomes of disease with ABO blood groups and Rh factor in the Georgian population. The effect of blood type on the severity of infection in COVID-19 positive patients admitted to the First University Clinic of Tbilisi State University (Tbilisi, Georgia) from December 2020 to September 2021 was analyzed retrospectively. The odds ratio (OR) criterion was used to determine the influence of the blood group on the risk of COVID-19 infection and of severe course of the disease. The incidence of COVID-19 was 1.65-fold higher in the patients with blood group II(A), and average twice lower in patients with blood groups III(B) and IV(AB), compared with the ABO blood group distribution in healthy donors of the region. The percentage of patients transferring in ICU with I(O) and II(A) blood groups was enough high (42-40%), whereas in patients with III(B) and IV(AB) blood groups very low (12-6%). There were not revealed any statistically significant differences in the distribution of the patients with Rh+ and Rh- blood groups in healthy and COVID-19 infected individuals (including those transferred in the ICU). The link between patients' ABO blood groups and receptivity to COVID-19 infection, progression and severity of the disease, has been detected. These results are relevant in terms of elucidating the mechanisms and risk factors of infecting and severity course of COVID-19 disease. Ratiani L, Sanikidze TV, Ormotsadze G, Pachkoria E, Sordia G. Role of ABO Blood Groups in Susceptibility and Severity of COVID-19 in the Georgian Population. Indian J Crit Care Med 2022;26(4):487-490.	yes
2022	Influence of Nutritional Status and Physical Exercise on Immune Response in Metabolic Syndrome.	Metabolic Syndrome (MetS) is a cluster of metabolic alterations mostly related to visceral adiposity, which in turn promotes glucose intolerance and a chronic systemic inflammatory state, characterized by immune cell infiltration. Such immune system activation increases the risk of severe disease subsequent to viral infections. Strong correlations between elevated body mass index (BMI), type-2-diabetes and increased risk of hospitalization after pandemic influenza H1N1 infection have been described. Similarly, a correlation between elevated blood glucose level and SARS-CoV-2 infection severity and mortality has been described, indicating MetS as an important predictor of clinical outcomes in patients with COVID-19. Adipose secretome, including two of the most abundant and well-studied adipokines, leptin and interleukin-6, is involved in the regulation of energy metabolism and obesity-related low-grade inflammation. Similarly, skeletal muscle hormones-called myokines-released in response to physical exercise affect both metabolic homeostasis and immune system function. Of note, several circulating hormones originate from both adipose tissue and skeletal muscle and display different functions, depending on the metabolic context. This review aims to summarize recent data in the field of exercise immunology, investigating the acute and chronic effects of exercise on myokines release and immune system function.	no

2022	Effect of Comorbid Diabetes on Clinical Characteristics of COVID-19 Patients Infected by the Wild-Type or Delta Variant of SARS-CoV-2.	Diabetes is one of the most common comorbidities in COVID-19 patients that pertains to disease severity, but the causal mechanism regarding its negative impact on COVID-19 outcome has yet been uncovered. We retrospectively analyzed 459 COVID-19 patients admitted in early 2020 and 336 COVID-19 patients admitted in August 2021, with their demographic information, medical history, vaccination status (if applied), and laboratory data reported. Among COVID-19 patients, compared to the non-diabetic group, the diabetic group exhibited elder age, higher proportion of patients with other major comorbidities, more severe dysfunction of innate immune cells, more refractory blood coagulopathy and more detrimental organ damage. For the wild-type SARS-CoV-2 infection, diabetic comorbidity was associated with COVID-19 severity but not mortality, and the glycemic levels in the non-diabetic group upon infection experienced high and analogous to those in the diabetic group. Besides, infected by the delta variant of SARS-CoV-2, the non-diabetic patients did not demonstrate hyperglycemia, and despite different vaccination statuses, the diabetic patients exhibited comparable antibody responses to non-diabetic, showing the robustness of acquired immunity. SARS-CoV-2 infection may superimpose the deterioration of innate immune systems in diabetic patients, which contributes to their worsened disease outcome, but timely COVID-19 immunization could provide adequate protection in diabetic population that leads to favored prognosis.	no
2022	Caspase-4/11 exacerbates disease severity in SARS-CoV-2 infection by promoting inflammation and immunothrombosis.	Severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) is a worldwide health concern, and new treatment strategies are needed. Targeting inflammatory innate immunity pathways holds therapeutic promise, but effective molecular targets remain elusive. Here, we show that human caspase-4 (CASP4) and its mouse homolog, caspase-11 (CASP11), are up-regulated in SARS–CoV-2 infections and that CASP4 expression correlates with severity of SARS–CoV-2 infection in humans. SARS–CoV-2–infected Casp11−/− mice were protected from severe weight loss and lung pathology, including blood vessel damage, compared to wild-type (WT) mice and mice lacking the caspase downstream effector gasdermin-D (Gsdmd−/−). Notably, viral titers were similar regardless of CASP11 knockout. Global transcriptomics of SARS–CoV-2–infected WT, Casp11−/−, and Gsdmd−/− lungs identified restrained expression of inflammatory molecules and altered neutrophil gene signatures in Casp11−/− mice. We confirmed that protein levels of inflammatory mediators interleukin (IL)-1β, IL-6, and CXCL1, as well as neutrophil functions, were reduced in Casp11−/− lungs. Additionally, Casp11−/− lungs accumulated less von Willebrand factor, a marker for endothelial damage, but expressed more Kruppel-Like Factor 2, a transcription factor that maintains vascular integrity. Overall, our results demonstrate that CASP4/11 promotes detrimental SARS–CoV-2–induced inflammation and coagulopathy, largely independently of GSDMD, identifying CASP4/11 as a promising drug target for treatment and prevention of severe COVID-19.	yes

2022	Type-H, and Type-L COVID-19: are they different subtypes or the same?	SARS-CoV-2 infection, which causes severe pneumonia, caused an epidemic that started in Wuhan, China in December 2019 and spread to the whole world. COVID-19 mainly affects the respiratory system and causes the development of severe pneumonia and related acute respiratory distress syndrome (ARDS) in some patients. We aimed to investigate whether COVID-19 pneumonia cases can be evaluated in different categories in clinical and radiological terms. COVID-19 associated ARDS cases being treated with the diagnosis of severe pneumonia between March 21, 2020 and June 15, 2020 in Anesthesia Intensive Care Unit were examined and divided into 2 groups (type-L and type-H, total 29 cases) according to their clinical findings (according to whether they benefited from high PEEP and their lung compliance) and lung computed tomography findings (according to the severity of the ground glass appearance). The groups were compared with each other in terms of inflammatory markers [CRP (C reactive protein), ferritin, D Dimer, PCT (procalcitonin), white blood cell, lymphocyte count, arterial blood gas analysis] and imaging findings. It was observed that the prone position was beneficial in improving oxygenation in both H-type and L-type patients. 7 of 22 L-type patients were intubated and 5 of these patients died. There was no statistical difference between the two groups in terms of intubation times, hospital stays, cytokine levels, prone position application responses and mortality rates. Are there two separate forms of COVID-19 pneumonia, such as h-type and l-type, or are they intertwined and describe the early and late stages of the disease? This question needs to be discussed. In addition, we believe that subtyping COVID-19 pneumonia patients does not make a difference in the treatments to be applied.	no
2022	Human T-lymphotropic virus type 1 and novel coronavirus disease 2019; More complex than just a simple coinfection.	The recent coronavirus disease 2019 (COVID-19) significantly affected many people worldwide, especially those with underlying diseases. While some people with underlying illnesses, including cardiovascular diseases, are more vulnerable to develop severe COVID-19, other populations, including people who have autoimmune diseases, may develop severe diseases similar to the general population. The severity and outcome of COVID-19 are reviewed in individuals with underlying viral diseases, including acquired immune deficiency syndrome and hepatitis, however, some infectious diseases, including human T-lymphotropic virus type 1 (HTLV-1) diseases, is under-reported in the literature. HTLV-1 is a sexually transmitted disease that is endemic in some parts of the world. Infected patients may develop clinical symptoms of HTLV-1 associated myelopathy / tropical spastic paraparesis (HAM/TSP) and adult T cell leukemia (ATL) or may remain asymptomatic during their life. To the best of our knowledge, no clinical studies evaluate the severity and outcomes of SARS-CoV-2 infection in HTLV-1 infected patients. We aimed to review the pathogenesis of both of these viral infections and discuss their similarities in provoking immune responses. Although HTLV-1 infected patients may have had variable degrees of inflammation and immune system dysregulation, the available data is limited to conclude that HTLV-1 infected patients may be more vulnerable to developing severe COVID-19 in contrast to the general population.	yes

2022	The severity and clinical characteristics of COVID-19 among patients with type 2 diabetes mellitus in Jazan, Saudi Arabia.	The objectives of the current study were to assess the severity and clinical characteristics of coronavirus disease 2019 (COVID-19) among Saudi adults with type 2 diabetes mellitus (T2DM) in Jazan region, Saudi Arabia. This retrospective cohort study included 412 patients with COVID-19 selected randomly from the Health Electronic Surveillance Network system, which contains the primary data on COVID-19 infections in Jazan. COVID-19 disease duration was significantly longer in patients with T2DM (mean=10.7 days) compared with those without T2DM (mean=8.3 days) (P=.01). Six (7%) patients experienced an increase in blood glucose concentrations and had to escalate their total daily insulin dose accordingly. Median fasting and random blood glucose levels increased after infection with COVID-19 (pre-COVID median=119 and 172 mg/dL, respectively; post-COVID median=148 and 216 mg/dL, respectively) (P=.02). The total insulin dose pre-COVID (median=42 units/d) increased after infection with COVID-19 (median=58 units/d) (P=.01). Most patients with T2DM had clinical COVID-19 symptoms (91%) and the remainder (9%) were asymptomatic. A large proportion (80%) of T2DM patients with mild COVID-19 symptoms self-isolated at home. COVID-19 patients with T2DM (11%) who had an oxygen saturation of ≤ 90% and admitted to the intensive care unit were higher than those without T2DM (5%) (P=<.001). COVID-19 patients with T2DM (9%) had higher mortality rate than COVID-19 patients without T2DM (1%) (P=<.001). COVID-19 patients with T2DM were associated with a higher risk of admission to the intensive care unit and mortality than COVID-19 patients without T2DM.	no
2022	ABO Blood System and COVID-19 Susceptibility: Anti-A and Anti-B Antibodies Are the Key Points.	The implication of the ABO blood group in COVID-19 disease was formulated early, at the beginning of the COVID-19 pandemic more than 2 years ago. It has now been established that the A blood group is associated with more susceptibility and severe symptoms of COVID-19, while the O blood group shows protection against viral infection. In this review, we summarize the underlying pathophysiology of ABO blood groups and COVID-19 to explain the molecular aspects behind the protective mechanism in the O blood group. A or B antigens are not associated with a different risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than that of other antigens. In this case, the cornerstone is natural anti-A and anti-B antibodies from the ABO system. They are capable of interfering with the S protein (SARS-CoV-2) and angiotensin-converting enzyme 2 (ACE2; host cell receptor), thereby conferring protection to patients with sufficient antibodies (O blood group). Indeed, the titers of natural antibodies and the IgG isotype (specific to the O blood group) may be determinants of susceptibility and severity. Moreover, older adults are associated with a higher risk of bad outcomes due to the lack of antibodies and the upregulation of ACE2 expression during senescence. A better understanding of the role of the molecular mechanism of ABO blood groups in COVID-19 facilitates better prognostic stratification of the disease. Furthermore, it could represent an opportunity for new therapeutic strategies.	yes

2022	A glucose-like metabolite deficient in diabetes inhibits cellular entry of SARS-CoV-2.	The severity and mortality of COVID-19 are associated with pre-existing medical comorbidities such as diabetes mellitus. However, the underlying causes for increased susceptibility to viral infection in patients with diabetes is not fully understood. Here we identify several small-molecule metabolites from human blood with effective antiviral activity against SARS-CoV-2, one of which, 1,5-anhydro-D-glucitol (1,5-AG), is associated with diabetes mellitus. The serum 1,5-AG level is significantly lower in patients with diabetes. In vitro, the level of SARS-CoV-2 replication is higher in the presence of serum from patients with diabetes than from healthy individuals and this is counteracted by supplementation of 1,5-AG to the serum from patients. Diabetic (db/db) mice undergo SARS-CoV-2 infection accompanied by much higher viral loads and more severe respiratory tissue damage when compared to wild-type mice. Sustained supplementation of 1,5-AG in diabetic mice reduces SARS-CoV-2 loads and disease severity to similar levels in nondiabetic mice. Mechanistically, 1,5-AG directly binds the S2 subunit of the SARS-CoV-2 spike protein, thereby interrupting spike-mediated virus-host membrane fusion. Our results reveal a mechanism that contributes to COVID-19 pathogenesis in the diabetic population and suggest that 1,5-AG supplementation may be beneficial to diabetic patients against severe COVID-19.	yes
2022	Relationship Between ABO Blood Types and Coronavirus Disease 2019 Severity.	Severe Acute Respiratory Syndrome Coronavirus-2 infection spreads rapidly around the world. The blood groups are recognized to influence susceptibility to certain viruses.The aim of this research was to determine any potential role of the patients' ABO and Rh blood groups in both the acquisition and severity of coronavirus disease 2019 (COVID-19). As a growing global health problem, to find any marker for COVID-19 may help to identify high-risk individuals and ease the strain on health system. The patients who were hospitalized between March and August 2020 with a diagnosis of COVID-19 and had a documented ABO blood type in medical database were examined retrospectively. Patients were grouped as survivors (followed up in pandemic wards /or intensive care unit [ICU]) and non-survivors. Their ABO blood types were correlated with general population's blood types. The labaratory findings of patients were evaluated according to the blood types. A total of 492 patients included, 233 (47.4%) were male. The mean age was 58.9±17.5. Data of ABO blood groups of 51966 individuals in general population was used as a control group; the number of the patients in Rh (-) blood type 0, were significantly lower than the control group (p=0.008). Among the whole patient group (survivors and non-survivors), Blood type A 210 (42%) was the most common and type AB 52 (10%) was the least common. However, no statistically significant difference was noted between survivors (pandemic wards/ICU) and non-survivors unlike the previous studies (p=0.514). No correlation was found between laboratory findings (Hemoglobin, red cell distribution width, platelet, white blood cell, lymphocyte, D-Dimer, C-reactive protein, ferritin) and ABO blood groups of COVID-19 patients (p>0.05). There was no association found between the ABO blood type and COVID-19 infection rate or disease severity. No evidence was noted to support the use of ABO blood type as a marker for COVID-19. Further efforts are warranted to better predict outcomes of hospitalized COVID-19 patients.	yes

2022	Exploring COVID-19 Vaccine Side Effects: A Correlational Study Using Python.	The COVID-19 pandemic had a great impact on the socio-economic stability of every country. To curb the effect and risk of transmission, governments implemented various measures including the mandatory vaccination of their citizens. However, despite these efforts, many people are still hesitant to take the vaccine because of various reasons and biases. This paper attempts to explore the perceptions of the people who have undergone vaccinations regarding the various side effects to provide inputs to vaccine manufacturers and assist people in making informed decisions in selecting the appropriate vaccine for them. The study further explored the correlation and association of age, weight category, diet category, blood type, and sleeping patterns with the severity of the selected vaccine side effects. The results revealed that vaccine side effects are associated with the vaccine type. Age, gender, weight category, diet category, blood type, and sleeping patterns have significant relationships to one or more side effects.	yes
2022	Single-cell transcriptomics reveal a unique memory-like NK cell subset that accumulates with ageing and correlates with disease severity in COVID-19.	Natural killer (NK) cells are innate lymphoid cells that mediate antitumour and antiviral responses. However, very little is known about how ageing influences human NK cells, especially at the single-cell level. We applied single-cell sequencing (scRNA-seq) to human lymphocytes and NK cells from 4 young and 4 elderly individuals and then analysed the transcriptome data using Seurat. We detected the proportion and phenotype of NK cell subsets in peripheral blood samples from a total of 62 young and 52 elderly healthy donors by flow cytometry. We also used flow cytometry to examine the effector functions of NK cell subsets upon IFN-α/IL-12+IL-15/K562/IL-2 stimulation in vitro in peripheral blood samples from a total of 64 young and 63 elderly healthy donors. We finally studied and integrated single-cell transcriptomes of NK cells from 15 young and 41 elderly COVID-19 patients with those from 12 young and 6 elderly healthy control individuals to investigate the impacts of ageing on NK cell subsets in COVID-19 disease. We discovered a memory-like NK subpopulation (NK2) exhibiting the largest distribution change between elderly and young individuals among lymphocytes. Notably, we discovered a unique NK subset that was predominantly CD52 + NK2 cells (NK2.1). These memory-like NK2.1 cells accumulated with age, exhibited proinflammatory characteristics, and displayed a type I interferon response state. Integrative analyses of a large-cohort COVID-19 dataset and our datasets revealed that NK2.1 cells from elderly COVID-19 patients are enriched for type I interferon signalling, which is positively correlated with disease severity in COVID-19. We identified a unique memory-like NK cell subset that accumulates with ageing and correlates with disease severity in COVID-19. Our results identify memory-like NK2.1 cells as a potential target for developing immunotherapies for infectious diseases and for addressing age-related dysfunctions of the immune system.	no

2022	The Side Effects of COVID-19 Vaccines and Its Association With ABO Blood Type Among the General Surgeons in Saudi Arabia.	Introduction The benefits of vaccination outweigh its risks as it protects approximately two to three million individuals from infectious diseases annually. With the emergence of the coronavirus disease 2019 (COVID-19) pandemic, new vaccines have been developed. However, it is crucial to follow and recognize the side effects of COVID-19 vaccines. Previous studies have shown a relationship between ABO blood groups and coronavirus. Some vaccination side effects, such as muscle pain at the injection site and fatigue, may impair an individual's ability to perform tasks that require fine motor skills, such as those performed by a general surgeon. Therefore, this study aimed to identify the association between ABO blood groups and the side effects of COVID-19 vaccines among general surgeons in Saudi Arabia. Method A cross-sectional online survey-based study regarding the side effects following COVID-19 vaccination was conducted among Saudi and non-Saudi general surgeons working in public and private hospitals in Saudi Arabia who had received one or two doses of mRNA-based COVID-19 vaccines. Results A total of 612 surgeons responded. Approximately, 74.7% of the respondents reported side effects after receiving vaccines. Tiredness was the most commonly reported side effect of the vaccine, followed by severe local pain at the site of injection. Approximately, 16.2% of the participants started showing side effects 12 hours after receiving the vaccine. There was a significant relationship between the type of vaccine administered and the appearance of side effects ($p = 0.004$). The rate of appearance of side effects was higher in participants who received the Pfizer vaccine. However, there was no significant relationship between the appearance of side effects and age, gender, blood group, number of doses, and past history of COVID-19 infection ($p > 0.05$). Of the total participants, 256 (41.8%) stated that the side effects of the vaccine affected their work performance. Moreover, there was no significant difference in side effects, symptoms appearing after vaccination, the onset of symptoms, and duration of symptoms between the participants who received one dose and those who received two doses of the vaccine. In addition, there was no significant relationship between the severity of side effects and age, past history of COVID-19 infection, number of doses, and blood type ($p > 0.05$). However, there was a significant relationship between the severity of side effects and gender and type of vaccine ($p = 0.000$ and 0.004, respectively). A high percentage of females and those who received the AstraZeneca vaccine stated that their side effects affected their work performance. Conclusion Three-quarters of the participants reported side effects after the COVID-19 vaccination, which affected the work performance of 41% of participating general surgeons. There was no significant relationship between the appearance of symptoms and age, gender, blood group, number of doses, and past history of COVID-19 infection. However, there was a significant relationship between the severity of side effects and gender and type of vaccination. Future large-scale studies are recommended to further evaluate the implication of ABO blood type on COVID-19.	yes

2022	A composite ranking of risk factors for COVID-19 time-to-event data from a Turkish cohort.	Having a complete and reliable list of risk factors from routine laboratory blood test for COVID-19 disease severity and mortality is important for patient care and hospital management. It is common to use meta-analysis to combine analysis results from different studies to make it more reproducible. In this paper, we propose to run multiple analyses on the same set of data to produce a more robust list of risk factors. With our time-to-event survival data, the standard survival analysis were extended in three directions. The first is to extend from tests and corresponding p-values to machine learning and their prediction performance. The second is to extend from single-variable to multiple-variable analysis. The third is to expand from analyzing time-to-decease data with death as the event of interest to analyzing time-to-hospital-release data to treat early recovery as a meaningful event as well. Our extension of the type of analyses leads to ten ranking lists. We conclude that 20 out of 30 factors are deemed to be reliably associated to faster-death or faster-recovery. Considering correlation among factors and evidenced by stepwise variable selection in random survival forest, 10 ~ 15 factors seem to be able to achieve the optimal prognosis performance. Our final list of risk factors contain calcium, white blood cell and neutrophils count, urea and creatine, d-dimer, red cell distribution widths, age, ferritin, glucose, lactate dehydrogenase, lymphocyte, basophils, anemia related factors (hemoglobin, hematocrit, mean corpuscular hemoglobin concentration), sodium, potassium, eosinophils, and aspartate aminotransferase.	yes
2022	A raising dawn of pentoxifylline in management of inflammatory disorders in Covid-19.	The existing pandemic viral infection caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) leads to coronavirus disease 2019 (Covid-19). SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE2) as an entry-point into affected cells and down-regulation of ACE2 by this virus triggers the release of pro-inflammatory cytokines and up-regulation of angiotensin II. These changes may lead to hypercytokinemia and the development of cytokine storm with the development of acute lung injury and acute respiratory distress syndrome. Different repurposed had been in use in the management of Covid-19, one of these agents is pentoxifylline (PTX) which has anti-inflammatory and antioxidant properties. Therefore, the objective of the present mini-review is to highlight the potential role of PTX in Covid-19 regarding its anti-inflammatory and antioxidant effects. PTX is a non-selective phosphodiesterase inhibitor that increases intracellular cyclic adenosine monophosphate which stimulates protein kinase A and inhibits leukotriene and tumor necrosis factor. PTX has antiviral, anti-inflammatory and immunomodulatory effects, thus it may attenuate SARS-CoV-2-induced hyperinflammation and related complications. As well, PTX can reduce hyper-viscosity and coagulopathy in Covid-19 through increasing red blood cell deformability and inhibition of platelet aggregations. In conclusion, PTX is a non-selective phosphodiesterase drug, that has anti-inflammatory and antioxidant effects thereby can reduce SARS-CoV-2 infection-hyperinflammation and oxidative stress. Besides, PTX improves red blood cells (RBCs) deformability and reduces blood viscosity so can mitigate Covid-19-induced hyper-viscosity and RBCs hyper-aggregation which is linked with the development of coagulopathy. Taken together, PTX seems to be an effective agent against Covid-19 severity.	no

2022	CSF Biomarkers in COVID-19 Associated Encephalopathy and Encephalitis Predict Long-Term Outcome.	Patients with coronavirus disease 2019 (COVID-19) frequently develop acute encephalopathy and encephalitis, but whether these complications are the result from viral-induced cytokine storm syndrome or anti-neural autoimmunity is still unclear. In this study, we aimed to evaluate the diagnostic and prognostic role of CSF and serum biomarkers of inflammation (a wide array of cytokines, antibodies against neural antigens, and IgG oligoclonal bands), and neuroaxonal damage (14-3-3 protein and neurofilament light [NfL]) in patients with acute COVID-19 and associated neurologic manifestations (neuro-COVID). We prospectively included 60 hospitalized neuro-COVID patients, 25 (42%) of them with encephalopathy and 14 (23%) with encephalitis, and followed them for 18 months. We found that, compared to healthy controls (HC), neuro-COVID patients presented elevated levels of IL-18, IL-6, and IL-8 in both serum and CSF. MCP1 was elevated only in CSF, while IL-10, IL-1RA, IP-10, MIG and NfL were increased only in serum. Patients with COVID-associated encephalitis or encephalopathy had distinct serum and CSF cytokine profiles compared with HC, but no differences were found when both clinical groups were compared to each other. Antibodies against neural antigens were negative in both groups. While the levels of neuroaxonal damage markers, 14-3-3 and NfL, and the proinflammatory cytokines IL-18, IL-1RA and IL-8 significantly associated with acute COVID-19 severity, only the levels of 14-3-3 and NfL in CSF significantly correlated with the degree of neurologic disability in the daily activities at 18 months follow-up. Thus, the inflammatory process promoted by SARS-CoV-2 infection might include blood-brain barrier disruption in patients with neurological involvement. In conclusion, the fact that the levels of pro-inflammatory cytokines do not predict the long-term functional outcome suggests that the prognosis is more related to neuronal damage than to the acute neuroinflammatory process.	no
2022	Long-term persistence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein-specific and neutralizing antibodies in recovered COVID-19 patients.	Understanding antibody responses after natural severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can guide the coronavirus disease 2019 (COVID-19) vaccine schedule, especially in resource-limited settings. This study aimed to assess the dynamics of SARS-CoV-2 antibodies, including anti-spike protein 1 (S1) immunoglobulin (Ig)G, anti-receptor-binding domain (RBD) total Ig, anti-S1 IgA, and neutralizing antibody against wild-type SARS-CoV-2 over time in a cohort of patients who were previously infected with the wild-type SARS-CoV-2. Between March and May 2020, 531 individuals with virologically confirmed cases of wild-type SARS-CoV-2 infection were enrolled in our immunological study. Blood samples were collected at 3-, 6-, 9-, and 12-months post symptom onset or detection of SARS-CoV-2 by RT-PCR (in asymptomatic individuals). The neutralizing titers against SARS-CoV-2 were detected in 95.2%, 86.7%, 85.0%, and 85.4% of recovered COVID-19 patients at 3, 6, 9, and 12 months after symptom onset, respectively. The seropositivity rate of anti-S1 IgG, anti-RBD total Ig, anti-S1 IgA, and neutralizing titers remained at 68.6%, 89.6%, 77.1%, and 85.4%, respectively, at 12 months after symptom onset. We observed a high level of correlation between neutralizing and SARS-CoV-2 spike protein-specific antibody titers. The half-life of neutralizing titers was estimated at 100.7 days (95% confidence interval = 44.5-327.4 days, R2 = 0.106). These results support that the decline in serum antibody levels over time in both participants with severe disease and mild disease were depended on the symptom severity, and the individuals with high IgG antibody titers	no

		experienced a significantly longer persistence of SARS-CoV-2-specific antibody responses than those with lower titers.	
2022	ABO and Rh blood groups, demographics, and comorbidities in COVID-19 related deaths: A retrospective study in Split-Dalmatia County, Croatia.	Blood group phenotypes have been associated with COVID-19 susceptibility and severity. This study aimed to examine ABO/Rh blood group distribution in COVID-19-related deaths considering demographics and pathological conditions. We conducted a retrospective study at the University Hospital Center Split, Croatia, that included 245 COVID-19 positive individuals that died from April 8, 2020, to January 25, 2021. We extracted data on their blood groups, demographics, and pre-existing comorbidities and compared findings with general population data from blood group donations (n = 101,357) and non-COVID-19 deaths from 2019 (n = 4968). The proportion of dead males was significantly higher than in non-COVID-19 cases (63.7% vs. 48.9%, P < 0.001), while the proportion of older individuals did not differ. The prevailing pre-existing diseases were hypertension (59.6%), diabetes (37.1%), heart failure (28.8%), digestive disorder (26.5%), and solid tumor (21.6%). The ABO distribution in the deceased and donors' group showed significant differences, with the higher prevalence of A/AB group and lower prevalence of 0, but with individual differences significant only for AB and non-AB groups. There was a reduced proportion of females within the deceased with group 0 (P = 0.014) and a higher proportion of AB individuals with coronary heart disease (P = 0.024). The study confirmed a higher risk of death in males. The lower proportion of type 0 in deceased individuals was greater in females, implying that group 0 is not necessarily an independent protective factor. Coronary heart disease was identified as a potential risk factor for AB individuals.	yes

2022	Association of Covid-19 with blood type A in relation to blood sugar, urea, and blood test (D-dimer and ferritin) in patients from Al-Najaf.	COVID-19 is an emerging infectious disease caused by the novel enveloped single-stranded RNA virus quickly declared a pandemic. This study aimed to investigate the severity of COVID-19 infection in patients with blood group type A. A cross-sectional study was conducted at Al-Amal specialized hospital, Al-Najaf (March 8 to March 20/2021). The study included 123 hospitalized patients (63 females and 60 males), aged between 15-95 years, diagnosed with COVID-19, tested for blood group, blood sugar, blood urea, D-dimer, and serum ferritin. Results indicated significant differences in blood sugar and D-dimer in patients with type A blood group at P>0.05. At the same time, no significant difference was found in blood urea and ferritin at P>0.05. The majority of patients showed elevated levels of blood sugar, blood urea, serum D-dimer and ferritin. COVID-19 can infect people of all ages and causes severe infection in all blood groups.	yes
2022	Does the Serum Concentration of Angiotensin II Type 1 Receptor Have an Effect on the Severity of COVID-19? A Prospective Preliminary Observational Study among Healthcare Professionals.	SARS-CoV-2 is a virus that causes severe respiratory distress syndrome. The pathophysiology of COVID-19 is related to the renin-angiotensin system (RAS). SARS-CoV-2, a vector of COVID-19, uses angiotensin-converting enzyme 2 (ACE-2), which is highly expressed in human lung tissue, nasal cavity, and oral mucosa, to gain access into human cells. After entering the cell, SARS-CoV-2 inhibits ACE-2, thus favouring the ACE/Ang II/angiotensin II type 1 receptor (AT1R) axis, which plays a role in the development of acute lung injury (ALI). This study aimed to analyse the influence of angiotensin 1 receptor (AT1R) levels in the serum on the course of the severity of symptoms in healthcare professionals who had a SARS-CoV-2 infection. This prospective observational study was conducted on a group of 82 participants. The study group included physicians and nurses who had a COVID-19 infection confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2. The control group consisted of healthy medical professionals who had not had a SARS-CoV-2 infection or who had no symptoms of COVID-19 and who tested negative for SARS-CoV-2 on the day of examination. We analysed the correlation between AT1R concentration and the severity of COVID-19, as well as with sex, age, blood group, and comorbidities. There were no statistically significant differences in the mean values of AT1R concentration in the recovered individuals and the non-COVID-19 subjects (3.29 vs. 3.76 ng/mL; $p = 0.32$). The ROC curve for the AT1R assay showed an optimal cut-off point of 1.33 (AUC = 0.44; 95% CI = 0.32-0.57; $p = 0.37$). There was also no correlation between AT1R concentration and the severity of symptoms associated with COVID-19. Blood type analysis showed statistically significantly lower levels of AT1R in COVID-19-recovered participants with blood group A than in those with blood group O. In conclusion, AT1R concentration does not affect the severity of symptoms associated with COVID-19 among healthcare professionals.	yes

2022	ABO Blood Groups Are Not Associated With COVID-19 Disease Incidence and Severity When Correcting for Ethnicity Differences in Blood Type.	To determine if blood type is a risk factor for coronavirus disease 2019 (COVID-19) disease incidence and severity after correcting for ethnicity differences between novel infections and known ABO blood type frequency differences. We performed a retrospective analysis on all severe acute respiratory system coronavirus 2 (SARS-CoV-2) infections and disease severity across two major testing sites in Colorado. We evaluated all individuals with a SARS-CoV-2 nucleic acid test (NAT) and a known blood type between March 1, 2020, and June 1, 2020. We then created a prediction algorithm based on the corrected blood types by ethnicity using data from the Colorado Department of Health and established blood types by ethnicity. We applied this prediction algorithm to all patients in our sample. Of 8,676 patients, 485 (5.6%) had a positive SARS-CoV-2 NAT test and 8,191 (94.4%) had a negative test. All patients had ABO blood types that mirrored the expected blood type distribution within the state of Colorado ($P = .15$, $\chi 2$ statistic = 5.31). No differences in expected blood groups were present between ethnicity-adjusted SARS-CoV-2-negative and SARS-CoV-2-positive patients ($\chi 2 = 3.416313$, $P = .332$). Blood type is not associated with COVID-19 disease incidence or severity after correcting for ethnicity differences in expected blood type frequencies.	yes
2022	Distinct Immune Response at 1 Year Post-COVID-19 According to Disease Severity.	Despite the fact of ongoing worldwide vaccination programs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), understanding longevity, breadth, and type of immune response to coronavirus disease-19 (COVID-19) is still important to optimize the vaccination strategy and estimate the risk of reinfection. Therefore, we performed thorough immunological assessments 1 year post-COVID-19 with different severity. We analyzed peripheral blood mononuclear cells and plasma samples at 1 year post-COVID-19 in patients who experienced asymptomatic, mild, and severe illness to assess titers of various isotypes of antibodies (Abs) against SARS-CoV-2 antigens, phagocytic capability, and memory B- and T-cell responses. A total of 24 patients (7, 9, and 8 asymptomatic, mild, and severe patients, respectively) and eight healthy volunteers were included in this study. We firstly showed that disease severity is correlated with parameters of immune responses at 1 year post-COVID-19 that play an important role in protecting against reinfection with SARS-CoV-2, namely, the phagocytic capacity of Abs and memory B-cell responses. Various immune responses at 1 year post-COVID-19, particularly the phagocytic capacity and memory B-cell responses, were dependent on the severity of the prior COVID-19. Our data could provide a clue for a tailored vaccination strategy after natural infection according to the severity of COVID-19.	yes

2022	Genetic Landscape of the ACE2 Coronavirus Receptor.	SARS-CoV-2, the causal agent of COVID-19, enters human cells using the ACE2 (angiotensin-converting enzyme 2) protein as a receptor. ACE2 is thus key to the infection and treatment of the coronavirus. ACE2 is highly expressed in the heart and respiratory and gastrointestinal tracts, playing important regulatory roles in the cardiovascular and other biological systems. However, the genetic basis of the ACE2 protein levels is not well understood. We have conducted the largest genome-wide association meta-analysis of plasma ACE2 levels in >28 000 individuals of the SCALLOP Consortium (Systematic and Combined Analysis of Olink Proteins). We summarize the cross-sectional epidemiological correlates of circulating ACE2. Using the summary statistics-based high-definition likelihood method, we estimate relevant genetic correlations with cardiometabolic phenotypes, COVID-19, and other human complex traits and diseases. We perform causal inference of soluble ACE2 on vascular disease outcomes and COVID-19 severity using mendelian randomization. We also perform in silico functional analysis by integrating with other types of omics data. We identified 10 loci, including 8 novel, capturing 30% of the heritability of the protein. We detected that plasma ACE2 was genetically correlated with vascular diseases, severe COVID-19, and a wide range of human complex diseases and medications. An X-chromosome cis-protein quantitative trait loci-based mendelian randomization analysis suggested a causal effect of elevated ACE2 levels on COVID-19 severity (odds ratio, 1.63 [95% CI, 1.10-2.42]; P =0.01), hospitalization (odds ratio, 1.52 [95% CI, 1.05-2.21]; P =0.03), and infection (odds ratio, 1.60 [95% CI, 1.08-2.37]; P =0.02). Tissue- and cell type-specific transcriptomic and epigenomic analysis revealed that the ACE2 regulatory variants were enriched for DNA methylation sites in blood immune cells. Human plasma ACE2 shares a genetic basis with cardiovascular disease, COVID-19, and other related diseases. The genetic architecture of the ACE2 protein is mapped, providing a useful resource for further biological and clinical studies on this coronavirus receptor.	yes

2022	Definition of the Immune Parameters Related to COVID-19 Severity.	A relevant portion of patients with disease caused by the severe acute respiratory syndrome coronavirus 2 (COVID-19) experience negative outcome, and several laboratory tests have been proposed to predict disease severity. Among others, dramatic changes in peripheral blood cells have been described. We developed and validated a laboratory score solely based on blood cell parameters to predict survival in hospitalized COVID-19 patients. We retrospectively analyzed 1,619 blood cell count from 226 consecutively hospitalized COVID-19 patients to select parameters for inclusion in a laboratory score predicting severity of disease and survival. The score was derived from lymphocyte- and granulocyte-associated parameters and validated on a separate cohort of 140 consecutive COVID-19 patients. Using ROC curve analysis, a best cutoff for score of 30.6 was derived, which was associated to an overall 82.0% sensitivity (95% CI: 78-84) and 82.5% specificity (95% CI: 80-84) for detecting outcome. The scoring trend effectively separated survivor and non-survivor groups, starting 2 weeks before the end of the hospitalization period. Patients' score time points were also classified into mild, moderate, severe, and critical according to the symptomatic oxygen therapy administered. Fluctuations of the score should be recorded to highlight a favorable or unfortunate trend of the disease. The predictive score was found to reflect and anticipate the disease gravity, defined by the type of the oxygen support used, giving a proof of its clinical relevance. It offers a fast and reliable tool for supporting clinical decisions and, most important, triage in terms of not only prioritization but also allocation of limited medical resources, especially in the period when therapies are still symptomatic and many are under development. In fact, a prolonged and progressive increase of the score can suggest impaired chances of survival and/or an urgent need for intensive care unit admission.	yes
2022	Serum IL-28A/IFN-λ2 is linked to disease severity of COVID-19.	Type III interferons (IFNs) play an important role in respiratory viral infections, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This study aimed to determine whether the expression of serum type III IFNs predicted disease severity among patients with the coronavirus disease (COVID-19). A retrospective cohort study was conducted of patients admitted to a single hospital between March 21, 2020, and March 31, 2021. Patients were divided into mild to moderate I (MM) and moderate II to severe (MS) groups based on the COVID-19 severity classification developed by the Japanese Ministry of Health, Labor and Welfare. A total of 257 patients were included in the analysis. Human interleukin-28A (IL-28A/IFN-λ2) expression was significantly lower, and interleukin (IL)-6 expression was significantly higher in the MS group than in the MM group (both $p < 0.001$). In addition, IL-28A/IFN-λ2 was statistically significantly inversely correlated with the time from disease onset to negative SARS-CoV-2 PCR results ($p = 0.049$). Multivariable logistic regression analysis showed that IL-28A/IFN-λ2 was an independent predictor of disease severity ($p = 0.021$). The low expression of IL-28A/IFN-λ2 may serve as a serum biomarker that predicts the severity of COVID-19, possibly through the mechanism of delayed viral elimination.	yes

2022	Expression analysis of IFNAR1 and TYK2 transcripts in COVID-19 patients.	As a member of JAK family of non-receptor tyrosine kinases, TYK2 has a crucial role in regulation of immune responses. This protein has a crucial role in constant expression of IFNAR1 on surface of cells and initiation of type I IFN signaling. In the current study, we measured expression of IFNAR1 and TYK2 levels in venous blood samples of COVID-19 patients and matched controls. TYK2 was significantly down-regulated in male patients compared with male controls (RME = 0.34, P value = 0.03). Though, levels of TYK2 were not different between female cases and female controls, or between ICU-admitted and non-ICU-admitted cases. Expression of IFNAR1 was not different either between COVID-19 cases and controls or between patients required ICU admission and non-ICU-admitted cases. However, none of these transcripts can properly diffrentiate COVID-19 cases from controls or separate patients based on disease severity. The current study proposes down-regulation of TYK2 as a molecular mechanism for incapacity of SARS-CoV-2 in induction of a competent IFN response.	yes
2022	Higher levels of von Willebrand factor in hospitalised patient plasma provides an explanation for the association of ABO blood group and secretor status with COVID19 severity.	NA	yes
2022	DNA methylation profiles in pneumonia patients reflect changes in cell types and pneumonia severity.	Immune cell-type composition changes with age, potentially weakening the response to infectious diseases. Profiling epigenetics marks of immune cells can help us understand the relationship with disease severity. We therefore leveraged a targeted DNA methylation method to study the differences in a cohort of pneumonia patients (both COVID-19 positive and negative) and unaffected individuals from peripheral blood.This approach allowed us to predict the pneumonia diagnosis with high accuracy (AUC = 0.92), and the PCR positivity to the SARS-CoV-2 viral genome with moderate, albeit lower, accuracy (AUC = 0.77). We were also able to predict the severity of pneumonia (PORT score) with an R^2 = 0.69. By estimating immune cellular frequency from DNA methylation data, patients under the age of 65 positive to the SARS-CoV-2 genome (as revealed by PCR) showed an increase in T cells, and specifically in CD8+ cells, compared to the negative control group. Conversely, we observed a decreased frequency of neutrophils in the positive compared to the negative group. No significant difference was found in patients over the age of 65. The results suggest that this DNA methylation-based approach can be used as a cost-effective and clinically useful biomarker platform for predicting pneumonias and their severity.	yes

2022	Monitoring of anti-SARS-CoV-2 IgG antibody immune responses in two cohorts of Hungarian healthcare workers following infection or immunization	Összefoglaló. Bevezetés: A SARS-CoV-2-fertőzések és az anti-SARS-CoV-2-vakcinák által kiváltott immunvédelem tartóssága, nagysága és különbségeinek háttere nem teljesen tisztázott, az oltási protokollok optimális időzítése vitatott. Célkitűzés: A humorális immunválaszok nagyságát, időbeli változását, a reinfekciók gyakoriságát, demográfiai és klinikai paraméterekkel való összefüggését vizsgáltuk magyarországi egészségügyi dolgozóknál. Módszerek: Megyei egyetemi oktató kórházunkban prospektív, longitudinális vizsgálatot végeztünk egészségügyi dolgozók két csoportjában. 1. kohorsz: SARS-CoV-2-fertőzésen átesett, oltatlan 42 dolgozó (nő: 100%) antinukleokapszid-IgG-szintjét mértük 8 hónapon keresztül (2020. június-2021. február). Az immunválasznak a változását és az életkorral, a krónikus betegségekkel, a vércsoporttal és a tünetek súlyosságával való összefüggését vizsgáltuk. 2. kohorsz: két dózis mRNS-vakcinával (Pfizer-BioNTech) végzett immunizálást követően, fertőzésnaiv 49 dolgozó (nő: 73%) anti-spike-RBD-protein-IgG-szintjét monitoroztuk 8 hónapig (2020. december-2021. augusztus). Medián analízis, lineáris regresszió, ANCOVA, Kruskal-Wallis- és Skillings-Mack-teszt-elemzéseket végeztünk. Eredmények: 1. kohorsz: az IgG-szintek átlagosan a betegség 4-es súlyossági kategóriájában voltak a legmagasabbak, a negatív tartományba csökkenés medián ideje 6 hónap volt. 2. kohorsz: a második vakcina hatására az IgG-szint a 25-szörösére nőtt, majd 210 nap után a csúcsszint 6%-ra csökkent. Az ellenanyagtiter negatív összefüggést mutatott az idősebb életkorral és a férfinemmel. Tünetmentes (újra)fertőződést valószínűsítettünk a fertőzésen átesettek 17%-ánál és az immunizált kohorsz 14%-ánál. Az érintettek magas kockázatú osztályokon dolgoztak. Következtetés: 6 hónap után mind a fertőzésen átesettek, mind az immunizáltak jelentősen csökkenő IgG-védelmet mutattak. A (re)infekciók átlagosan 15%-ban, tünetmentesen zajlottak. Az eredmények megerősítik az oltás hatékonyságát a betegség megelőzésében, a harmadik emlékeztető vakcina fontosságát 6 hónap után és az anti-SARS-CoV-2-IgG-monitorozás potenciális értékét. Orv Hetil. 2022; 163(12): 455-462. The length, level and variation of immune responses to infection with SARS-CoV-2 or following anti-SARS-CoV-2 vaccination remains unclear, optimal (re)vaccination protocols remain debated. We investigated the magnitude of humoral immune responses, their over-time changes, the frequency of (re)infections and the association with demographic and clinical parameters in Hungarian healthcare workers. We conducted a prospective, longitudinal study in two groups of healthcare workers of a public, county-level teaching hospital. Cohort 1: The anti-nucleocapsid IgG levels of 42 workers (female: 100%) were followed up over 8 months after SARS-CoV-2 infection (June 2020-February 2021). The change in humoral immune response and its associations with age, existing chronic conditions, blood type and severity of symptoms were investigated. Cohort 2: The anti-spike-RBD protein IgG levels of 49 workers (female: 73%) with no prior COVID-19 infection were monitored over 8 months (December 2020-August 2021) following immunisation with two doses of mRNA vaccine (Pfizer-BioNTech). Analyses included median analysis, linear regression, ANCOVA, Kruskal-Wallis and Skilling-Mack tests. Cohort 1: IgG levels were on average the highest among those in illness severity category 4, the median time of IgG level reduction below the positive test cut-off was 6 months. Cohort 2: The IgG levels increased 25-fold between the first and second immunisations, but decreased to 6% of the peak level after 210 days. They showed an overall negative association with older age	no

		and male sex. The suspected levels of (re)infections were 17% and 14% within the infected and the immunised cohorts, respectively, all symptomless. Those affected all worked on high-risk wards. Both the infected and the immunised cohorts showed significantly declining IgG protections beyond 6 months. The average observed rate of (re)infections was 15%, all asymptomatic. Our findings are confirmative of the effectiveness of vaccination to prevent illness, the importance of booster vaccination due to declining humoral immune protection beyond 6 months, and the potential value of anti-SARS-CoV-2 IgG monitoring. Orv Hetil. 2022; 163(12): 455-462.	
2022	Complications of Autoimmune Hemolytic Anemia.	Autoimmune hemolytic anemia (AHIA) is the group of acquired autoimmune conditions resulting from the development of autologous antibodies directed against autologous red blood cell antigens resulting in red cell lysis. Beyond the presence, severity, and duration of hemolysis which can lead to symptomatic anemia, additional complications at presentation and during treatment require a high degree of clinical vigilance. These include among others cutaneous, thrombotic, renal disorders, and infectious disorders. Complications can be due to the presence of the pathologic antibody itself, the process of hemolysis, or attributed to treatment. Comprehensive management of AIHA requires awareness and assessment of complications at diagnosis, during, and following treatment.	no
2022	Association Between Red Blood Cell Distribution Width and COVID-19 Severity in Delta Variant SARS-CoV-2 Infection.	Studies have discovered that wild-type SARS-CoV-2 infections are commonly linked to abnormalities in the hematological profiles of COVID-19 patients, one such abnormality being characterized by elevations in red blood cell distribution width (RDW). Whether this linkage reoccurs in delta variant SARS-CoV-2 infection remains unexamined. Here we compared baseline blood parameters in COVID-19 patients infected by wild type and its delta variant, respectively. Our results here point to that although the delta variant has shown increased	yes

		virulence, transmissibility, and vaccine escape, it has a minimally negative impact on RDW values that were previously found prognostic for COVID-19 severity.	
2022	Genetic association of IL17 and the importance of ABO blood group antigens in saliva to COVID-19.	The outbreak of COVID-19 caused by infection with SARS-CoV-2 virus has become a worldwide pandemic, and the number of patients presenting with respiratory failure is rapidly increasing in Japan. An international meta-analysis has been conducted to identify genetic factors associated with the onset and severity of COVID-19, but these factors have yet to be fully clarified. Here, we carried out genomic analysis based on a genome-wide association study (GWAS) in Japanese COVID-19 patients to determine whether genetic factors reported to be associated with the onset or severity of COVID-19 in the international meta-GWAS are replicated in the Japanese population, and whether new genetic factors exist. Although no significant genome-wide association was detected in the Japanese GWAS, an integrated analysis with the international meta-GWAS identified for the first time the involvement of the IL17A/IL17F gene in the severity of COVID-19. Among nine genes reported in the international meta-GWAS as genes involved in the onset of COVID-19, the association of FOXP4-AS1, ABO, and IFNAR2 genes was replicated in the Japanese population. Moreover, combined analysis of ABO and FUT2 genotypes revealed that the presence of oral AB antigens was significantly associated with the onset of COVID-19. FOXP4-AS1 and IFNAR2 were also significantly associated in the integrated analysis of the Japanese GWAS and international meta-GWAS when compared with severe COVID-19 cases and the general population. This made it clear that these two genes were also involved in not only the onset but also the severity of COVID-19. In particular, FOXP4-AS1 was not found to be associated with the severity of COVID-19 in the international meta-GWAS, but an integrated analysis with the Japanese GWAS revealed an association with severity. Individuals with the SNP risk allele found between IL17A and IL17F had significantly lower mRNA expression levels of IL17F, suggesting that activation of the innate immune response by IL17F may play an important role in the severity of SARS-CoV-2 infection.	yes
2022	Autoantibodies targeting GPCRs and RAS-related molecules associate with COVID-19 severity.	COVID-19 shares the feature of autoantibody production with systemic autoimmune diseases. In order to understand the role of these immune globulins in the pathogenesis of the disease, it is important to explore the autoantibody spectra. Here we show, by a cross-sectional study of 246 individuals, that autoantibodies targeting G protein-coupled receptors (GPCR) and RAS-related molecules associate with the clinical severity of COVID-19. Patients with moderate and severe disease are characterized by higher autoantibody levels than healthy controls and those with mild COVID-19 disease. Among the anti-GPCR autoantibodies, machine learning classification identifies the chemokine receptor CXCR3 and the RAS-related molecule AGTR1 as targets for antibodies with the strongest association to disease severity. Besides antibody levels, autoantibody network signatures are also changing in patients with intermediate or high disease severity. Although our current and previous studies identify anti-GPCR antibodies as natural components of human biology, their production is deregulated in	yes

		COVID-19 and their level and pattern alterations might predict COVID-19 disease severity.	
2022	Type 1 diabetes is associated with significant changes of ACE and ACE2 expression in peripheral blood mononuclear cells.	The renin-angiotensin system (RAS), which is a key mediator of cardiovascular homeostasis, has two main axes. The classic one, including angiotensin-converting enzyme (ACE) and Angiotensin (Ang) II, promoting vasoconstriction, and the "alternative" one, including ACE2 and Ang1-7, with opposed actions to AngII. ACE2 has been identified as the main receptor of SARS-CoV2, whereby it enters the cells, leading to the downregulation of surface ACE2 and RAS tissue unbalance. Given that diabetes is associated with an increase in COVID-19 severity and death, we aimed at evaluating RAS expression in patients with type 1 diabetes (T1D). This is a case-control study comparing 39 T1D patients to 33 controls, with a median age of 29 and 32 years, and no comorbidities. ACE and ACE2 gene expression was assessed in peripheral blood mononuclear cells. T1D patients had higher ACE expression and circulating AngII, which were related to glucose levels. T1D patients had lower ACE2 expression. However, ACE2 expression was also related to the sex of participants, being higher in the female group. T1D women did not show the same increase of ACE2 expression that was seen in control women. T1D promotes the increase of ACE, AngII, and ACE/ACE2, which might contribute to the higher cardiovascular risk, as well as to severe tissue injury induced by SARS-CoV2 in these patients. The ratio ACE/ACE2 does not differ between men and women with T1D, which might explain why CVD or COVID-19 do not show substantial gender differences in these patients.	no

2022	Whole-genome sequencing reveals host factors underlying critical COVID-19.	Critical COVID-19 is caused by immune-mediated inflammatory lung injury. Host genetic variation influences the development of illness requiring critical care 1 or hospitalization 2-4 after infection with SARS-CoV-2. The GenOMICC (Genetics of Mortality in Critical Care) study enables the comparison of genomes from individuals who are critically ill with those of population controls to find underlying disease mechanisms. Here we use whole-genome sequencing in 7,491 critically ill individuals compared with 48,400 controls to discover and replicate 23 independent variants that significantly predispose to critical COVID-19. We identify 16 new independent associations, including variants within genes that are involved in interferon signalling (IL10RB and PLSCR1), leucocyte differentiation (BCL11A) and blood-type antigen secretor status (FUT2). Using transcriptome-wide association and colocalization to infer the effect of gene expression on disease severity, we find evidence that implicates multiple genes-including reduced expression of a membrane flippase (ATP11A), and increased expression of a mucin (MUC1)-in critical disease. Mendelian randomization provides evidence in support of causal roles for myeloid cell adhesion molecules (SELE, ICAM5 and CD209) and the coagulation factor F8, all of which are potentially druggable targets. Our results are broadly consistent with a multi-component model of COVID-19 pathophysiology, in which at least two distinct mechanisms can predispose to life-threatening disease: failure to control viral replication; or an enhanced tendency towards pulmonary inflammation and intravascular coagulation. We show that comparison between cases of critical illness and population controls is highly efficient for the detection of therapeutically relevant mechanisms of disease.	yes
2022	ACE and ACE2 Gene Variants Are Associated With Severe Outcomes of COVID-19 in Men.	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current coronavirus disease 2019 (COVID-19) pandemic, affecting more than 219 countries and causing the death of more than 5 million people worldwide. The genetic background represents a factor that predisposes the way the host responds to SARS-CoV-2 infection. In this sense, genetic variants of ACE and ACE2 could explain the observed interindividual variability to COVID-19 outcomes. In order to improve the understanding of how genetic variants of ACE and ACE2 are involved in the severity of COVID-19, we included a total of 481 individuals who showed clinical manifestations of COVID-19 and were diagnosed by reverse transcription PCR (RT-PCR). Genomic DNA was extracted from peripheral blood and saliva samples. ACE insertion/deletion polymorphism was evaluated by the high-resolution melting method; ACE single-nucleotide polymorphism (SNP) (rs4344) and ACE2 SNPs (rs2285666 and rs2074192) were genotyped using TaqMan probes. We assessed the association of ACE and ACE2 polymorphisms with disease severity using logistic regression analysis adjusted by age, sex, hypertension, type 2 diabetes, and obesity. The severity of the illness in our study population was divided as 31% mild, 26% severe, and 43% critical illness; additionally, 18% of individuals died, of whom 54% were male. Our results showed in the codominant model a contribution of ACE2 gene rs2285666 T/T genotype to critical outcome [odds ratio (OR) = 1.83; 95%CI = 1.01-3.29; p = 0.04] and to require oxygen supplementation (OR = 1.76; 95%CI = 1.01-3.04; p = 0.04), in addition to a strong association of the T allele of this variant to develop critical illness in male individuals (OR = 1.81; 95%CI = 1.10-2.98; p = 0.02). We suggest that the T allele of rs2285666 represents a risk factor for severe and critical outcomes of	no

		COVID-19, especially for men, regardless of age, hypertension, obesity, and type 2 diabetes.	
2022	Kinetics of Neutralizing Antibody Responses Against SARS-CoV-2 Delta Variant in Patients Infected at the Beginning of the Pandemic.	We investigated the kinetics of the neutralizing antibody responses to the severe acute respiratory syndrome-coronavirus-2 delta variant over the course of 1 year in 16 patients infected at the beginning of the pandemic. In patients with severe disease, neutralizing responses to the delta variant were detectable, albeit at lower levels than responses to the wild type. Neutralizing responses to the delta variant were undetectable, however, in asymptomatic persons. This finding implies that the vaccination strategy for persons with past natural infection should depend on the severity of the previous infection.	yes
2022	Genetic Loci Associated With COVID-19 Positivity and Hospitalization in White, Black, and Hispanic Veterans of the VA Million Veteran Program.	SARS-CoV-2 has caused symptomatic COVID-19 and widespread death across the globe. We sought to determine genetic variants contributing to COVID-19 susceptibility and hospitalization in a large biobank linked to a national United States health system. We identified 19,168 (3.7%) lab-confirmed COVID-19 cases among Million Veteran Program participants between March 1, 2020, and February 2, 2021, including 11,778 Whites, 4,893 Blacks, and 2,497 Hispanics. A multi-population genome-wide association study (GWAS) for COVID-19 outcomes identified four independent genetic variants (rs8176719, rs73062389, rs60870724, and rs73910904) contributing to COVID-19 positivity, including one novel locus found exclusively among Hispanics. We replicated eight of nine previously reported genetic associations at an alpha of 0.05 in at least one population-specific or the multi-population meta-analysis for one of the four MVP COVID-19 outcomes. We used rs8176719 and three additional variants to accurately infer ABO blood types. We found that A, AB, and B blood types were associated with testing positive for COVID-19 compared with O blood type with the highest risk for the A blood group. We did not observe any genome-wide significant associations for COVID-19 severity outcomes among those testing positive. Our study replicates prior GWAS findings associated with testing positive for COVID-19 among mostly White samples and extends findings at three loci to Black and Hispanic individuals. We also report a new locus among Hispanics	yes

		requiring further investigation. These findings may aid in the identification of novel therapeutic agents to decrease the morbidity and mortality of COVID-19 across all major ancestral populations.	
2022	Specialized interferon action in COVID-19.	The impacts of interferon (IFN) signaling on COVID-19 pathology are multiple, with both protective and harmful effects being documented. We report here a multiomics investigation of systemic IFN signaling in hospitalized COVID-19 patients, defining the multiomics biosignatures associated with varying levels of 12 different type I, II, and III IFNs. The antiviral transcriptional response in circulating immune cells is strongly associated with a specific subset of IFNs, most prominently IFNA2 and IFNG. In contrast, proteomics signatures indicative of endothelial damage and platelet activation associate with high levels of IFNB1 and IFNA6. Seroconversion and time since hospitalization associate with a significant decrease in a specific subset of IFNs. Additionally, differential IFN subtype production is linked to distinct constellations of circulating myeloid and lymphoid immune cell types. Each IFN has a unique metabolic signature, with IFNG being the most associated with activation of the kynurenine pathway. IFNs also show differential relationships with clinical markers of poor prognosis and disease severity. For example, whereas IFNG has the strongest association with C-reactive protein and other immune markers of poor prognosis, IFNB1 associates with increased neutrophil to lymphocyte ratio, a marker of late severe disease. Altogether, these results reveal specialized IFN action in COVID-19, with potential diagnostic and therapeutic implications.	yes

2022	Multiple early factors anticipate post-acute COVID-19 sequelae.	Post-acute sequelae of COVID-19 (PASC) represent an emerging global crisis. However, quantifiable risk factors for PASC and their biological associations are poorly resolved. We executed a deep multi-omic, longitudinal investigation of 309 COVID-19 patients from initial diagnosis to convalescence (2-3 months later), integrated with clinical data and patient-reported symptoms. We resolved four PASC-anticipating risk factors at the time of initial COVID-19 diagnosis: type 2 diabetes, SARS-CoV-2 RNAemia, Epstein-Barr virus viremia, and specific auto-antibodies. In patients with gastrointestinal PASC, SARS-CoV-2-specific and CMV-specific CD8 + T cells exhibited unique dynamics during recovery from COVID-19. Analysis of symptom-associated immunological signatures revealed coordinated immunity polarization into four endotypes, exhibiting divergent acute severity and PASC. We find that immunological associations between PASC factors diminish over time, leading to distinct convalescent immune states. Detectability of most PASC factors at COVID-19 diagnosis emphasizes the importance of early disease measurements for understanding emergent chronic conditions and suggests PASC treatment strategies.	no
2022	Distribution of Interferon Lambda 4 Single Nucleotide Polymorphism rs11322783 Genotypes in Patients with COVID-19.	Type III interferons (IFN-III), also known as IFN-Lambda, have a pivotal role during SARS-CoV-2 infection. IFN-Lambda response among individuals is heterogeneous and its association with COVID-19 symptoms severity needs to be further clarified. We analyzed the genotype frequencies of IFNL4 single nucleotide polymorphism (SNP) rs11322783 in patients with COVID-19 (n = 128), in comparison with a validated data set of European healthy controls (n = 14152). The IFNL4 SNP was also analyzed according to the haematological and clinical parameters of patients with COVID-19. The distributions of IFNL4 genotypes among SARS-CoV-2 positive patients [TT/TT 41.4% (n = 53), TT/ΔG 47.7% (n = 61) and ΔG/ΔG 10.9% (n = 14)] and healthy controls were comparable. Different levels of white blood cells (p = 0.036) and neutrophils (p = 0.042) were found in the IFNL4 different genotypes in patients with COVID-19; the ΔG/ΔG genotype was more represented in the groups with low white blood cells and neutrophils. There were no differences in major inflammation parameters (C-reactive protein, D-dimer, Albumin, and Lactate-dehydrogenase (LDH)] and survival rate according to the IFNL4 genotypes. In conclusion, although patients with COVID-19 did not exhibit a different distribution of the IFNL4 SNP, the ΔG/ΔG genotype was associated with a lower count of immune cell populations. These findings need to be confirmed in larger groups of patients with COVID-19 and the role of IFNL4 SNP needs to be also investigated in other respiratory viral infections.	yes
2022	Stratification of hospitalized COVID-19 patients into clinical severity progression groups by immuno-phenotyping and machine learning.	Quantitative or qualitative differences in immunity may drive clinical severity in COVID-19. Although longitudinal studies to record the course of immunological changes are ample, they do not necessarily predict clinical progression at the time of hospital admission. Here we show, by a machine learning approach using serum pro-inflammatory, anti-inflammatory and anti-viral cytokine and anti-SARS-CoV-2 antibody measurements as input data, that COVID-19 patients cluster into three distinct immune phenotype groups. These immune-types, determined by unsupervised hierarchical clustering that is agnostic to severity, predict clinical course. The identified immune-types do not associate with disease duration at hospital admittance, but rather reflect variations in the nature and kinetics of individual patient's immune response. Thus, our work provides an immune-type based scheme to stratify COVID-19 patients at hospital admittance into high and low risk	no

		clinical categories with distinct cytokine and antibody profiles that may guide personalized therapy.	
2022	Neutralizing Antibody Responses to SARS-CoV-2 in Recovered COVID-19 Patients Are Variable and Correlate With Disease Severity and Receptor-Binding Domain Recognition.	Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) caused outbreaks of the pandemic starting from the end of 2019 and, despite ongoing vaccination campaigns, still influences health services and economic factors globally. Understanding immune protection elicited by natural infection is of critical importance for public health policy. This knowledge is instrumental to set scientific parameters for the release of "immunity pass" adopted with different criteria across Europe and other countries and to provide guidelines for the vaccination of COVID-19 recovered patients. Here, we characterized the humoral response triggered by SARS-CoV-2 natural infection by analyzing serum samples from 94 COVID-19 convalescent patients with three serological platforms, including live virus neutralization, pseudovirus neutralization, and ELISA. We found that neutralization potency varies greatly across individuals, is significantly higher in severe patients compared with mild ones, and correlates with both Spike and receptor-binding domain (RBD) recognition. We also show that RBD-targeting antibodies consistently represent only a modest proportion of Spike-specific IgG, suggesting broad specificity of the humoral response in naturally infected individuals. Collectively, this study contributes to the characterization of the humoral immune response in the context of natural SARS-CoV-2 infection, highlighting its variability in terms of neutralization activity, with implications for immune protection in COVID-19 recovered patients.	yes
2022	COVID-19 mRNA Vaccination, ABO Blood Type and the Severity of Self-Reported Reactogenicity in a Large Healthcare System: A Brief Report of a Cross-Sectional Study.	Introduction It has been anecdotally observed that ABO blood type may have an impact on the severity of the side-effects experienced by those receiving mRNA vaccination for COVID-19. Methods As part of a larger study, a retrospective cross-sectional survey was made available to approximately 33,000 front-line healthcare workers, students and volunteers who were offered voluntary vaccination in a state-wide healthcare system during phase one of the state's vaccine roll-out. A secondary endpoint of the survey was to determine if there was any relationship between vaccination reactogenicity and ABO blood type. Results 4009 responses were received - a 12.15% response rate. 3700 respondents answered the blood type question, and of those, 2878 knew their blood type. By Kruskal-Wallis test, there was no statistically significant association between any blood type and any side effect for either of the COVID-19 mRNA vaccines. Conclusions COVID-19 mRNA vaccination may cause significant reactogenicity. However, ABO blood type does not appear to be a predictor of vaccine reactogenicity.	no

2022	Peculiar characteristics of new-onset Type 1 Diabetes during COVID-19 pandemic.	The COVID-19 pandemic period is having a strong impact on the management of diabetes as well as other chronic diseases as shown by the most severe clinical presentation at onset. The aim of this study was to evaluate the severity of diabetic ketoacidosis (DKA) in youth with newly diagnosed type 1 diabetes in "Santissima Annunziata Hospital" (Chieti, Italy) during COVID-19 pandemic in comparison to the five previous years. A retrospective population-based incidence study was performed. Data were obtained from hospital records of 172 patients with new onset type 1 diabetes divided into two groups according to the diagnosis: Group I, between January 2015 and February 2020; Group II, between March 2020 and April 2021. Data regarding anthropometric, socio-economic and laboratory test were analyzed. DKA (pH < 7.30) and different severity of the disease (severe pH < 7.10; moderate pH < 7.20, mild pH < 7.30) were evaluated. A Spearman correlation between pH values and the main variables of interest was performed. DKA frequency was increased by 19 percentage in Group II compared to Group I (55% vs 36%; P = 0.03) with a significant increased risk of severe DKA cases compared to the previous five years (severe DKA 22.5% vs. 8.4%, P = 0.01). pH values were significantly related with HbA1c, blood glucose and c-peptide values in all groups. In addition, in Group II but not in Group I, pH values correlated with Triglycerides and TG/HDL cholesterol ratio. During COVID-19 pandemic the risk of more severe clinical presentation of type 1 diabetes at onset is increased. The correlation with lipid profile might suppose an additional effect of lifestyle changes beside the delay in the diagnosis. Modifications of health care system need to be implemented during this peculiar situation in order to avoid such a relevant complication at onset.	no
2022	Heterozygote Advantage of the Type II Deiodinase Thr92Ala Polymorphism on Intrahospital Mortality of COVID-19.	The type 2 deiodinase and its Thr92Ala-DIO2 polymorphism have been linked to clinical outcomes in acute lung injury and pulmonary fibrosis. Our objectives were to evaluate were cumulative mortality during admission according to Thr92Ala-DIO2 polymorphism. Here we conducted an observational, longitudinal, and prospective cohort study to investigate a possible association between the Thr92Ala-DIO2 polymorphism and intrahospital mortality from COVID-19 in adult patients admitted between June and August 2020. Blood biochemistry, thyroid function tests, length of stay, comorbidities, complications, and severity scores were also studied according to Thr92Ala-DIO2 polymorphism. In total, 220 consecutive patients (median age 62; 48-74 years) were stratified into 3 subgroups: Thr/Thr (n = 79), Thr/Ala (n = 119), and Ala/Ala (n = 23). While the overall mortality was 17.3%, the lethality was lower in Ala/Thr patients (12.6%) than in Thr/Thr patients (21.7%) or Ala/Ala patients (23%). The heterozygous genotype (Thr/Ala) was associated with a 47% reduced risk of intrahospital mortality whereas univariate and multivariate logistic regression adjusted for multiple covariates revealed a reduction that ranged from 51% to 66%. The association of the Thr/Ala genotype with better clinical outcomes was confirmed in a metanalysis of 5 studies, including the present one. Here we provide evidence for a protective role played by Thr92Ala-DIO2 heterozygosity in patients with COVID-19. This protective effect follows an inheritance model known as overdominance, in which the phenotype of the heterozygote lies outside the phenotypical range of both homozygous.	no
2022	Association of Rhesus factor blood type with risk of SARS-CoV-2	NA	yes

	infection and COVID-19 severity.		
2022	Allelic Variants Within the ABO Blood Group Phenotype Confer Protection Against Critical COVID-19 Hospital Presentation.	Introduction: Coronavirus disease 2019 (COVID-19) disease severity differs widely due to numerous factors including ABO gene-derived susceptibility or resistance. The objective of this study was to investigate the association of the ABO blood group and genetic variations of the ABO gene with COVID-19 severity in a heterogeneous hospital population sample from the United Arab Emirates, with the use of an epidemiological and candidate gene approach from a genome-wide association study (GWAS). Methods: In this cross-sectional study, a total of 646 participants who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were recruited from multiple hospitals and population-based (quarantine camps) recruitment sites from March 2020 to February 2021. The participants were divided into two groups based on the severity of COVID-19: noncritical (n = 453) and critical [intensive care unit (ICU) patients] (n = 193), as per the COVID-19 Reporting and Data System (CO-RADS) classification. The multivariate logistic regression analysis demonstrated the association of ABO blood type as well as circulating anti-A antibodies and anti-B antibodies as well as A and B antigens, in association with critical COVID-19 hospital presentation. A candidate gene analysis approach was conducted from a GWAS where we examined 240 single nucleotide polymorphisms (SNPs) (position in chr9 : 136125788-136150617) in the ABO gene, in association with critical COVID-19 hospital presentation. Results: Patients with blood group O [odds ratio (OR): 0.51 (0.33, 0.79); p = 0.003] were less likely to develop critical COVID-19 symptoms. Eight alleles have been identified to be associated with a protective effect of blood group O in ABO 3'untranslated region (UTR): rs199969472 (p = 0.0052), rs34266669 (p = 0.0052), rs76700116 (p = 0.0052), rs7849280 (p = 0.0052), rs34039247 (p = 0.0104), rs10901251 (p = 0.0165), rs9411475 (p = 0.0377), and rs13291798 (p = 0.0377). Conclusion: Our findings suggest that there are novel allelic variants that link genetic variants of the ABO gene and ABO blood groups contributing to the reduced risk of critical COVID-19 disease. This study is the first study to combine genetic and serological evidence of the involvement of the ABO blood groups and the ABO gene allelic associations with COVID-19 severity within the Middle Eastern population.	yes

2022	Association between FY*02N.01 and the severity of COVID-19: initial observations.	The pro-inflammatory immune response underlies severe cases of COVID-19. Antigens of the Duffy blood group systems are receptors for pro-inflammation chemokines. The ACKR1 c.-67T>C gene variation silences the expression of Duffy antigens on erythrocytes and individuals presenting this variant in homozygosity have impaired inflammatory response control. Our aim was to evaluate the association between the ACKR1 c.-67T>C and the severity of COVID-19. This was a retrospective single-center case-control study, enrolling 164 participants who were divided into four groups: 1) Death: COVID-19 patients who died during hospitalization; 2) Hospital Discharge: COVID-19 patients who were discharged for home after hospitalizations; 3) Convalescent Plasma Donors: COVID-19 patients who were not hospitalized, and; 4) Controls: patients with diagnosis other than COVID-19. Patients were genotyped for the ACKR1 c.-67T>C (FY*02 N.01 allele) and the frequency of individuals presenting the altered allele was compared between the groups. The groups significantly differed in terms of the percentage of patients presenting at least one FY*02N.01 allele: 36.8% (Death group), 37% (Hospital Discharge group), 16.1% (Convalescent Plasma group) and 16.2% (Control group) ($p = 0.027$). The self-declared race ($p < 0.001$) and the occurrence of in hospital death ($p = 0.058$) were independently associated with the presence of the FY*02N.01 allele. Hypertension ($p < 0.001$), age ($p < 0.001$) and the presence of at least one FY*02N.01 allele ($p = 0.009$) were independently associated with the need for hospitalization. There is a suggestive association between the presence of the FY*02N.01 and the severity of COVID-19. This may be a mechanism underlying the worse prognosis for Afro-descendants infected with SARS-CoV-2.	yes
2022	RNA Sequencing in COVID-19 patients identifies neutrophil activation biomarkers as a promising diagnostic platform for infections.	Infection with the SARS-CoV2 virus can vary from asymptomatic, or flu-like with moderate disease, up to critically severe. Severe disease, termed COVID-19, involves acute respiratory deterioration that is frequently fatal. To understand the highly variable presentation, and identify biomarkers for disease severity, blood RNA from COVID-19 patient in an intensive care unit was analyzed by whole transcriptome RNA sequencing. Both SARS-CoV2 infection and the severity of COVID-19 syndrome were associated with up to 25-fold increased expression of neutrophil-related transcripts, such as neutrophil defensin 1 (DEFA1), and 3-5-fold reductions in T cell related transcripts such as the T cell receptor (TCR). The DEFA1 RNA level detected SARS-CoV2 viremia with 95.5% sensitivity, when viremia was measured by ddPCR of whole blood RNA. Purified CD15+ neutrophils from COVID-19 patients were increased in abundance and showed striking increases in nuclear DNA staining by DAPI. Concurrently, they showed >10-fold higher elastase activity than normal controls, and correcting for their increased abundance, still showed 5-fold higher elastase activity per cell. Despite higher CD15+ neutrophil elastase activity, elastase activity was extremely low in plasma from the same patients. Collectively, the data supports the model that increased neutrophil and decreased T cell activity is associated with increased COVID-19 severity, and suggests that blood DEFA1 RNA levels and neutrophil elastase activity, both involved in neutrophil extracellular traps (NETs), may be informative biomarkers of host immune activity after viral infection.	no

2022	Detection and quantification of antibody to SARS CoV 2 receptor binding domain provides enhanced sensitivity, specificity and utility.	Accurate and sensitive detection of antibody to SARS-CoV-2 remains an essential component of the pandemic response. Measuring antibody that predicts neutralising activity and the vaccine response is an absolute requirement for laboratory-based confirmatory and reference activity. The viral receptor binding domain (RBD) constitutes the prime target antigen for neutralising antibody. A double antigen binding assay (DABA), providing the most sensitive format has been exploited in a novel hybrid manner employing a solid-phase S1 preferentially presenting RBD, coupled with a labelled RBD conjugate, used in a two-step sequential assay for detection and measurement of antibody to RBD (anti-RBD). This class and species neutral assay showed a specificity of 100 % on 825 pre COVID-19 samples and a potential sensitivity of 99.6 % on 276 recovery samples, predicting quantitatively the presence of neutralising antibody determined by pseudo-type neutralization and by plaque reduction. Anti-RBD is also measurable in ferrets immunised with ChadOx1 nCoV-19 vaccine and in humans immunised with both AstraZeneca and Pfizer vaccines. This assay detects anti-RBD at presentation with illness, demonstrates its elevation with disease severity, its sequel to asymptomatic infection and its persistence after the loss of antibody to the nucleoprotein (anti-NP). It also provides serological confirmation of prior infection and offers a secure measure for seroprevalence and studies of vaccine immunisation in human and animal populations. The hybrid DABA also displays the attributes necessary for the detection and quantification of anti-RBD to be used in clinical practice. An absence of detectable anti-RBD by this assay predicates the need for passive immune prophylaxis in at-risk patients.	no

2022	Development and Validation of a Treatment Benefit Index to Identify Hospitalized Patients With COVID-19 Who May Benefit From Convalescent Plasma.	Identifying which patients with COVID-19 are likely to benefit from COVID-19 convalescent plasma (CCP) treatment may have a large public health impact. To develop an index for predicting the expected relative treatment benefit from CCP compared with treatment without CCP for patients hospitalized for COVID-19 using patients' baseline characteristics. This prognostic study used data from the COMPILE study, ie, a meta-analysis of pooled individual patient data from 8 randomized clinical trials (RCTs) evaluating CCP vs control in adults hospitalized for COVID-19 who were not receiving mechanical ventilation at randomization. A combination of baseline characteristics, termed the treatment benefit index (TBI), was developed based on 2287 patients in COMPILE using a proportional odds model, with baseline characteristics selected via cross-validation. The TBI was externally validated on 4 external data sets: the Expanded Access Program (1896 participants), a study conducted under Emergency Use Authorization (210 participants), and 2 RCTs (with 80 and 309 participants). Receipt of CCP. World Health Organization (WHO) 11-point ordinal COVID-19 clinical status scale and 2 derivatives of it (ie, WHO score of 7-10, indicating mechanical ventilation to death, and WHO score of 10, indicating death) at day 14 and day 28 after randomization. Day 14 WHO 11-point ordinal scale was used as the primary outcome to develop the TBI. A total of 2287 patients were included in the derivation cohort, with a mean (SD) age of 60.3 (15.2) years and 815 (35.6%) women. The TBI provided a continuous gradation of benefit, and, for clinical utility, it was operationalized into groups of expected large clinical benefit (B1; 629 participants in the derivation cohort [27.5%]), moderate benefit (B2; 953 [41.7%]), and potential harm or no benefit (B3; 705 [30.8%]). Patients with preexisting conditions (diabetes, cardiovascular and pulmonary diseases), with blood type A or AB, and at an early COVID-19 stage (low baseline WHO scores) were expected to benefit most, while those without preexisting conditions and at more advanced stages of COVID-19 could potentially be harmed. In the derivation cohort, odds ratios for worse outcome, where smaller odds ratios indicate larger benefit from CCP, were 0.69 (95% credible interval [CrI], 0.48-1.06) for B1, 0.82 (95% CrI, 0.61-1.11) for B2, and 1.58 (95% CrI, 1.14-2.17) for B3. Testing on 4 external datasets supported the validation of the derived TBIs. The findings of this study suggest that the CCP TBI is a simple tool that can quantify the relative benefit from CCP treatment for an individual patient hospitalized with COVID-19 that can be used to guide treatment recommendations. The TBI precision medicine approach could be especially helpful in a pandemic.	no

2022	Innovative FO-SPR Label-free Strategy for Detecting Anti-RBD Antibodies in COVID-19 Patient Serum and Whole Blood.	The ongoing COVID-19 pandemic has emphasized the urgent need for rapid, accurate, and large-scale diagnostic tools. Next to this, the significance of serological tests (i.e., detection of SARS-CoV-2 antibodies) also became apparent for studying patients' immune status and past viral infection. In this work, we present a novel approach for not only measuring antibody levels but also profiling of binding kinetics of the complete polyclonal antibody response against the receptor binding domain (RBD) of SARS-CoV-2 spike protein, an aspect not possible to achieve with traditional serological tests. This fiber optic surface plasmon resonance (FO-SPR)-based label-free method was successfully accomplished in COVID-19 patient serum and, for the first time, directly in undiluted whole blood, omitting the need for any sample preparation. Notably, this bioassay (1) was on par with FO-SPR sandwich bioassays (traditionally regarded as more sensitive) in distinguishing COVID-19 from control samples, irrespective of the type of sample matrix, and (2) had a significantly shorter time-to-result of only 30 min compared to >1 or 4 h for the FO-SPR sandwich bioassay and the conventional ELISA, respectively. Finally, the label-free approach revealed that no direct correlation was present between antibody levels and their kinetic profiling in different COVID-19 patients, as another evidence to support previous hypothesis that antibody-binding kinetics against the antigen in patient blood might play a role in the COVID-19 severity. Taking all this into account, the presented work positions the FO-SPR technology at the forefront of other COVID-19 serological tests, with a huge potential toward other applications in need for quantification and kinetic profiling of antibodies.	no
2022	Potential Therapeutic Use of the Rosemary Diterpene Carnosic Acid for Alzheimer's Disease, Parkinson's Disease, and Long-COVID through NRF2 Activation to Counteract the NLRP3 Inflammasome.	Rosemary (Rosmarinus officinalis [family Lamiaceae]), an herb of economic and gustatory repute, is employed in traditional medicines in many countries. Rosemary contains carnosic acid (CA) and carnosol (CS), abietane-type phenolic diterpenes, which account for most of its biological and pharmacological actions, although claims have also been made for contributions of another constituent, rosmarinic acid. This review focuses on the potential applications of CA and CS for Alzheimer's disease (AD), Parkinson's disease (PD), and coronavirus disease 2019 (COVID-19), in part via inhibition of the NLRP3 inflammasome. CA exerts antioxidant, anti-inflammatory, and neuroprotective effects via phase 2 enzyme induction initiated by activation of the KEAP1/NRF2 transcriptional pathway, which in turn attenuates NLRP3 activation. In addition, we propose that CA-related compounds may serve as therapeutics against the brain-related after-effects of SARS-CoV-2 infection, termed "long-COVID." One factor that contributes to COVID-19 is cytokine storm emanating from macrophages as a result of unregulated inflammation in and around lung epithelial and endovascular cells. Additionally, neurological aftereffects such as anxiety and "brain fog" are becoming a major issue for both the pandemic and post-pandemic period. Many reports hold that unregulated NLRP3 inflammasome activation may potentially contribute to the severity of COVID-19 and its aftermath. It is therefore possible that suppression of NLRP3 inflammasome activity may prove efficacious against both acute lung disease and chronic neurological after-effects. Because CA has been shown to not only act systemically but also to penetrate the blood-brain barrier and reach the brain parenchyma to exert neuroprotective effects, we discuss the evidence that CA or rosemary extracts containing CA may represent an effective countermeasure against both acute and chronic pathological events	no

		initiated by SARS-CoV-2 infection as well as other chronic neurodegenerative diseases including AD and PD.	

2022	Can Renal Parameters Predict the Mortality of Hospitalized COVID-19 Patients?	Our study aimed to analyze whether renal parameters can predict mortality from COVID-19 disease in hospitalized patients. This retrospective cohort includes all adult patients with confirmed COVID-19 disease who were consecutively admitted to the tertiary hospital during the 4-month period (September 1 to December 31, 2020). We analyzed their basic laboratory values, urinalysis, comorbidities, length of hospitalization, and survival. The RIFLE and KDIGO criteria were used for AKI and CKD grading, respectively. To display renal function evolution and the severity of renal damage, we subdivided patients further into 6 groups as follows: group 1 (normal renal function), group 2 (CKD grades 2 + 3a), group 3 (AKI-DROP defined as whose s-Cr level dropped by >33.3% during the hospitalization), group 4 (CKD 3b), group 5 (CKD 4 + 5), and group 6 (AKI-RISE defined as whose s-Cr level was elevated by ≥50% within 7 days or by ≥26.5 µmol/L within 48 h during hospitalization). Then, we used eGFR on admission independently of renal damage to check whether it can predict mortality. Only 4 groups were used: group I - normal renal function (eGFR > 1.5 mL/s), group II - mild renal involvement (eGFR 0.75-1.5), group III - moderate (eGFR 0.5-0.75), and group IV - severe (GFR <0.5). A total of 680 patients were included in our cohort; among them, 244 patients displayed normal renal function, 207 patients fulfilled AKI, and 229 patients suffered from CKD. In total, a significantly higher mortality rate was found in the AKI and the CKD groups versus normal renal function - 37.2% and 32.3% versus 9.4%, respectively ($p < 0.001$). In addition, the groups 1-6 divided by severity of renal damage reported mortality of 9.4%, 21.2%, 24.1%, 48.7%, 62.8%, and 55.1%, respectively ($p < 0.001$). The mean hospitalization duration of alive patients with normal renal findings was 9.5 days, while it was 12.1 days in patients with any renal damage ($p < 0.001$). When all patients were compared according to eGFR on admission, the mortality was as follows: group I (normal) 9.8%, group II (mild) 22.1%, group III (moderate) 40.9%, and group IV (severe) 50.5%, respectively ($p < 0.001$). It was a significantly better mortality predictor than CRP on admission (AUC 0.7053 vs. 0.6053). Mortality in patients with abnormal renal function was 3 times higher compared to patients with normal renal function. Also, patients with renal damage had a worse and longer hospitalization course. Lastly, eGFR on admission, independently of renal damage type, was an excellent tool for predicting mortality. Further, the change in s-Cr levels during hospitalization reflected the mortality prognosis.	

2022	Clinical characteristics and histopathology of COVID-19 related deaths in South African adults.	Comparisons of histopathological features and microbiological findings between decedents with respiratory symptoms due to SARS-CoV-2 infection or other causes, in settings with high prevalence of HIV and Mycobacterium tuberculosis (MTB) infections have not been reported. Deaths associated with a positive ante-mortem SARS-CoV-2 PCR test and/or respiratory disease symptoms at Chris Hani Baragwanath Academic Hospital in Soweto, South Africa from 15th April to 2nd November 2020, during the first wave of the South African COVID-19 epidemic, were investigated. Deceased adult patients had post-mortem minimally-invasive tissue sampling (MITS) performed to investigate for SARS-CoV-2 infection and molecular detection of putative pathogens on blood and lung samples, and histopathology examination of lung, liver and heart tissue. During the study period MITS were done in patients displaying symptoms of respiratory disease including 75 COVID-19-related deaths (COVID+) and 42 non-COVID-19-related deaths (COVID-). The prevalence of HIV-infection was lower in COVID+ (27%) than in the COVID- (64%), MTB detection was also less common among COVID+ (3% vs 13%). Lung histopathology findings showed differences between COVID+ and COVID- in the severity of the morphological appearance of Type-II pneumocytes, alveolar injury and repair initiated by SARS-CoV-2 infection. In the liver necrotising granulomatous inflammation was more common among COVID+. No differences were found in heart analyses. The prevalence of bacterial co-infections was higher in COVID+. Most indicators of respiratory distress syndrome were undifferentiated between COVID+ and COVID- except for Type-II pneumocytes. HIV or MTB infection does not appear in these data to have a meaningful correspondence with COVID-related deaths.	yes
2022	Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection.	A proportion of patients surviving acute coronavirus disease 2019 (COVID-19) infection develop post-acute COVID syndrome (long COVID (LC)) lasting longer than 12 weeks. Here, we studied individuals with LC compared to age- and gender-matched recovered individuals without LC, unexposed donors and individuals infected with other coronaviruses. Patients with LC had highly activated innate immune cells, lacked naive T and B cells and showed elevated expression of type I IFN (IFN-β) and type III IFN (IFN-λ1) that remained persistently high at 8 months after infection. Using a log-linear classification model, we defined an optimal set of analytes that had the strongest association with LC among the 28 analytes measured. Combinations of the inflammatory mediators IFN-β, PTX3, IFN-γ, IFN-λ2/3 and IL-6 associated with LC with 78.5-81.6% accuracy. This work defines immunological parameters associated with LC and suggests future opportunities for prevention and treatment.	no

2022	Role of the SARS-CoV-2 virus in the appearance of new onset type 1 diabetes mellitus in children in Gran Canaria, Spain.	It has been hypothesized that SARS-CoV-2 may play a role in the development of different forms of diabetes mellitus (DM). The Canary Islands have the highest incidence of type 1 DM (T1DM) reported in Spain (30-35/100,000 children under 14 years/year). In 2020-2021 we observed the highest incidence so far on the island of Gran Canaria, as a result of which we decided to evaluate the possible role of COVID-19 in the increased number of onsets. We examined the presence of IgG antibodies against SARS-CoV-2 in children with new onset T1DM between October 2020 and August 2021. We compared recent T1DM incidence with that of the previous 10 years. Forty-two patients were diagnosed with T1DM (48.1/100,000 patients/year), representing a nonsignificant 25.7% increase from the expected incidence. Of the 33 patients who consented to the study, 32 presented negative IgG values, with only one patient reflecting undiagnosed past infection. Forty-four percent of patients presented with ketoacidosis at onset, which was similar to previous years. We conclude that there is no direct relationship between the increased incidence of T1DM and SARS-CoV-2 in the region. The COVID-19 pandemic did not result in an increased severity of T1DM presentation.	no
2022	Can B-Type Natriuretic Peptide (BNP) Levels Serve as an Early Predictor of Clinical Severity in Patients with COVID-19 Pneumonia?	COVID-19 has continued to aggressively spread and kill. The incidence of complications and associated mortality rates are high. Cardiac damage, which is related to survival, is one of these. The purpose of this study is to assess the role of BNP, a cardiac biomarker, in predicting mortality in COVID-19. This single-center, prospective observational study was performed from July to September 2020 in a tertiary university hospital designated for the treatment of COVID-19 patients. Patients whose diagnoses were confirmed with real-time polymerase chain reaction (RT-PCR) tested nasopharyngeal swabs and with thoracic computed tomography (CT) findings compatible with COVID-19 pneumonia were included in the study. All clinical and laboratory data were obtained within the first 24 hours of hospital admission. To determine the risk of in-hospital death, patients were followed from admission until their discharge (1 to 15 days). The primary outcome was in-hospital death, defined as the case-fatality ratio. Among all biomarkers that were included in the multivariate analysis only high BNP levels was independently associated with mortality [Mean 1.012, 95% CI (1.005 - 1.02 pg/mL) ($p = 0.002$)]. Mortality was found to be significantly associated with older age and higher BNP, LDH, AST, HGB, PLT, ferritin, D-dimer, and CRP levels. In addition, mortality was found to be higher with longer duration of hospitalization ($p = 0.041$). Our fundamental goal for COVID-19 is to determine whether the hospitalized patients are in the mortality risk group at an early stage of disease. Adding measurement of BNP levels to routine laboratory tests for COVID-19 may be a practical approach to determine the patients with a high risk of mortality.	no

2022	Demographic and Clinical Factors Associated with Reactivity of Anti-SARS-CoV-2 Antibodies in Serbian Convalescent Plasma Donors.	Passive immunotherapy with convalescent COVID-19 plasma (CCP) is used as a therapeutic procedure in many countries, including Serbia. In this study, we analyzed the association between demographic factors, COVID-19 severity and the reactivity of anti-SARS-CoV-2 antibodies (Abs) in Serbian CCP donors. Individuals (n = 468) recovered from confirmed SARS-CoV-2 infection, and who were willing to donate their plasma for passive immunization of COVID-19 patients were enrolled in the study. Plasma samples were tested for the presence of IgG reactive to SARS-CoV-2 spike glycoprotein (S1) and nucleocapsid antigens. Individuals were characterized according to age, gender, comorbidities, COVID-19 severity, ABO blood type and RhD factor. Total of 420 candidates (420/468; 89.74%) reached the levels of anti-SARS-CoV-2 IgG that qualified them for inclusion in CCP donation program. Further statistical analysis showed that male individuals (p = 0.034), older age groups (p < 0.001), existence of hypertension (p = 0.008), and severe COVID-19 (p = 0.000) are linked with higher levels of anti-SARS-CoV-2 Abs. These findings will guide the selection of CCP donors in Serbia. Further studies need to be conducted to assess the neutralization potency and clinical efficiency of CCP collected from Serbian donors with high anti-SARS-CoV-2 IgG reactivity.	no
2022	Role of Exercise Intensity on Th1/Th2 Immune Modulations During the COVID-19 Pandemic.	The COVID-19 pandemic has led to several pioneering scientific discoveries resulting in no effective solutions with the exception of vaccination. Moderate exercise is a significant non-pharmacological strategy, to reduce the infection-related burden of COVID-19, especially in patients who are obese, elderly, and with additional comorbidities. The imbalance of T helper type 1 (Th1) or T helper type 2 (Th2) cells has been well documented among populations who have suffered as a result of the COVID-19 pandemic, and who are at maximum risk of infection and mortality. Moderate and low intensity exercise can benefit persons at risk from the disease and survivors by favorable modulation in Th1/Th2 ratios. Moreover, in COVID-19 patients, mild to moderate intensity aerobic exercise also increases immune system function but high intensity aerobic exercise may have adverse effects on immune responses. In addition, sustained hypoxia in COVID-19 patients has been reported to cause organ failure and cell death. Hypoxic conditions have also been highlighted to be triggered in COVID-19-susceptible individuals and COVID-19 survivors. This suggests that hypoxia inducible factor (HIF 1α) might be an important focus for researchers investigating effective strategies to minimize the effects of the pandemic. Intermittent hypoxic preconditioning (IHP) is a method of exposing subjects to short bouts of moderate hypoxia interspersed with brief periods of normal oxygen concentrations (recovery). This methodology inhibits the production of pro-inflammatory factors, activates HIF-1α to activate target genes, and subsequently leads to a higher production of red blood cells and hemoglobin. This increases angiogenesis and increases oxygen transport capacity. These factors can help alleviate virus induced cardiopulmonary hemodynamic disorders and endothelial dysfunction. Therefore, during the COVID-19 pandemic we propose that populations should engage in low to moderate exercise individually designed, prescribed and specific, that utilizes IHP including pranayama (yoga), swimming and high-altitude hiking exercise. This would be beneficial in affecting HIF-1α to combat the disease and its severity. Therefore, the promotion of certain exercises should be considered by all sections of the population. However, exercise recommendations and prescription for COVID-19 patients	no

		should be structured to match individual levels of capability and adaptability.	
2022	Correlation between ABO Blood Group Phenotype and the Risk of COVID-19 Infection and Severity of Disease in a Saudi Arabian Cohort.	Disease severity among patients infected with SARS-CoV-2 varies remarkably. Preliminary studies reported that the ABO blood group system confers differential viral susceptibility and disease severity caused by SARS-CoV-2. Thus, differences in ABO blood group phenotypes may partly explain the observed heterogeneity in COVID-19 severity patterns, and could help identify individuals at increased risk. Herein, we explored the association between ABO blood group phenotypes and COVID-19 susceptibility and severity in a Saudi Arabian cohort. In this retrospective cohort study, we performed ABO typing on a total of 373 Saudi patients infected with SARS-CoV-2 and conducted association analysis between ABO blood group phenotype and COVID-19 infection severity. We then performed gender-stratified analysis by dividing the participating patients into two groups by gender, and classified them according to age. The frequencies of blood group phenotypes A, B, AB and O were 27.3, 23.6, 5.4 and 43.7%, respectively. We found that blood group phenotype O was associated with a lower risk of testing positive for COVID-19 infection (OR 0.76 95% CI 0.62-0.95, p = 0.0113), while blood group phenotype B was associated with higher odds of testing positive (OR 1.51 95% CI 1.17-1.93, p = 0.0009). However, blood group phenotype B was associated with increased risk in the mild and moderate group but not the severe COVID-19 infection group. Blood group phenotype O was protective in all severity groups. Our findings provide evidence that blood group phenotype B is a risk for COVID-19 disease while blood group phenotype O is protective from COVID-19 infection. However, further	yes

		studies are necessary to validate these associations in a larger sample size and among individuals of different ethnic groups.	
2022	Country-level factors dynamics and ABO/Rh blood groups contribution to COVID-19 mortality.	The identification of factors associated to COVID-19 mortality is important to design effective containment measures and safeguard at-risk categories. In the last year, several investigations have tried to ascertain key features to predict the COVID-19 mortality tolls in relation to country-specific dynamics and population structure. Most studies focused on the first wave of the COVID-19 pandemic observed in the first half of 2020. Numerous studies have reported significant associations between COVID-19 mortality and relevant variables, for instance obesity, healthcare system indicators such as hospital beds density, and bacillus Calmette-Guerin immunization. In this work, we investigated the role of ABO/Rh blood groups at three different stages of the pandemic while accounting for demographic, economic, and health system related confounding factors. Using a machine learning approach, we found that the "B+" blood group frequency is an important factor at all stages of the pandemic, confirming previous findings that blood groups are linked to COVID-19 severity and fatal outcome.	yes
2021	SIT1 transporter as a potential novel target in treatment of COVID-19.	Studies published earlier this year demonstrated the association of the solute carrier SLC6A20 gene with the risk and severity of COVID-19. The SLC6A20 protein product (Sodium-dependent Imino Transporter 1 (SIT1)) is involved in the transport of amino acids, including glycine. Here we summarized the results of recent studies demonstrating the interaction of SIT1 with the ACE2 receptor for SARS-CoV-2 as well as an observed association of SLC6A20 with the risk and traits of Type 2 diabetes (T2D). Recently, it was also proposed that SLC6A20 represents the novel regulator of glycine levels and that glycine has beneficial effects against the proinflammatory cytokine secretion induced by SARS-CoV-2 infection. Ivermectin, as a partial agonist of glycine-gated chloride channels, was also recently suggested to interfere with the COVID-19 cytokine storm by inducing the activation of glycine receptors. Furthermore, plasma glycine levels are found to be decreased in diabetic patients. Thus, further clinical trials are warranted to confirm the potential favorable effects of targeting the SIT1 transporter and glycine levels in the treatment of COVID-19, particularly for the severe case of disease associated with hyperglycemia, inflammation, and T2D.	no

		These findings suggest that SIT1 may potentially represent one of the missing pieces in the complex puzzle observed between these two pandemic diseases and the potential novel target for their efficient treatment.	
2021	Susceptibility of ABO blood group to COVID-19 infections: clinico-hematological, radiological, and complications analysis.	In the wake of the COVID-19 pandemic, research indicates that the COVID-19 disease susceptibility varies among individuals depending on their ABO blood groups. Researchers globally commenced investigating potential methods to stratify cases according to prognosis depending on several clinical parameters. Since there is evidence of a link between ABO blood groups and disease susceptibility, it could be argued that there is a link between blood groups and disease manifestation and progression. The current study investigates whether clinical manifestation, laboratory, and imaging findings vary among ABO blood groups of hospitalized confirmed COVID-19 patients.This retrospective cohort study was conducted between March 1, 2020 and March 31, 2021 in King Faisal Specialist Hospital and Research Centre Riyadh and Jeddah, Saudi Arabia. Demographic information, clinical information, laboratory findings, and imaging investigations were extracted from the data warehouse for all confirmed COVID-19 patients.A total of 285 admitted patients were included in the study. Of these, 81 (28.4%) were blood group A, 43 (15.1%) were blood group B, 11 (3.9%) were blood group AB, and 150 (52.6%) were blood group O. This was almost consistent with the distribution of blood groups among the Saudi Arabia community. The majority of the study participants (79.6% [n=227]) were asymptomatic. The upper respiratory tract infection (P=.014) and shortness of breath showed statistically significant differences between the ABO blood group (P=.009). Moreover, the incidence of the symptoms was highly observed in blood group O followed by A then B except for pharyngeal exudate observed in blood group A. The one-way ANOVA test indicated that among the studied hematological parameters, glucose (P=.004), absolute lymphocyte count (P=.001), and IgA (P=.036) showed statistically significant differences between the means of the ABO blood group. The differences in both X-ray and computed tomography scan findings were statistically nonsignificant among the ABO age group. Only 86 (30.3%) patients were admitted to an intensive care unit, and the majority of them were blood groups O 28.7% (n=43) and A 37.0% (n=30). However, the differences in complications' outcomes were statistically nonsignificant among the ABO age group.ABO blood groups among hospitalized COVID-19 patients are not associated with clinical, hematological, radiological, and complications abnormality.	yes

2021	Assessment of Post-Vaccination Antibody Response Eight Months after the Administration of BNT1622b2 Vaccine to Healthcare Workers with Particular Emphasis on the Impact of Previous COVID-19 Infection.	At the end of 2020, COVID-19 vaccination programs were initiated in many countries, including Poland. The first vaccine approved in Poland was the BNT162b2 mRNA preparation (Pfizer/BioNTech), and the first vaccinated group were healthcare workers. The aim of the present study was to evaluate post-vaccine antibody titers 8 months after the second vaccine dose had been administered to a group of employees of the Hospital of the Ministry of the Interior and Administration in Olsztyn (Poland). The employees were divided into two groups: persons who had COVID-19 in the fourth quarter of 2020 and were vaccinated in January-February 2021, and persons without a history of COVID-19 who were vaccinated during the same period. The analyzed material was venous blood serum collected from 100 hospital employees on 23-28 September 2021. The level of anti-SARS-CoV-2 S antibodies was measured with a Roche Cobas e411 analyzer using the electrochemiluminescence (ECLIA) method. The study demonstrated that persons with a history of SARS-CoV-2 infection had significantly higher antibody levels (taking into account gender, age, type of work performed, and severity of post-vaccination symptoms) than employees without a history of COVID-19. The study also revealed that the type of work, age, gender, and the course of SARS-CoV-2 infection can influence the humoral immune response. The presented results may prove helpful in the context of administering additional vaccine doses.	no
2021	Absence of correlation between ABO Rh(D) blood group and neutralizing antibody titers in SARS-CoV-2 convalescent plasma donors.	Several studies have described associations between ABO blood group and SARS-CoV-2 infection severity in hospitalized patients where group A individuals are over-represented and group O individuals may have a lower infection rate. In convalescent individuals, group B blood donors have higher neutralizing SARS-CoV-2 antibody titers. We analyzed whether there was any correlation of ABO Rh(D) blood group with SARS-CoV-2 infection and with neutralizing antibodies in Australian convalescent plasma (CP) donors. ABO Rh(D) distribution and demographics of CP donors (n = 765) were compared with the total blood donor panel (n = 488,028), plasmapheresis donors (n = 203,176) and whole blood donors (n = 282,437) from 2020. The presence of neutralizing antibodies in CP donors was measured using the Vero E6 cell microneutralization assay. The distribution of ABO group in CP donors compared to the total donor panel was not significantly different ($p = .177$). There were significantly more group AB donors in the plasmapheresis subset ($p = .005$) and group O individuals were over-represented in the whole blood donor subset ($p < .0001$). There was no significant difference in neutralizing antibody levels among CP donors with differing ABO blood groups ($p = .872$). ABO Rh(D) blood group distribution was not found to be significantly different between convalescent plasma donors and general blood donors in our large sample group. Inherent blood donor selection biases associated with clinical demand accounted for some differences within CP donors. The levels of SARS-CoV-2 neutralizing antibodies were also not significantly associated with ABO Rh(D) group.	yes

2021	Effects of selected inherited factors on susceptibility to SARS-CoV-2 infection and COVID-19 progression.	Genetic predispositions may influence geographical and interethnic differences in COVID-19 prevalence and mortality in affected populations. Of the many genes implicated in COVID-19 progression, a substantial number have no direct functional link on virus transfer/viability or on the host immune system. To address this knowledge deficit, a large number of in silico studies have recently been published. However, the results of these studies often contradict the findings of studies involving real patients. For example, the ACE2 has been shown to play an important role in regulating coronavirus entry into cells, but none of its variations have been directly associated with COVID-19 susceptibility or severity. Consistently was reported that increased risk of COVID-19 is associated with blood group A and with the APOE4 allele. Among other genes with potential impacts are the genes for CCR5, IL-10, CD14, TMPRSS2 and angiotensin-converting enzyme. Variants within the protein-coding genes OAS1 and LZTFL1 (transferred to the human genome from Neanderthals) are understood to be among the strongest predictors of disease severity. The intensive research efforts have helped to identify the genes and polymorphisms that contribute to SARS-CoV-2 infection and COVID-19 severity.	yes
2021	Relationship between AB0 blood groups and selected pregnancy conditions and neonatal diseases.	The influence of the blood group on the occurrence and severity of diseases has aroused the curiosity of scientists for many years. The AB0 group system is the best known and described blood group system. It is also the only system whose antibodies are constantly present in the blood serum. The most common blood type in Poland, according to data provided by Honorary blood donation and blood therapy, is group A Rh+ (plus), while the least common is group AB Rh- (minus). In studies of pregnant women scientists discovered the influence of blood type in the development of preeclampsia, gestational diabetes, the risk of preterm labor, and even COVID-19 infection. The impact of the mothers' blood group also affects the birth weight of newborns, as well as the development of hemolytic disease of the newborn due to the heterospecificity of AB0. The influence of the blood group on the increased risk of developing certain diseases and complications of the neonatal period has also been proven. Therefore, it seems important to study blood groups of pregnant women and newborns of different nationalities, correlate the results with available reports and use this knowledge in everyday clinical practice. This will help to increase the speed of detection of diseases in pregnancy and neonatal period. It will also facilitate the management of the patient depending on their blood group.	no

2021	Association of ABO blood group with COVID-19 severity, acute phase reactants and mortality.	Coronavirus disease 2019 (COVID-19) is the ongoing pandemic with multitude of manifestations and association of ABO blood group in South-East Asian population needs to be explored. It was a retrospective study of patients with COVID-19. Blood group A, B, O, and AB were identified in every participant, irrespective of their RH type and allotted groups 1, 2,3, and 4, respectively. Correlation between blood group and lab parameters was presented as histogram distributed among the four groups. Multivariate regression and logistic regression were used for inferential statistics. The cohort included 1067 patients: 521 (48.8%) participants had blood group O as the prevalent blood type. Overall, 10.6% COVID-19-related mortality was observed at our center. Mortality was 13.9% in blood group A, 9.5% in group B, 10% in group C, and 10.2% in AB blood group (p = 0.412). IL-6 was elevated in blood group A (median [IQR]: 23.6 [17.5,43.8]), Procalcitonin in blood group B (median [IQR]: 0.54 [0.3,0.7]), D-dimers and CRP in group AB (median [IQR]: 21.5 [9,34]; 24 [9,49], respectively). Regarding severity of COVID-19 disease, no statistical difference was seen between the blood groups. Alteration of the acute phase reactants was not positively associated with any specific blood type. In conclusion, this investigation did not show significant association of blood groups with severity and of COVID-19 disease and COVID-19-associated mortality.	yes
2021	Krebs von den Lungen-6 (KL-6) as a clinical marker for severe COVID-19: A systematic review and meta-analyses.	Krebs von den Lungen-6 (KL-6) is a molecule that is predominantly expressed by damaged alveolar type II cells, and has been proposed as a marker of COVID-19 and the severity of the disease. Here, we performed a meta-analysis to determine whether KL-6 could be used as a prognostic factor for severe COVID-19. PubMed, Cochrane and Google Scholar were searched until April 20, 2021, and 7 studies were included. KL-6 was considered as the outcome and pooled in meta-analyses. All included studies compared KL-6 in severe and non-severe patients. Serum KL-6 was higher in severe COVID-19 patients compared to non-severe (n = 6; SMD = 1.25; 95% CI: 0.99-1.5; P < 0.001) and healthy controls (n = 4; SMD = 3.07; 95% CI: 1.36-4.8; P < 0.001). This data collection revealed the potential clinical significance of KL-6 as a non-expensive predictive biomarker in severe COVID-19 and for the categorization of COVID-19 clinical severity.	no

2021	N-Terminal Pro-B-Type Natriuretic Peptide as a Biomarker for the Severity and Outcomes With COVID-19 in a Nationwide Hospitalized Cohort.	Background Currently, there is limited research on the prognostic value of NT-proBNP (N-terminal pro-B-type natriuretic peptide) as a biomarker in COVID-19. We proposed the a priori hypothesis that an elevated NT-proBNP concentration at admission is associated with increased in-hospital mortality. Methods and Results In this prospective, observational cohort study of the American Heart Association's COVID-19 Cardiovascular Disease Registry, 4675 patients hospitalized with COVID-19 were divided into normal and elevated NT-proBNP cohorts by standard age-adjusted heart failure thresholds, as well as separated by quintiles. Patients with elevated NT-proBNP (n=1344; 28.7%) were older, with more cardiovascular risk factors, and had a significantly higher rate of in-hospital mortality (37% versus 16%; P <0.001) and shorter median time to death (7 versus 9 days; P <0.001) than those with normal values. Analysis by quintile of NT-proBNP revealed a steep graded relationship with mortality (7.1%-40.2%; P <0.001). NT-proBNP was also associated with major adverse cardiac events, intensive care unit admission, intubation, shock, and cardiac arrest (P <0.001 for each). In subgroup analyses, NT-proBNP, but not prior heart failure, was associated with increased risk of in-hospital mortality. Adjusting for cardiovascular risk factors with presenting vital signs, an elevated NT-proBNP was associated with 2-fold higher adjusted odds of death (adjusted odds ratio [OR], 2.23; 95% CI, 1.80-2.76), and the log-transformed NT-proBNP with other biomarkers projected a 21% increased risk of death for each 2-fold increase (adjusted OR, 1.21; 95% CI, 1.08-1.34). Conclusions Elevated NT-proBNP levels on admission for COVID-19 are associated with an increased risk of in-hospital mortality and other complications in patients with and without heart failure.	no
2021	Gut microbiota in a population highly affected by obesity and type 2 diabetes and susceptibility to COVID-19.	Coronavirus disease 2019 (COVID-19) is a disease produced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and it is currently causing a catastrophic pandemic affecting humans worldwide. This disease has been lethal for approximately 3.12 million people around the world since January 2020. Globally, among the most affected countries, Mexico ranks third in deaths after the United States of America and Brazil. Although the high number of deceased people might also be explained by social aspects and lifestyle customs in Mexico, there is a relationship between this high proportion of deaths and comorbidities such as high blood pressure (HBP), type 2 diabetes, obesity, and metabolic syndrome. The official epidemiological figures reported by the Mexican government have indicated that 18.4% of the population suffers from HBP, close to 10.3% of adults suffer from type 2 diabetes, and approximately 36.1% of the population suffers from obesity. Disbalances in the gut microbiota (GM) have been associated with these diseases and with COVID-19 severity, presumably due to inflammatory dysfunction. Recent data about the association between GM dysbiosis and metabolic diseases could suggest that the high levels of susceptibility to SARS-CoV-2 infection and COVID-19 morbidity in the Mexican population are primarily due to the prevalence of type 2 diabetes, obesity, and metabolic syndrome.	no

2021	Haematological profile of COVID-19 patients from a centre in Singapore.	Haematological markers such as absolute lymphopenia have been associated with severe COVID-19 infection. However, in the literature to date, the cohorts described have typically included patients who were moderate to severely unwell with pneumonia and who required intensive care stay. It is uncertain if these markers apply to a population with less severe illness. We sought to describe the haematological profile of patients with mild disease with COVID-19 admitted to a single centre in Singapore. We examined 554 consecutive PCR positive SARS-COV-2 patients admitted to a single tertiary healthcare institution from Feb 2020 to April 2020. In all patients a full blood count was obtained within 24 h of presentation. Patients with pneumonia had higher neutrophil percentages (66.5 ± 11.6 vs 55.2 ± 12.6%, $p < 0.001$), lower absolute lymphocyte count (1.5 ± 1.1 vs 1.9 ± 2.1 x109/L, $p < 0.011$) and absolute eosinophil count (0.2 ± 0.9 vs 0.7 ± 1.8 × 109/L, $p = 0.002$). Platelet counts (210 ± 56 vs 230 ± 61, $p = 0.020$) were slightly lower in the group with pneumonia. We did not demonstrate significant differences in the neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in patients with or without pneumonia. Sixty-eight patients (12.3%) had peripheral eosinophilia. This was more common in migrant workers living in dormitories. Neutrophilia and lymphopenia were found to be markers associated with severe COVID-19 illness. We did not find that combined haematological parameters: neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio, had any association with disease severity in our cohort of patients with mild-moderate disease. Migrant workers living in dormitories had eosinophilia which may reflect concurrent chronic parasitic infection.	yes
2021	Effect of ABO blood groups on length of hospital stay according to age in Covid-19 patients.	Coronavirus Disease 2019 (COVID-19) is a novel viral disease with person-to-person transmission that has spread to many countries since the end of 2019. Although many unknowns were resolved within a year and the vaccine is available, it is still a major global health problem. COVID-19 infection may present with a considerably wide spectrum of severity and host factors play a significant role in determining the course of the disease. One of these factors is blood groups. Based on previous experience, it is believed that the ABO blood group type affects prognosis, treatment response and length of stay in the hospital. In this study, our aim was to evaluate whether the blood group had an effect on the length of the hospital stay. To the best of our knowledge, no previous studies have assessed the effect of ABO blood groups, as well as age, on the length of the hospital stay in these settings. In this retrospective cohort study, 969 patients admitted to our hospital between March 15, 2020 and May 15, 2020 were evaluated. The patients were divided into 4 groups according to ABO blood groups. The effect of the ABO blood group by age on the course of the disease, need for intensive care, duration of hospitalization and mortality in patients with COVID-19 infection, especially in geriatric patients, was evaluated. Of all the patients, 9.1% required admission to the intensive care unit (ICU), of whom 83% died. The average length of ICU stay was 11 days (0 - 59). The observed mortality rates in blood groups A, B, AB and 0 were 86.4%, 93.3%, 80.0% and 70.8%, respectively, indicating similar death rates in all ABO blood types. When the Rh phenotype was taken into consideration, no significant changes in results were seen. As a result, we could not observe a significant relationship between blood groups and clinical outcomes in this study, which included a sample of Turkish patients with COVID-19.	no

2021	Expert Consensus Statements on the Use of Corticosteroids in Non-severe COVID-19.	There is strong evidence for the use of corticosteroid in the management of severe coronavirus disease-2019 (COVID-19). However, there is still uncertainty about the timing of corticosteroids. We undertook a modified Delphi study to develop expert consensus statements on the early identification of a subset of patients from non-severe COVID-19 who may benefit from using corticosteroids. A modified Delphi was conducted with two anonymous surveys between April 30, 2021, and May 3, 2021. An expert panel of 35 experts was selected and invited to participate through e-mail. The consensus was defined as >70% votes in multiple-choice questions (MCQ) on Likert-scale type statements, while strong consensus as >90% votes in MCQ or >50% votes for "very important" on Likert-scale questions in the final round. Twenty experts completed two rounds of the survey. There was strong consensus for the increased work of breathing (95%), a positive six-minute walk test (90%), thorax computed tomography severity score of >14/25 (85%), new-onset organ dysfunction (using clinical or biochemical criteria) (80%), and C-reactive protein >5 times the upper limit of normal (70%) as the criteria for patients' selection. The experts recommended using oral or intravenous (IV) low-dose corticosteroids (the equivalent of 6 mg/day dexamethasone) for 5-10 days and monitoring of oxygen saturation, body temperature, clinical scoring system, blood sugar, and inflammatory markers for any "red-flag" signs. The experts recommended against indiscriminate use of corticosteroids in mild to moderate COVID-19 without the signs of clinical worsening. Oral or IV low-dose corticosteroids (the equivalent of 6 mg/day dexamethasone) for 5-10 days are recommended for patients with features of disease progression based on clinical, biochemical, or radiological criteria after 5 days from symptom onset under close monitoring. How to cite this article: Nasa P, Chaudhry D, Govil D, Daga MK, Jain R, Chhallani AA, et al. Expert Consensus Statements on the Use of Corticosteroids in Non-severe COVID-19. Indian J Crit Care Med 2021;25(11):1280-1285.	no
2021	Relative Ratios of Human Seasonal Coronavirus Antibodies Predict the Efficiency of Cross-Neutralization of SARS-CoV-2 Spike Binding to ACE2.	Antibodies raised against human seasonal coronaviruses (sCoVs), which are responsible for the common cold, are known to cross-react with SARS-CoV-2 antigens. This prompts questions about their protective role against SARS-CoV-2 infections and COVID-19 severity. However, the relationship between sCoVs exposure and SARS-CoV-2 correlates of protection are not clearly identified. We performed a cross-sectional analysis of cross-reactivity and cross-neutralization to SARS-CoV-2 antigens (S-RBD, S-trimer, N) using pre-pandemic sera from four different groups: pediatrics and adolescents, individuals 21 to 70 years of age, older than 70 years of age, and individuals living with HCV or HIV. Data was then further analysed using machine learning to identify predictive patterns of neutralization based on sCoVs serology. Antibody cross-reactivity to SARS-CoV-2 antigens varied between 1.6% and 15.3% depending on the cohort and the isotype-antigen pair analyzed. We also show a range of neutralizing activity (0-45%) with median inhibition ranging from 17.6 % to 23.3 % in serum that interferes with SARS-CoV-2 spike attachment to ACE2 independently of age group. While the abundance of sCoV antibodies did not directly correlate with neutralization, we show that neutralizing activity is rather dependent on relative ratios of IgGs in sera directed to all four sCoV spike proteins. More specifically, we identified antibodies to NL63 and OC43 as being the most important predictors of neutralization. Our data support the concept that exposure to sCoVs triggers antibody responses that influence the efficiency of SARS-CoV-2 spike binding to ACE2, which may potentially impact COVID-19 disease severity through other latent	no

		variables. This study was supported by a grant by the CIHR (VR2 - 172722) and by a grant supplement by the CITF, and by a NRC Collaborative R&D Initiative Grant (PR031-1).	
2021	A Deep Look Into COVID-19 Severity Through Dynamic Changes in Blood Cytokine Levels.	An excessive inflammatory response to SARS-CoV-2 is thought to be a major cause of disease severity and mortality in patients with COVID-19. Longitudinal analysis of cytokine release can expand our understanding of the initial stages of disease development and help to identify early markers serving as predictors of disease severity. In this study, we performed a comprehensive analysis of 46 cytokines (including chemokines and growth factors) in the peripheral blood of a large cohort of COVID-19 patients (n=444). The patients were classified into five severity groups. Longitudinal analysis of all patients revealed two groups of cytokines, characterizing the "early" and "late" stages of the disease course and the switch between type 1 and type 2 immunity. We found significantly increased levels of cytokines associated with different severities of COVID-19, and levels of some cytokines were significantly higher during the first three days from symptom onset (DfSO) in patients who eventually required intensive care unit (ICU) therapy. Additionally, we identified nine cytokines, TNF-α, IL-10, MIG, IL-6, IP-10, M-CSF, G-CSF, GM-CSF, and IFN-α2, that can be used as good predictors of ICU requirement at 4-6 DfSO.	yes

2021	Dysregulation of ACE (Angiotensin-Converting Enzyme)-2 and Renin-Angiotensin Peptides in SARS-CoV-2 Mediated Mortality and End-Organ Injuries.	ACE (angiotensin-converting enzyme)-2 as the target for SARS-CoV-2 also negatively regulates the renin-angiotensin system. Pathological activation of ADAM17 (A disintegrin and metalloproteinase-17) may potentiate inflammation and diminish ACE2-mediated tissue protection through proteolytic shedding, contributing to SARS-CoV-2 pathogenesis. We aim to examine plasma soluble ACE2 and angiotensin profiles in relation to outcomes by enrolling consecutive patients admitted for COVID-19 with baseline blood collection at admission and repeated sampling at 7 days. The primary outcome was 90-day mortality, and secondary outcomes were the incidence of end-organ injuries. Overall, 242 patients were included, the median age was 63 (52-74) years, 155 (64.0%) were men, and 57 (23.6%) patients reached the primary end point. Baseline soluble ACE2 was elevated in COVID-19 but was not associated with disease severity or mortality. In contrast, an upward trajectory of soluble ACE2 at repeat sampling was independently associated with an elevated risk of mortality and incidence of acute myocardial injury and circulatory shock. Similarly, an increase in soluble tumor necrosis factor receptor levels was also associated with adverse outcomes. Plasma Ang I, Ang 1-7 (angiotensin 1-7) levels, and the Ang 1-7/Ang II (angiotensin II) ratio were elevated during SARS-CoV-2 infection related to downregulation of ACE activity at baseline. Moreover, patients having an upward trajectory of soluble ACE2 were characterized by an imbalance in the Ang 1-7/Ang II ratio. The observed dysregulation of ACE2 and angiotensin peptides with disease progression suggest a potential role of ADAM17 inhibition and enhancing the beneficial Ang 1-7/Mas axis to improve outcomes against SARS-CoV-2 infection.	no
2021	Factors Affecting the Incidence, Progression, and Severity of COVID-19 in Type 1 Diabetes Mellitus.	This study screened for factors affecting coronavirus disease 2019 (COVID-19) incidence in type 1 diabetes mellitus (T1DM) patients, appraised vitamin D's efficacy in preventing COVID-19, and assessed the effects of clinical characteristics, glycemic status, vitamin D, and hydroxychloroquine administration on COVID-19's progression and severity in T1DM patients. This retrospective research on 150 adults was conducted at Security Forces Hospital, Riyadh, KSA. Participants were allocated to three groups (50/group): control, T1DM, and T1DM with COVID-19. Participants' fasting blood glucose (FBG), glycated hemoglobin (HbA1c), complete blood count, vitamin D, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, lactate dehydrogenase (LDH), prothrombin time, activated partial thromboplastin time, D-dimer, liver and kidney function, and hydroxychloroquine treatment were retrieved and analyzed. The percentages of comorbidities and not taking hydroxychloroquine were significantly higher among T1DM patients with COVID-19 than patients with T1DM only. Mean vitamin D level was significantly lower in T1DM with COVID-19 patients than in the other two groups. Vitamin D showed a significant negative correlation with LDH, CRP, ESR, ferritin, and D-dimer, which was the most reliable predictor of COVID-19 severity in T1DM patients. Comorbidities and vitamin D deficiency are risk factors for COVID-19 in patients with T1DM. Patients who do not take hydroxychloroquine and have higher FBG and HbA1c levels are vulnerable to COVID-19. Vitamin D may be useful for preventing COVID-19 in T1DM patients. Comorbidities, higher FBG and HbA1c levels, not taking hydroxychloroquine, and vitamin D inadequacy elevate COVID-19 progression and severity in patients with T1DM.	yes

2021	Cardiovascular health and risk of hospitalization with COVID-19: A Mendelian Randomization study.	Susceptibility to and severity of COVID-19 is associated with risk factors for and presence of cardiovascular disease. We performed a 2-sample Mendelian randomization to determine whether blood pressure (BP), body mass index (BMI), presence of type 2 diabetes (T2DM) and coronary artery disease (CAD) are causally related to presentation with severe COVID-19. Variant-exposure instrumental variable associations were determined from most recently published genome-wide association and meta-analysis studies (GWAS) with publicly available summary-level GWAS data. Variant-outcome associations were obtained from a recent GWAS meta-analysis of laboratory confirmed diagnosis of COVID-19 with severity determined according to need for hospitalization/death. We also examined reverse causality using exposure as diagnosis of severe COVID-19 causing cardiovascular disease. We found no evidence for a causal association of cardiovascular risk factors/disease with severe COVID-19 (compared to population controls), nor evidence of reverse causality. Causal odds ratios (OR, by inverse variance weighted regression) for BP (OR for COVID-19 diagnosis 1.00 [95% confidence interval (CI): 0.99-1.01, P = 0.604] per genetically predicted increase in BP) and T2DM (OR for COVID-19 diagnosis to that of genetically predicted T2DM 1.02 [95% CI: 0.9-1.05, P = 0.927], in particular, were close to unity with relatively narrow confidence intervals. The association between cardiovascular risk factors/disease with that of hospitalization with COVID-19 reported in observational studies could be due to residual confounding by socioeconomic factors and /or those that influence the indication for hospital admission.	no
2021	Early high-titer convalescent plasma therapy in patients with moderate and severe COVID-19.	The use of COVID-19 convalescent plasma (CCP) has been approved by the FDA. We assessed the outcome of patients with moderate and severe COVID-19 following convalescent plasma therapy and the association with variables such as antibody titer in CCP units and transfusion time. In this prospective cohort study, 3097 patients with moderate and severe COVID-19 (according to WHO Progression Scale) had heterogeneous demographic and clinical characteristics received plasma with an unknown titer at the transfusion time. Firstly, information about age, sex, blood group, the time interval from hospitalization to CCP transfusion, underlying disease, and antibody titer with the outcome were investigated. Then, multivariate logistic regression and area under the curve (AUC) were performed for the association between disease severity and intubation variables with transfusion time and outcome. Patients with younger age receiving CCP in the first five days of hospitalization had lower mortality ($P < 0.0001$). Moreover, patients without the underlying disease had lower mortality ($P < 0.001$). The mortality rate also decreased in severe patients who were intubated receiving CCP for less than five days ($P < 0.001$). In patients with moderate severity (score less than 5) who received IgG antibody levels above 1:320 in less than five days had lower mortality ($P < 0.0001$). Our findings suggested that COVID-19 patients with the moderate type of disease receiving CCP units with high antibody titers in the early stages of the disease experienced greater effectiveness of CCP therapy.	no

2021	The Renin-Angiotensin System: A Key Role in SARS-CoV-2-Induced COVID-19.	The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), was first identified in Eastern Asia (Wuhan, China) in December 2019. The virus then spread to Europe and across all continents where it has led to higher mortality and morbidity, and was declared as a pandemic by the World Health Organization (WHO) in March 2020. Recently, different vaccines have been produced and seem to be more or less effective in protecting from COVID-19. The renin-angiotensin system (RAS), an essential enzymatic cascade involved in maintaining blood pressure and electrolyte balance, is involved in the pathogenicity of COVID-19, since the angiotensin-converting enzyme II (ACE2) acts as the cellular receptor for SARS-CoV-2 in many human tissues and organs. In fact, the viral entrance promotes a downregulation of ACE2 followed by RAS balance dysregulation and an overactivation of the angiotensin II (Ang II)-angiotensin II type I receptor (AT1R) axis, which is characterized by a strong vasoconstriction and the induction of the profibrotic, proapoptotic and proinflammatory signalizations in the lungs and other organs. This mechanism features a massive cytokine storm, hypercoagulation, an acute respiratory distress syndrome (ARDS) and subsequent multiple organ damage. While all individuals are vulnerable to SARS-CoV-2, the disease outcome and severity differ among people and countries and depend on a dual interaction between the virus and the affected host. Many studies have already pointed out the importance of host genetic polymorphisms (especially in the RAS) as well as other related factors such age, gender, lifestyle and habits and underlying pathologies or comorbidities (diabetes and cardiovascular diseases) that could render individuals at higher risk of infection and pathogenicity. In this review, we explore the correlation between all these risk factors as well as how and why they could account for severe post-COVID-19 complications.	no
2021	Upregulated type I interferon responses in asymptomatic COVID-19 infection are associated with improved clinical outcome.	Understanding key host protective mechanisms against SARS-CoV-2 infection can help improve treatment modalities for COVID-19. We used a blood transcriptome approach to study biomarkers associated with differing severity of COVID-19, comparing severe and mild Symptomatic disease with Asymptomatic COVID-19 and uninfected Controls. There was suppression of antigen presentation but upregulation of inflammatory and viral mRNA translation associated pathways in Symptomatic as compared with Asymptomatic cases. In severe COVID-19, CD177 a neutrophil marker, was upregulated while interferon stimulated genes (ISGs) were downregulated. Asymptomatic COVID-19 cases displayed upregulation of ISGs and humoral response genes with downregulation of ICAM3 and TLR8. Compared across the COVID-19 disease spectrum, we found type I interferon (IFN) responses to be significantly upregulated (IFNAR2, IRF2BP1, IRF4, MAVS, SAMHD1, TRIM1), or downregulated (SOCS3, IRF2BP2, IRF2BPL) in Asymptomatic as compared with mild and severe COVID-19, with the dysregulation of an increasing number of ISGs associated with progressive disease. These data suggest that initial early responses against SARS-CoV-2 may be effectively controlled by ISGs. Therefore, we hypothesize that treatment with type I interferons in the early stage of COVID-19 may limit disease progression by limiting SARS-CoV-2 in the host.	yes

2021	Genetic ancestry effects on the response to viral infection are pervasive but cell type specific.	Humans differ in their susceptibility to infectious disease, partly owing to variation in the immune response after infection. We used single-cell RNA sequencing to quantify variation in the response to influenza infection in peripheral blood mononuclear cells from European- and African-ancestry males. Genetic ancestry effects are common but highly cell type specific. Higher levels of European ancestry are associated with increased type I interferon pathway activity in early infection, which predicts reduced viral titers at later time points. Substantial population-associated variation is explained by cis - expression quantitative trait loci that are differentiated by genetic ancestry. Furthermore, genetic ancestry–associated genes are enriched among genes correlated with COVID-19 disease severity, suggesting that the early immune response contributes to ancestry-associated differences for multiple viral infection outcomes.	no
2021	[Influence of SARS-CoV-2 vaccination on the epidemiological and clinical characteristics of imported COVID-19 cases in Chengdu].	Objective: To analyze the epidemiological and clinical characteristics of imported COVID-19 cases after SARS-CoV-2 vaccination and to provide evidence for the prevention and control of COVID-19. Methods: The imported COVID-19 cases in Chengdu as of April 15, 2021 were divided into the vaccinated group and unvaccinated group according to the history of SARS-CoV-2 vaccination. The epidemiological and clinical data of the cases were collected retrospectively, and the differences in epidemiological and clinical characteristics of the two groups were compared. Laboratory tests consisted of nucleic acid test, clinical index test, serum antibody test and lymphocyte test. Software WPS2019 was used for data management and software R 4.0.3 was used for statistical analysis. Results: A total of 75 COVID-19 cases were included in the analysis, in which 20 had received SARS-CoV-2 vaccination and only 4 with clinical symptoms, 55 patients did not receive SARS-CoV-2 vaccination, and 16 had clinical symptoms. In vaccinated group, the first injection time of vaccination ranged from July to November 2020, and 10 cases received two doses of vaccine simultaneously and 10 cases received two doses of vaccine at intervals of 14-57 days. The intervals between the completion of vaccination and the onset ranged from 87 days to 224 days. The differences in classification and clinical type between the two groups were significant. Significant differences were observed in case classification and clinical type between vaccinated group and unvaccinated group ($P < 0.05$). The vaccinated group had a relatively high proportion of asymptomatic infections (40.00%, 8/20), while mild infections were mainly observed in the unvaccinated group(76.36%,42/55). The differences in Ct values (ORF1ab gene and N gene) at the diagnosis were not significant between vaccinated group and unvaccinated group ($P > 0.05$), similar results were also observed in lymphocyte subtypes, procalcitonin and C-reactive protein level comparisons. Serum amyloid A level was higher in unvaccinated group than in vaccinated group ($P < 0.05$). However, the SARS-CoV-2 related serum antibody of IgM, IgG and total antibody levels were significantly higher in vaccinated group ($P < 0.05$). Conclusions: Risk of infection still exists with SARS-CoV-2 after vaccination, which can facilitate the production of specific serum antibody of IgM and IgG when people are exposed to the virus. It has a certain protective effect on SARS-CoV-2 infected persons. Vaccination can reduce the clinical symptoms and mitigate disease severity.	no

2021	Profiling Antibody Response Patterns in COVID-19: Spike S1-Reactive IgA Signature in the Evolution of SARS-CoV-2 Infection.	This contribution explores in a new statistical perspective the antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 141 coronavirus disease 2019 (COVID-19) patients exhibiting a broad range of clinical manifestations. This cohort accurately reflects the characteristics of the first wave of the SARS-CoV-2 pandemic in Italy. We determined the IgM, IgA, and IgG levels towards SARS-CoV-2 S1, S2, and NP antigens, evaluating their neutralizing activity and relationship with clinical signatures. Moreover, we longitudinally followed 72 patients up to 9 months postsymptoms onset to study the persistence of the levels of antibodies. Our results showed that the majority of COVID-19 patients developed an early virus-specific antibody response. The magnitude and the neutralizing properties of the response were heterogeneous regardless of the severity of the disease. Antibody levels dropped over time, even though spike reactive IgG and IgA were still detectable up to 9 months. Early baseline antibody levels were key drivers of the subsequent antibody production and the long-lasting protection against SARS-CoV-2. Importantly, we identified anti-S1 IgA as a good surrogate marker to predict the clinical course of COVID-19. Characterizing the antibody response after SARS-CoV-2 infection is relevant for the early clinical management of patients as soon as they are diagnosed and for implementing the current vaccination strategies.	no
2021	Severe COVID-19 is associated with hyperactivation of the alternative complement pathway.	Severe coronavirus disease 2019 (COVID-19) is characterized by impaired type I interferon activity and a state of hyperinflammation leading to acute respiratory distress syndrome. The complement system has recently emerged as a key player in triggering and maintaining the inflammatory state, but the role of this molecular cascade in severe COVID-19 is still poorly characterized. We aimed at assessing the contribution of complement pathways at both the protein and transcriptomic levels. To this end, we systematically assessed the RNA levels of 28 complement genes in the circulating whole blood of patients with COVID-19 and healthy controls, including genes of the alternative pathway, for which data remain scarce. We found differential expression of genes involved in the complement system, yet with various expression patterns: whereas patients displaying moderate disease had elevated expression of classical pathway genes, severe disease was associated with increased lectin and alternative pathway activation, which correlated with inflammation and coagulopathy markers. Additionally, properdin, a pivotal positive regulator of the alternative pathway, showed high RNA expression but was found at low protein concentrations in patients with a severe and critical disease, suggesting its deposition at the sites of complement activation. Notably, low properdin levels were significantly associated with the use of mechanical ventilation (area under the curve = 0.82; P = .002). This study sheds light on the role of the alternative pathway in severe COVID-19 and provides additional rationale for the testing of drugs inhibiting the alternative pathway of the complement system.	no

2021	Association of ABO and Rh Blood Group in Susceptibility, Severity, and Mortality of Coronavirus Disease 2019: A Hospital-Based Study From Delhi, India.	ABO and Rh blood group systems are associated with many diseases including cancerous, infectious, non-infectious, bacterial and viral diseases. Studies have shown association of blood groups A and O with higher and lower odds for coronavirus disease 2019 positivity, respectively. This is a single-center, retrospective study conducted at Sir Ganga Ram Hospital, Delhi. We investigated the association of ABO and Rh blood groups with susceptibility to coronavirus disease 2019 infection, severity of disease, recovery period, and mortality of patients. Patients were enrolled from April 8, 2020 to October 4, 2020. A total of 2,586 real-time PCR (RT-PCR)-confirmed coronavirus disease 2019 (COVID-19) patients were recruited. Data was analyzed using chi-square test, odds ratio, and Mann-Whitney test to determine the association of blood groups. In the 2,586 COVID-19-infected patients, the frequencies of A, B, O, and AB were 29.93%, 41.80%, 21.19%, and 7.98%, respectively. Of the patients, 98.07% were Rh positive. Blood group A (odds ratio, 1.53; CI, 1.40-1.66; $p < 0.001$) and B (odds ratio, 1.15; CI, 1.06-1.24; $p < 0.001$) is observed to be significantly associated with COVID-19 susceptibility, whereas blood group O (odds ratio, 0.65; CI, 0.59-0.71; $p < 0.001$) and AB (odds ratio, 0.66; CI, 0.59-0.71; $p < 0.001$) have low risk of COVID-19 infection. A, B, and Rh+ are found to be more susceptible to COVID-19 infection, whereas blood groups O, AB, and Rh- are at a lower risk of COVID-19 infection. No association was found between blood groups and susceptibility to severity of disease and mortality.	no
2021	Plasma Gradient of Soluble Urokinase-Type Plasminogen Activator Receptor Is Linked to Pathogenic Plasma Proteome and Immune Transcriptome and Stratifies Outcomes in Severe COVID-19.	Disease caused by SARS-CoV-2 coronavirus (COVID-19) led to significant morbidity and mortality worldwide. A systemic hyper-inflammation characterizes severe COVID-19 disease, often associated with acute respiratory distress syndrome (ARDS). Blood biomarkers capable of risk stratification are of great importance in effective triage and critical care of severe COVID-19 patients. Flow cytometry and next-generation sequencing were done on peripheral blood cells and urokinase-type plasminogen activator receptor (suPAR), and cytokines were measured from and mass spectrometry-based proteomics was done on plasma samples from an Indian cohort of COVID-19 patients. Publicly available single-cell RNA sequencing data were analyzed for validation of primary data. Statistical analyses were performed to validate risk stratification. We report here higher plasma abundance of suPAR, expressed by an abnormally expanded myeloid cell population, in severe COVID-19 patients with ARDS. The plasma suPAR level was found to be linked to a characteristic plasma proteome, associated with coagulation disorders and complement activation. Receiver operator characteristic curve analysis to predict mortality identified a cutoff value of suPAR at 1,996.809 pg/ml (odds ratio: 2.9286, 95% confidence interval 1.0427-8.2257). Lower-than-cutoff suPAR levels were associated with a differential expression of the immune transcriptome as well as favorable clinical outcomes, in terms of both survival benefit (hazard ratio: 0.3615, 95% confidence interval 0.1433-0.912) and faster disease remission in our patient cohort. Thus, we identified suPAR as a key pathogenic circulating molecule linking systemic hyperinflammation to the hypercoagulable state and stratifying clinical outcomes in severe COVID-19 patients with ARDS.	no

2021	COVID-19 Infection in Kidney Transplant Recipients From a Single Center in Iran.	COVID-19 has been spreading rapidly throughout the world, with nearly every country thus far documenting this infection. In this study, our aim was to evaluate the risk factors for increased mortality in deceased donor kidney transplant recipients with COVID-19 at a single center in Iran. This was a retrospective study in a single center. During the 17-month ongoing COVID19 pandemic in Iran, there were 153 deceased donor kidney recipients at our center with suspected COVID19 symptoms. Of these patients, 138 had positive COVID-19 tests, and thus a therapeutic regimen was commenced for these patients. Data were analyzed with SPSS version 16 software. The patients were predominantly male (83, 60.1%) with a median age of 47.09 ± 13.75 years and a median time since transplant of 51 months (IQR, 1-276 months). Among these patients, 84 (60.8%) had hypertension and 43 (31.2%) had diabetes mellitus. We observed a significant relationship between disease severity and mortality ($P < .001$). After risk adjustments for age, presence of diabetes mellitus and hypertension and blood group type were factors that showed a significantly higher risk of death. Deceased donor kidney transplant recipients with confirmed COVID-19 experienced less fever as an initial symptom. However, recipients with COVID-19 and an underlying disease had a higher rate of mortality, severity of infection, and progression of disease. Appropriate management of renal complications and vaccinations in deceased donor kidney transplant recipients may help lead to more favorable outcomes.	no
2021	Impact of ABO and Rhesus blood groups on COVID-19 susceptibility and severity: A case-control study.	Early evidence from China suggested that blood groups may be involved in susceptibility to COVID-19. Several subsequent studies reported controversial results. We conducted a retrospective matched case-control study that aims to investigate the association between blood groups and the risk and/or severity of COVID-19. We compared the blood groups distribution of 474 patients admitted to the hospital for COVID-19 between March 2020 and March 2021, to that of a positive control group of outpatients infected with COVID-19 and matched them for sex and age, as well as to the distribution in the general population. Three hundred and eighteen HC+ pairs with available blood group information were matched. The proportion of group A Rh+ in hospitalized patients (HC+) was 39.9% (CI 35.2%-44.7%), compared to 44.8% (CI 39.8%-49.9%) and 32.3% in the positive outpatient controls (C+) and the general population (C-), respectively. Both COVID-19-positive groups (HC+ and C+) had significantly higher proportions of group A Rh+ compared to the general population ($p = 0.0019$ and $p < 0.001$, respectively), indicating that group A Rh+ increases susceptibility to COVID-19. Although blood group A Rh+ was more frequent in the outpatients C+ compared to the hospitalized group HC+, the association did not reach statistical significance, indicating that blood group A Rh+ is not associated with severity. There was no significant relationship between COVID-19 and other blood groups. Our findings indicate that blood group A Rh+ increases the susceptibility for COVID-19 but is not associated with higher disease severity.	yes

2021	Positive QuantiFERON test and the severity of COVID-19 disease: A prospective study.	A strong negative correlation is reported between the Bacille Calmette Guerin (BCG) index and COVID-19 mortality. The present study explored if frequent exposure to strong Th1 antigens like Mycobacteria or Salmonella have any effect on the progression of the disease in COVID-19 patients. This prospective comparative study comprised of 3 groups of 20 each of mild or asymptomatic COVID-19 patients (A), severely ill patients (S) and healthy volunteers with a COVID Negative report (H). QuantiFERON TB Gold (QFT) which is interferon gamma release assay (IGRA) against Mtb antigen was used to quantify immunity status of patients against the tuberculosis. Group S showed positive QFT in only 15% patients as against 50% QFT positive patients in group A and H. All fourteen patients in group S with QFT negative report died while 5 of six survived patients showed positive QFT report either on initial or repeat testing done at 6 weeks. The sixth survived patient was QFT negative but showed high antibody titre against H antigen (TH) on Widal test. All severely ill group S patients showed huge reduction of IGRA even to the mitogen stimulus thus suggesting gross general unresponsiveness of T cells. Presence of BCG scar showed no correlation with prevalence or progression of the disease. Population in an endemic area of tuberculosis and typhoid with good community exposure to these antigen is likely to withstand COVID -19 better and show reduced mortality following it.	no
2021	Interferon pathway lupus risk alleles modulate risk of death from acute COVID-19.	Type I interferon (IFN) is critical in our defense against viral infections. Increased type I IFN pathway activation is a genetic risk factor for systemic lupus erythematosus (SLE), and a number of common risk alleles contribute to the high IFN trait. We hypothesized that these common gain-of-function IFN pathway alleles may be associated with protection from mortality in acute COVID-19. We studied patients admitted with acute COVID-19 (756 European-American and 398 African-American ancestry). Ancestral backgrounds were analyzed separately, and mortality after acute COVID-19 was the primary outcome. In European-American ancestry, we found that a haplotype of interferon regulatory factor 5 (IRF5) and alleles of protein kinase cGMP-dependent 1 (PRKG1) were associated with mortality from COVID-19. Interestingly, these were much stronger risk factors in younger patients (OR=29.2 for PRKG1 in ages 45-54). Variants in the IRF7 and IRF8 genes were associated with mortality from COVID-19 in African-American subjects, and these genetic effects were more pronounced in older subjects. Combining genetic information with blood biomarker data such as C-reactive protein, troponin, and D-dimer resulted in significantly improved predictive capacity, and in both ancestral backgrounds the risk genotypes were most relevant in those with positive biomarkers (OR for death between 14 and 111 in high risk genetic/biomarker groups). This study confirms the critical role of the IFN pathway in defense against COVID-19 and viral infections, and supports the idea that some common SLE risk alleles exert protective effects in anti-viral immunity. We find that a number of IFN pathway lupus risk alleles significantly impact mortality following COVID-19 infection. These data support the idea that type I IFN pathway risk alleles for autoimmune disease may persist in high frequency in modern human populations due to a benefit in our defense against viral infections. We develop multivariate prediction models which combine genetics and known biomarkers of severity to result in greatly improved prediction of mortality in acute COVID-19. The specific associated alleles provide some clues about key points in our defense against COVID-19.	no

2021	Dysregulated Immune Responses in COVID-19 Patients Correlating With Disease Severity and Invasive Oxygen Requirements.	The prognosis of severe COVID-19 patients has motivated research communities to uncover mechanisms of SARS-CoV-2 pathogenesis also on a regional level. In this work, we aimed to understand the immunological dynamics of severe COVID-19 patients with different degrees of illness, and upon long-term recovery. We analyzed immune cellular subsets and SARS-CoV-2-specific antibody isotypes of 66 COVID-19 patients admitted to the Hospital Clínico Universidad de Chile, which were categorized according to the WHO ten-point clinical progression score. These included 29 moderate patients (score 4-5) and 37 severe patients under either high flow oxygen nasal cannula (18 patients, score 6), or invasive mechanical ventilation (19 patients, score 7-9), plus 28 convalescent patients and 28 healthy controls. Furthermore, six severe patients that recovered from the disease were longitudinally followed over 300 days. Our data indicate that severe COVID-19 patients display increased frequencies of plasmablasts, activated T cells and SARS-CoV-2-specific antibodies compared to moderate and convalescent patients. Remarkably, within the severe COVID-19 group, patients rapidly progressing into invasive mechanical ventilation show higher frequencies of plasmablasts, monocytes, eosinophils, Th1 cells and SARS-CoV-2-specific IgG than patients under high flow oxygen nasal cannula. These findings demonstrate that severe COVID-19 patients progressing into invasive mechanical ventilation show a distinctive type of immunity. In addition, patients that recover from severe COVID-19 begin to regain normal proportions of immune cells 100 days after hospital discharge and maintain high levels of SARS-CoV-2-specific IgG throughout the study, which is an indicative sign of immunological memory. Thus, this work can provide useful information to better understand the diverse outcomes of severe COVID-19 pathogenesis.	no
2021	Cardiac Fibrosis Is a Risk Factor for Severe COVID-19.	Increased left ventricular fibrosis has been reported in patients hospitalized with coronavirus disease 2019 (COVID-19). It is unclear whether this fibrosis is a consequence of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection or a risk factor for severe disease progression. We observed increased fibrosis in the left ventricular myocardium of deceased COVID-19 patients, compared with matched controls. We also detected increased mRNA levels of soluble interleukin-1 receptor-like 1 (sIL1-RL1) and transforming growth factor β1 (TGF-β1) in the left ventricular myocardium of deceased COVID-19 patients. Biochemical analysis of blood sampled from patients admitted to the emergency department (ED) with COVID-19 revealed highly elevated levels of TGF-β1 mRNA in these patients compared to controls. Left ventricular strain measured by echocardiography as a marker of pre-existing cardiac fibrosis correlated strongly with blood TGF-β1 mRNA levels and predicted disease severity in COVID-19 patients. In the left ventricular myocardium and lungs of COVID-19 patients, we found increased neuropilin-1 (NRP-1) RNA levels, which correlated strongly with the prevalence of pulmonary SARS-CoV-2 nucleocapsid. Cardiac and pulmonary fibrosis may therefore predispose these patients to increased cellular viral entry in the lung, which may explain the worse clinical outcome observed in our cohort. Our study demonstrates that patients at risk of clinical deterioration can be identified early by echocardiographic strain analysis and quantification of blood TGF-β1 mRNA performed at the time of first medical contact.	no

2021	Heart failure in type 2 diabetes: current perspectives on screening, diagnosis and management.	Type 2 diabetes is one of the most relevant risk factors for heart failure, the prevalence of which is increasing worldwide. The aim of the review is to highlight the current perspectives of the pathophysiology of heart failure as it pertains to type 2 diabetes. This review summarizes the proposed mechanistic bases, explaining the myocardial damage induced by diabetes-related stressors and other risk factors, i.e., cardiomyopathy in type 2 diabetes. We highlight the complex pathology of individuals with type 2 diabetes, including the relationship with chronic kidney disease, metabolic alterations, and heart failure. We also discuss the current criteria used for heart failure diagnosis and the gold standard screening tools for individuals with type 2 diabetes. Currently approved pharmacological therapies with primary use in type 2 diabetes and heart failure, and the treatment-guiding role of NT-proBNP are also presented. Finally, the influence of the presence of type 2 diabetes as well as heart failure on COVID-19 severity is briefly discussed.	no
2021	Association of Myocardial Enzyme Abnormality with Clinical Outcomes of Patients with COVID-19: A Retrospective Study.	It has been observed that COVID-19 may cause myocardial damage, but there are few detailed reports on myocardial enzyme abnormalities. In this retrospective study, we analyzed data from 157 consecutive laboratory-confirmed and hospitalized COVID-19 patients from Wuhan. We collected information on demographic and clinical characteristics, laboratory findings, and clinical outcomes. Logistic regression analysis was used to explore the risk factors associated with the severity of COVID-19. The association between myocardial enzyme abnormalities and the mortality was also investigated. The mortality in abnormal myocardial enzyme group was obviously higher than the normal group ($P < 0.001$). The majority of patients ($n = 72$, 97.3%) with normal cardiac enzyme group were of the common novel coronavirus pneumonia (NCP) type, whereas half of the patients with cardiac enzyme abnormalities ($n = 40$, 48.2%) developed critical and severe NCP type. The multivariable logistic regression analysis indicated that COVID-19 patients with increasing age ($P = 0.035$), higher levels of CRP ($P = 0.038$), and TNI ($P = 0.036$) were associated with increased death than other patients. Myocardial enzyme abnormality and myocardial injury were associated with the severity and fatal outcomes of COVID-19. Clinicians should pay attention to the markers of myocardial injury in COVID-19 patients, especially those with older age, comorbidities, and inflammation.	no
2021	Cerebral Palsy, COVID-19, and Neurolipidosis in an 18-Year-Old Female.	Since the novel coronavirus (COVID-19) pandemic started, children and young adults have seldom been placed in high-risk groups, despite reports that they are at increased risk of severe forms of the disease and death in the presence of comorbidities. Herein we report an autopsy case of an 18-year-old female with a history of cerebral palsy (CP), recurrent respiratory infections, and newly diagnosed COVID-19, and who expired 22 days after presenting with symptoms of the disease. Gross findings were concurrent with CP-significant hypotrophy, with deep and wide brain sulci. The lungs grossly were with increased weight and blood-filled. Histopathology of the respiratory system showed the well-established COVID-19-associated alveolar multinucleated cells, type two pneumocyte hyperplasia, and vascular changes. Furthermore, foci of groups of enlarged cells with foamy cytoplasm were identified in the pulmonary interstitium. Similar changes were also seen in the spleen, liver, and central nervous system, concurrent with an unrecognized lipid storage disease. The clinically unrecognized neurolipidosis, corresponding morphologically and clinically to Niemann-Pick disease type B, leading to interstitial lung disease and recurrent respiratory	no

		infections, inevitably played a role in the severity and progression of COVID-19 in our case, despite the age.	
2021	Can the Cytokine Profile According to ABO Blood Groups Be Related to Worse Outcome in COVID-19 Patients? Yes, They Can.	Severe status of coronavirus disease 2019 (COVID-19) is extremely associated to cytokine release. Moreover, it has been suggested that blood group is also associated with the prevalence and severity of this disease. However, the relationship between the cytokine profile and blood group remains unclear in COVID-19 patients. In this sense, we prospectively recruited 108 COVID-19 patients between March and April 2020 and divided according to ABO blood group. For the analysis of 45 cytokines, plasma samples were collected in the time of admission to hospital ward or intensive care unit and at the sixth day after hospital admission. The results show that there was a risk of more than two times lower of mechanical ventilation or death in patients with blood group O (log rank: $p = 0.042$). At first time, all statistically significant cytokine levels, except from hepatocyte growth factor, were higher in O blood group patients meanwhile the second time showed a significant drop, between 20% and 40%. In contrast, A/B/AB group presented a maintenance of cytokine levels during time. Hepatocyte growth factor showed a significant association with intubation or mortality risk in non-O blood group patients (OR: 4.229, 95% CI (2.064-8.665), $p < 0.001$) and also was the only one bad prognosis biomarker in O blood group patients (OR: 8.852, 95% CI (1.540-50.878), $p = 0.015$). Therefore, higher cytokine levels in O blood group are associated with a better outcome than A/B/AB group in COVID-19 patients.	no

2021	Prolonged Impairment of Short-Chain Fatty Acid and L-Isoleucine Biosynthesis in Gut Microbiome in Patients With COVID-19.	Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with altered gut microbiota composition. Phylogenetic groups of gut bacteria involved in the metabolism of short chain fatty acids (SCFAs) were depleted in SARS-CoV-2-infected patients. We aimed to characterize a functional profile of the gut microbiome in patients with COVID-19 before and after disease resolution. We performed shotgun metagenomic sequencing on fecal samples from 66 antibiotics-naïve patients with COVID-19 and 70 non-COVID-19 controls. Serial fecal samples were collected (at up to 6 times points) during hospitalization and beyond 1 month after discharge. We assessed gut microbial pathways in association with disease severity and blood inflammatory markers. We also determined changes of microbial functions in fecal samples before and after disease resolution and validated these functions using targeted analysis of fecal metabolites. Compared with non-COVID-19 controls, patients with COVID-19 with severe/critical illness showed significant alterations in gut microbiome functionality ($P < .001$), characterized by impaired capacity of gut microbiome for SCFA and L-isoleucine biosynthesis and enhanced capacity for urea production. Impaired SCFA and L-isoleucine biosynthesis in gut microbiome persisted beyond 30 days after recovery in patients with COVID-19. Targeted analysis of fecal metabolites showed significantly lower fecal concentrations of SCFAs and L-isoleucine in patients with COVID-19 before and after disease resolution. Lack of SCFA and L-isoleucine biosynthesis significantly correlated with disease severity and increased plasma concentrations of CXCL-10, NT- proB-type natriuretic peptide, and C-reactive protein (all $P < .05$). Gut microbiome of patients with COVID-19 displayed impaired capacity for SCFA and L-isoleucine biosynthesis that persisted even after disease resolution. These 2 microbial functions correlated with host immune response underscoring the importance of gut microbial functions in SARS-CoV-2 infection pathogenesis and outcome.	no
2021	Severe COVID-19 is characterized by the co-occurrence of moderate cytokine inflammation and severe monocyte dysregulation.	SARS-CoV-2 has been responsible for considerable mortality worldwide, owing in particular to pulmonary failures such as ARDS, but also to other visceral failures and secondary infections. Recent progress in the characterization of the immunological mechanisms that result in severe organ injury led to the emergence of two successive hypotheses simultaneously tested here: hyperinflammation with cytokine storm syndrome or dysregulation of protective immunity resulting in immunosuppression and unrestrained viral dissemination. In a prospective observational monocentric study of 134 patients, we analysed a panel of plasma inflammatory and anti-inflammatory cytokines and measured monocyte dysregulation via their membrane expression of HLA-DR. We first compared the results of patients with moderate forms hospitalized in an infectious disease unit with those of patients with severe forms hospitalized in an intensive care unit. In the latter group of patients, we then analysed the differences between the surviving and non-surviving groups and between the groups with or without secondary infections. Higher blood IL-6 levels, lower quantitative expression of HLA-DR on blood monocytes and higher IL-6/mHLA-DR ratios were statistically associated with the risk of severe forms of the disease and among the latter with death and the early onset of secondary infections. The unique immunological profile in patients with severe COVID-19 corresponds to a moderate cytokine inflammation associated with severe monocyte dysregulation. Individuals with major CSS were rare in our cohort of hospitalized	no

		patients, especially since the use of corticosteroids, but formed a very severe subgroup of the disease. None.	
2021	Durability of SARS-CoV-2-Specific T-Cell Responses at 12 Months Postinfection.	Characterizing the longevity and quality of cellular immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enhances understanding of coronavirus disease 2019 (COVID-19) immunity that influences clinical outcomes. Prior studies suggest SARS-CoV-2-specific T cells are present in peripheral blood 10 months after infection. Analysis of the function, durability, and diversity of cellular response long after natural infection, over a range of ages and disease phenotypes, is needed to identify preventative and therapeutic interventions. We identified participants in our multisite longitudinal, prospective cohort study 12 months after SARS-CoV-2 infection representing a range of disease severity. We investigated function, phenotypes, and frequency of T cells specific for SARS-CoV-2 using intracellular cytokine staining and spectral flow cytometry, and compared magnitude of SARS-CoV-2-specific antibodies. SARS-CoV-2-specific antibodies and T cells were detected 12 months postinfection. Severe acute illness was associated with higher frequencies of SARS-CoV-2-specific CD4 T cells and antibodies at 12 months. In contrast, polyfunctional and cytotoxic T cells responsive to SARS-CoV-2 were identified in participants over a wide spectrum of disease severity. SARS-CoV-2 infection induces polyfunctional memory T cells detectable at 12 months postinfection, with higher frequency noted in those who experienced severe disease.	no

2021	Asthma Phenotypes and COVID-19 Risk: A Population-based Observational Study.	Rationale: Studies have suggested some patients with asthma are at risk of severe coronavirus disease (COVID-19), but they have had limited data on asthma phenotype and have not considered if risks are specific to COVID-19. Objectives: To determine the effect of asthma phenotype on three levels of COVID-19 outcomes. Compare hospitalization rates with influenza and pneumonia. Methods: Electronic medical records were used to identify patients with asthma and match them to the general population. Patient-level data were linked to Public Health England severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test data, hospital, and mortality data. Asthma was phenotyped by medication, exacerbation history, and type 2 inflammation. The risk of each outcome, adjusted for major risk factors, was measured using Cox regression. Measurements and Main Results: A total of 434,348 patients with asthma and 748,327 matched patients were included. All patients with asthma had a significantly increased risk of a General Practice diagnosis of COVID-19. Asthma with regular inhaled corticosteroid (ICS) use (hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.01-1.61), intermittent ICS plus add-on asthma medication use (HR, 2.00; 95% CI, 1.43-2.79), regular ICS plus add-on use (HR, 1.63; 95% CI, 1.37-1.94), or with frequent exacerbations (HR, 1.82; 95% CI, 1.34-2.47) was significantly associated with hospitalization. These phenotypes were significantly associated with influenza and pneumonia hospitalizations. Only patients with regular ICS plus add-on asthma therapy (HR, 1.70; 95% CI, 1.27-2.26) or frequent exacerbations (HR, 1.66; 95% CI, 1.03-2.68) had a significantly higher risk of ICU admission or death. Atopy and blood eosinophil count were not associated with severe COVID-19 outcomes. Conclusions: More severe asthma was associated with more severe COVID-19 outcomes, but type 2 inflammation was not. The risk of COVID-19 hospitalization appeared to be similar to the risk with influenza or pneumonia.	no
2021	Neuro-COVID-19: an insidious virus in action.	The punishing effect of the pandemic outbreak of the disease termed COVID-19 (coronavirus disease-19) caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) impelled the author to gather the facts about the nature of this new pathogen. The aim of this paper was to discuss the mechanisms involved in the pathogenesis of neurological complications during the course of COVID-19. Neurological symptoms, such as impairment of taste or smell, headache, nausea and/or altered consciousness, are commonly described in COVID-19 patients, although there are emerging clinical reports of more serious conditions such as acute cerebrovascular accidents, encephalitis and demyelinating disease. Whether these manifestations are the direct consequence of viral invasion of the central nervous system, or are caused by indirect mechanisms, is yet to be established. Studies to date have indicated that neurological lesions found in the brains of COVID-19 patients are a combination of direct cytopathic effects caused by SARS-CoV-2 replication and indirect effects due to hypoxia, excessive cytokine reaction, impaired immune response, and cerebrovascular injury induced by viral infection. Studies are still pending into possible routes of SARS-CoV-2 neuroinvasion encompassing the haematopoietic pathway via the blood-brain barrier and retrograde axonal transport through the cranial nerves. A thorough understanding of SARS-CoV-2 involvement in neurological complications is still lacking. However, our knowledge about SARS-CoV-2 virulence is rapidly expanding, and that has inclined the author to prepare this comprehensive review in the hope that it will improve	no

		understanding about the molecular mechanisms underlying neurological abnormalities associated with COVID-19. A future detailed study should explore the diagnostics and disease mechanisms so as to enable the development of better therapeutic strategies to reduce the severity of COVID-19 neurological complications.	
2021	Serum Krebs von den Lungen-6 for Predicting the Severity of COVID-19 Lung Injury: A Systematic Review and Meta-Analysis.	Lung injury is common in coronavirus disease 2019 (COVID-19) patients. The severity of lung injury appears to be reflected in serum Krebs von den Lungen-6 (KL-6), a glycoprotein expressed on type II alveolar epithelium. This study aims to assess the role of serum KL-6 in reflecting the severity of lung injury in COVID-19 patients. A systematic search was conducted in Scopus, PubMed, Wiley Online Library, and ProQuest. Articles were screened based on several eligibility criteria and assessed for study quality using Newcastle-Ottawa Scale. This systematic review included four studies involving a total of 151 adult COVID-19 patients. Pooled analysis revealed that serum KL-6 was significantly higher in severe patients (SMD = 1.16; 95% CI = 0.69–1.63) with moderately high pooled sensitivity (79%; 95% CI = 61–91%) and specificity (86%; 95% CI = 72–95%). High serum KL-6 may depict more severe lung injury in COVID-19 patients with moderately high sensitivity and specificity.	no

2021	The MiR-320 Family Is Strongly Downregulated in Patients with COVID-19 Induced Severe Respiratory Failure.	A high incidence of thromboembolic events associated with high mortality has been reported in severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infections with respiratory failure. The present study characterized post-transcriptional gene regulation by global microRNA (miRNA) expression in relation to activated coagulation and inflammation in 21 critically ill SARS-CoV-2 patients. The cohort consisted of patients with moderate respiratory failure (n = 11) and severe respiratory failure (n = 10) at an acute stage (day 0-3) and in the later course of the disease (>7 days). All patients needed supplemental oxygen and severe patients were defined by the requirement of positive pressure ventilation (intubation). Levels of D-dimers, activated partial thromboplastin time (aPTT), C-reactive protein (CRP), and interleukin (IL)-6 were significantly higher in patients with severe compared with moderate respiratory failure. Concurrently, next generation sequencing (NGS) analysis demonstrated increased dysregulation of miRNA expression with progression of disease severity connected to extreme downregulation of miR-320a, miR-320b and miR-320c. Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis revealed involvement in the Hippo signaling pathway, the transforming growth factor (TGF)-β signaling pathway and in the regulation of adherens junctions. The expression of all miR-320 family members was significantly correlated with CRP, IL-6, and D-dimer levels. In conclusion, our analysis underlines the importance of thromboembolic processes in patients with respiratory failure and emphasizes miRNA-320s as potential biomarkers for severe progressive SARS-CoV-2 infection.	no
2021	Good Cholesterol Gone Bad? HDL and COVID-19.	The transmissible respiratory disease COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected millions of people worldwide since its first reported outbreak in December of 2019 in Wuhan, China. Since then, multiple studies have shown an inverse correlation between the levels of high-density lipoprotein (HDL) particles and the severity of COVID-19, with low HDL levels being associated with an increased risk of severe outcomes. Some studies revealed that HDL binds to SARS-CoV-2 particles via the virus's spike protein and, under certain conditions, such as low HDL particle concentrations, it facilitates SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2) and infection of host cells. Other studies, however, reported that HDL suppressed SARS-CoV-2 infection. In both cases, the ability of HDL to enhance or suppress virus infection appears to be dependent on the expression of the HDL receptor, namely, the Scavenger Receptor Class B type 1 (SR-B1), in the target cells. SR-B1 and HDL represent crucial mediators of cholesterol metabolism. Herein, we review the complex role of HDL and SR-B1 in SARS-CoV-2-induced disease. We also review recent advances in our understanding of HDL structure, properties, and function during SARS-CoV-2 infection and the resulting COVID-19 disease.	no

2021	Diabetes and COVID-19: Role of insulin resistance as a risk factor for COVID-19 severity.	Patients with diabetes are more susceptible to coronavirus disease 2019 (COVID-19), and as a consequence, develop more severe form of disease. This is partly due to a systemic inflammatory state and pro thrombotic milieu seen in metabolic syndrome. In this review, we attempt to explore the pathogenetic links between insulin resistance and COVID-19 disease severity. Insulin resistance is an underlying condition for metabolic syndromes, including type 2 diabetes, which impairs insulin signaling pathways affecting metabolic and cardiovascular homeostasis. A high concentration of circulating insulin shifts the balance to mitogen activated protein kinase (MAPK)-dependent signaling and causes endothelial cell damage. The phosphatidylinositol 3 kinase and MAPK dependent signaling pathways maintain a balance between nitric oxide-dependent vasodilator and endothelin-1 dependent vasoconstriction actions of insulin. Vascular smooth muscle cell dysfunction is responsible for inflammation and blood coagulation leading to microvascular and macrovascular complications in diabetes. Hyperactivity in renin-angiotensin system is implicated in development of islet oxidative stress and subsequent β-cell dysfunction, as it alters the islet blood flow. These deleterious effects of insulin resistance involving altered blood pressure, vascular dysfunction, and inflammation could be associated with increased severity in COVID-19 patients. We conclude that clinical and/or biochemical markers of insulin resistance should be included as prognostic markers in assessment of acute COVID-19 disease.	no
2021	High prevalence of post COVID-19 fatigue in patients with type 2 diabetes: A case-control study.	Post COVID-19 syndrome (PCS) has emerged as a major roadblock in the recovery of patients infected with SARS-CoV-2. Amongst many symptoms like myalgia, headache, cough, breathlessness; fatigue is is most prevalent and makes the patient severely debilitated. Research on PCS, in particular fatigue, in patients with diabetes has not been done. In this prospective study, we included patients with type 2 diabetes (T2D) who had COVID-19 (mild to moderate severity), and matched T2D patients who did not suffer from COVID-19. Demography, anthropometry, glycemic measures, treatment, and details of COVID-19 were recorded. Symptoms were scored using Chalder Fatigue Scale (reported as fatigue score, FS) and handgrip strength (in kg) was recorded by Jamar Hydraulic Hand Dynamometer. A total of 108 patients were included (cases, 52, controls, 56). Both groups were matched for age, duration of diabetes, BMI, TSH, serum albumin and vitamin D levels. T2D patients who had COVID-19 showed significantly more fatigue when compared with patients who did not have COVID-19 but both groups had comparable handgrip strength. Furthermore, patients with T2D with previous COVID-19 infection and who had FS > 4 have had significant higher inflammation markers during acute illness, and post COVID-19, had increased post prandial blood glucose levels, lost more weight, had reduced physical activity and showed significantly lower handgrip strength as compared to those with FS < 4. Patients with T2D who had COVID-19 infection as compared to those without had significantly more fatigue after the acute illness, and those with higher FS had reduced handgrip strength indicating sarcopenia, even after careful matching for common contributory factors to fatigue at baseline. Rehabilitation of those with FS>4 after acute infection would require careful attention to nutrition, glycemic control and graduated physical activity protocol.	no

2021	Fulminant H1N1 and severe acute respiratory syndrome coronavirus-2 infections with a 4-year interval without an identifiable underlying cause: a case report.	The clinical presentation of severe acute respiratory syndrome coronavirus-2 infection is highly variable from asymptomatic infection to fulminant disease. The reasons for the variation are only starting to unravel, with risk factors including age and certain comorbidities as well as genetic defects causing immunological perturbations in the interferon pathways. We report the case of an otherwise healthy Caucasian man, who at ages 60 and 64 years suffered from severe H1N1 influenza virus infection and severe acute respiratory syndrome coronavirus-2 infections, respectively. In both cases, there were acute kidney impairment and the need for intensive care unit admission as well as mechanical ventilation. Fortunately, after both infections there was full clinical recovery. The severity of the infections indicates an underlying impairment in the ability to control these kinds of infections. Challenge of patient peripheral blood mononuclear cells showed impaired type I and III antiviral interferon responses and reduced interferon-stimulated gene expression. However, despite investigation of patient samples by whole exome sequencing and enzyme-linked immunosorbent assay, no known disease-causing genetic variants related to interferon pathways were found, nor were interferon autoantibodies demonstrated. Thus, any underlying immunological cause of this unusual susceptibility to severe viral infections remains unresolved. The patient experienced very similar severe clinical pictures triggered by H1N1 and severe acute respiratory syndrome coronavirus-2 infections, indicating an underlying inability to contain these infections. We were unable to show that the patient had any of the currently known types of immune incompetence but identified genetic changes possibly contributing to the severe course of both infections. Further analyses to delineate contribution factors are needed.	no
2021	Metabolic Perturbation Associated With COVID-19 Disease Severity and SARS-CoV-2 Replication.	Viruses hijack host metabolic pathways for their replicative advantage. In this study, using patient-derived multiomics data and in vitro infection assays, we aimed to understand the role of key metabolic pathways that can regulate severe acute respiratory syndrome coronavirus-2 reproduction and their association with disease severity. We used multiomics platforms (targeted and untargeted proteomics and untargeted metabolomics) on patient samples and cell-line models along with immune phenotyping of metabolite transporters in patient blood cells to understand viral-induced metabolic modulations. We also modulated key metabolic pathways that were identified using multiomics data to regulate the viral reproduction in vitro. Coronavirus disease 2019 disease severity was characterized by increased plasma glucose and mannose levels. Immune phenotyping identified altered expression patterns of carbohydrate transporter, glucose transporter 1, in CD8 + T cells, intermediate and nonclassical monocytes, and amino acid transporter, xCT, in classical, intermediate, and nonclassical monocytes. In in vitro lung epithelial cell (Calu-3) infection model, we found that glycolysis and glutaminolysis are essential for virus replication, and blocking these metabolic pathways caused significant reduction in virus production. Taken together, we therefore hypothesized that severe acute respiratory syndrome coronavirus-2 utilizes and rewires pathways governing central carbon metabolism leading to the efflux of toxic metabolites and associated with disease severity. Thus, the host metabolic perturbation could be an attractive strategy to limit the viral replication and disease severity.	no

2021	A Role of Variance in Interferon Genes to Disease Severity in COVID-19 Patients.	The rapid rise and global consequences of the novel coronavirus disease 19 (COVID-19) have again brought the focus of the scientific community on the possible host factors involved in patient response and outcome to exposure to the virus. The disease severity remains highly unpredictable, and individuals with none of the aforementioned risk factors may still develop severe COVID-19. It was shown that genotype-related factors like an ABO Blood Group affect COVID-19 severity, and the risk of infection with SARS-CoV-2 was higher for patients with blood type A and lower for patients with blood type O. Currently it is not clear which specific genes are associated with COVID-19 severity. The comparative analysis of COVID-19 and other viral infections allows us to predict that the variants within the interferon pathway genes may serve as markers of the magnitude of immune response to specific pathogens. In particular, various members of Class III interferons (lambda) are reviewed in detail.	no
2021	Implementation of serological and molecular tools to inform COVID-19 patient management: protocol for the GENCOV prospective cohort study.	There is considerable variability in symptoms and severity of COVID-19 among patients infected by the SARS-CoV-2 virus. Linking host and virus genome sequence information to antibody response and biological information may identify patient or viral characteristics associated with poor and favourable outcomes. This study aims to (1) identify characteristics of the antibody response that result in maintained immune response and better outcomes, (2) determine the impact of genetic differences on infection severity and immune response, (3) determine the impact of viral lineage on antibody response and patient outcomes and (4) evaluate patient-reported outcomes of receiving host genome, antibody and viral lineage results. A prospective, observational cohort study is being conducted among adult patients with COVID-19 in the Greater Toronto Area. Blood samples are collected at baseline (during infection) and 1, 6 and 12 months after diagnosis. Serial antibody titres, isotype, antigen target and viral neutralisation will be assessed. Clinical data will be collected from chart reviews and patient surveys. Host genomes and T-cell and B-cell receptors will be sequenced. Viral genomes will be sequenced to identify viral lineage. Regression models will be used to test associations between antibody response, physiological response, genetic markers and patient outcomes. Pathogenic genomic variants related to disease severity, or negative outcomes will be identified and genome wide association will be conducted. Immune repertoire diversity during infection will be correlated with severity of COVID-19 symptoms and human leucocyte antigen-type associated with SARS-CoV-2 infection. Participants can learn their genome sequencing, antibody and viral sequencing results; patient-reported outcomes of receiving this information will be assessed through surveys and qualitative interviews. This study was approved by Clinical Trials Ontario Streamlined Ethics Review System (CTO Project ID: 3302) and the research ethics boards at participating hospitals. Study findings will be disseminated through peer-reviewed publications, conference presentations and end-users.	no

2021	Early IFN-α signatures and persistent dysfunction are distinguishing features of NK cells in severe COVID-19.	Longitudinal analyses of the innate immune system, including the earliest time points, are essential to understand the immunopathogenesis and clinical course of coronavirus disease (COVID-19). Here, we performed a detailed characterization of natural killer (NK) cells in 205 patients (403 samples; days 2 to 41 after symptom onset) from four independent cohorts using single-cell transcriptomics and proteomics together with functional studies. We found elevated interferon (IFN)-α plasma levels in early severe COVD-19 alongside increased NK cell expression of IFN-stimulated genes (ISGs) and genes involved in IFN-α signaling, while upregulation of tumor necrosis factor (TNF)-induced genes was observed in moderate diseases. NK cells exert anti-SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) activity but are functionally impaired in severe COVID-19. Further, NK cell dysfunction may be relevant for the development of fibrotic lung disease in severe COVID-19, as NK cells exhibited impaired anti-fibrotic activity. Our study indicates preferential IFN-α and TNF responses in severe and moderate COVID-19, respectively, and associates a prolonged IFN-α-induced NK cell response with poorer disease outcome.	no
2021	Uncovering Clinical Risk Factors and Predicting Severe COVID-19 Cases Using UK Biobank Data: Machine Learning Approach.	COVID-19 is a major public health concern. Given the extent of the pandemic, it is urgent to identify risk factors associated with disease severity. More accurate prediction of those at risk of developing severe infections is of high clinical importance. Based on the UK Biobank (UKBB), we aimed to build machine learning models to predict the risk of developing severe or fatal infections, and uncover major risk factors involved. We first restricted the analysis to infected individuals (n=7846), then performed analysis at a population level, considering those with no known infection as controls (ncontrols=465,728). Hospitalization was used as a proxy for severity. A total of 97 clinical variables (collected prior to the COVID-19 outbreak) covering demographic variables, comorbidities, blood measurements (eg, hematological/liver/renal function/metabolic parameters), anthropometric measures, and other risk factors (eg, smoking/drinking) were included as predictors. We also constructed a simplified (lite) prediction model using 27 covariates that can be more easily obtained (demographic and comorbidity data). XGboost (gradient-boosted trees) was used for prediction and predictive performance was assessed by cross-validation. Variable importance was quantified by Shapley values (ShapVal), permutation importance (PermImp), and accuracy gain. Shapley dependency and interaction plots were used to evaluate the pattern of relationships between risk factors and outcomes. A total of 2386 severe and 477 fatal cases were identified. For analyses within infected individuals (n=7846), our prediction model achieved area under the receiving-operating characteristic curve (AUC-ROC) of 0.723 (95% CI 0.711-0.736) and 0.814 (95% CI 0.791-0.838) for severe and fatal infections, respectively. The top 5 contributing factors (sorted by ShapVal) for severity were age, number of drugs taken (cnt_tx), cystatin C (reflecting renal function), waist-to-hip ratio (WHR), and Townsend deprivation index (TDI). For mortality, the top features were age, testosterone, cnt_tx, waist circumference (WC), and red cell distribution width. For analyses involving the whole UKBB population, AUCs for severity and fatality were 0.696 (95% CI 0.684-0.708) and 0.825 (95% CI 0.802-0.848), respectively. The same top 5 risk factors were identified for both outcomes, namely, age, cnt_tx, WC, WHR, and TDI. Apart from the above, age, cystatin C, TDI, and cnt_tx were among the top 10 across all 4 analyses. Other diseases top ranked by ShapVal or	yes

		PermImp were type 2 diabetes mellitus (T2DM), coronary artery disease, atrial fibrillation, and dementia, among others. For the "lite" models, predictive performances were broadly similar, with estimated AUCs of 0.716, 0.818, 0.696, and 0.830, respectively. The top ranked variables were similar to above, including age, cnt_tx, WC, sex (male), and T2DM. We identified numerous baseline clinical risk factors for severe/fatal infection by XGboost. For example, age, central obesity, impaired renal function, multiple comorbidities, and cardiometabolic abnormalities may predispose to poorer outcomes. The prediction models may be useful at a population level to identify those susceptible to developing severe/fatal infections, facilitating targeted prevention strategies. A risk-prediction tool is also available online. Further replications in independent cohorts are required to verify our findings.	
2021	Pre-existing Autoantibodies Neutralizing High Concentrations of Type I Interferons in Almost 10% of COVID-19 Patients Admitted to Intensive Care in Barcelona.	It is important to predict which patients infected by SARS-CoV-2 are at higher risk of life-threatening COVID-19. Several studies suggest that neutralizing auto-antibodies (auto-Abs) against type I interferons (IFNs) are predictive of critical COVID-19 pneumonia. We aimed to test for auto-Abs to type I IFN and describe the main characteristics of COVID-19 patients admitted to intensive care depending on whether or not these auto-Abs are present. Retrospective analysis of all COVID-19 patients admitted to an intensive care unit (ICU) in whom samples were available, from March 2020 to March 2021, in Barcelona, Spain. A total of 275 (70.5%) out of 390 patients admitted to ICU were tested for type I IFNs auto-antibodies (α2 and/or ω) by ELISA, being positive in 49 (17.8%) of them. Blocking activity of plasma diluted 1/10 for high concentrations (10 ng/mL) of IFNs was proven in 26 (9.5%) patients. Almost all the patients with neutralizing auto-Abs were men (92.3%). ICU patients with positive results for neutralizing IFNs auto-Abs did not show relevant differences in demographic, comorbidities, clinical features, and mortality, when compared with those with negative results. Nevertheless, some laboratory tests (leukocytosis, neutrophilia, thrombocytosis) related with COVID-19 severity, as well as acute kidney injury (17 [65.4%] vs. 100 [40.2%]; p = 0.013) were significantly	no

		higher in patients with auto-Abs. Auto-Abs neutralizing high concentrations of type I IFNs were found in 9.5% of patients admitted to the ICU for COVID-19 pneumonia in a hospital in Barcelona. These auto-Abs should be tested early upon diagnosis of SARS-CoV-2 infection, as they account for a significant proportion of life-threatening cases.	
2021	Human genetic basis of coronavirus disease 2019.	Coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in considerable morbidity and mortality worldwide. COVID-19 incidence, severity, and mortality rates differ greatly between populations, genders, ABO blood groups, human leukocyte antigen (HLA) genotypes, ethnic groups, and geographic backgrounds. This highly heterogeneous SARS-CoV-2 infection is multifactorial. Host genetic factors such as variants in the angiotensin-converting enzyme gene (ACE), the angiotensin-converting enzyme 2 gene (ACE2), the transmembrane protease serine 2 gene (TMPRSS2), along with HLA genotype, and ABO blood group help to explain individual susceptibility, severity, and outcomes of COVID-19. This review is focused on COVID-19 clinical and viral characteristics, pathogenesis, and genetic findings, with particular attention on genetic diversity and variants. The human genetic basis could provide scientific bases for disease prediction and targeted therapy to address the COVID-19 scourge.	yes

2021	A model integrating Killer Immunoglobulin-like Receptor (KIR) haplotypes for risk prediction of COVID-19 clinical disease severity.	Associations between inherited Killer Immunoglobulin-like Receptor (KIR) genotypes and the severity of multiple RNA virus infections have been reported. This prospective study was initiated to investigate if such an association exists for COVID-19. In this cohort study performed at Ankara University, 132 COVID-19 patients (56 asymptomatic, 51 mild-intermediate, and 25 patients with severe disease) were genotyped for KIR and ligands. Ankara University Donor Registry (n:449) KIR data was used for comparison. Clinical parameters (age, gender, comorbidities, blood group antigens, inflammation biomarkers) and KIR genotypes across cohorts of asymptomatic, mild-intermediate, or severe disease were compared to construct a risk prediction model based on multivariate binary logistic regression analysis with backward elimination method. Age, blood group, number of comorbidities, CRP, D-dimer, and telomeric and centromeric KIR genotypes (tAA, tAB1, and cAB1) along with their cognate ligands were found to differ between cohorts. Two prediction models were constructed; both included age, number of comorbidities, and blood group. Inclusion of the KIR genotypes in the second prediction model exp (-3.52 + 1.56 age group - 2.74 blood group (type A vs others) + 1.26 number of comorbidities - 2.46 tAB1 with ligand + 3.17 tAA with ligand) increased the predictive performance with a 92.9% correct classification for asymptomatic and 76% for severe cases (AUC: 0.93; $P < 0.0001$, 95% CI 0.88, 0.99). This novel risk model, consisting of KIR genotypes with their cognate ligands, and clinical parameters but excluding earlier published inflammation-related biomarkers allow for the prediction of the severity of COVID-19 infection prior to the onset of infection. This study is listed in the National COVID-19 clinical research studies database.	no

2021	Association of HLA genotypes, AB0 blood type and chemokine receptor 5 mutant CD195 with the clinical course of COVID-19.	COVID-19, the pandemic disease caused by infection with SARS-CoV-2, may take highly variable clinical courses, ranging from symptom-free and pauci-symptomatic to fatal disease. The goal of the current study was to assess the association of COVID-19 clinical courses controlled by patients' adaptive immune responses without progression to severe disease with patients' Human Leukocyte Antigen (HLA) genetics, AB0 blood group antigens, and the presence or absence of near-loss-of-function delta 32 deletion mutant of the C-C chemokine receptor type 5 (CCR5). An exploratory observational study including 157 adult COVID-19 convalescent patients was performed with a median follow-up of 250 days. The impact of different HLA genotypes, AB0 blood group antigens, and the CCR5 mutant CD195 were investigated for their role in the clinical course of COVID-19. In addition, this study addressed levels of severity and morbidity of COVID-19. The association of the immunogenetic background parameters were further related to patients' humoral antiviral immune response patterns by longitudinal observation. Univariate HLA analyses identified putatively protective HLA alleles (HLA class II DRB1*01:01 and HLA class I B*35:01, with a trend for DRB1*03:01). They were associated with reduced durations of disease instead decreased (rather than increased) total anti-S IgG levels. They had a higher virus neutralizing capacity compared to non-carriers. Conversely, analyses also identified HLA alleles (HLA class II DQB1*03:02 und HLA class I B*15:01) not associated with such benefit in the patient cohort of this study. Hierarchical testing by Cox regression analyses confirmed the significance of the protective effect of the HLA alleles identified (when assessed in composite) in terms of disease duration, whereas AB0 blood group antigen heterozygosity was found to be significantly associated with disease severity (rather than duration) in our cohort. A suggestive association of a heterozygous CCR5 delta 32 mutation status with prolonged disease duration was implied by univariate analyses but could not be confirmed by hierarchical multivariate testing. The current study shows that the presence of HLA class II DRB1*01:01 and HLA class I B*35:01 is of even stronger association with reduced disease duration in mild and moderate COVID-19 than age or any other potential risk factor assessed. Prospective studies in larger patient populations also including novel SARS-CoV-2 variants will be required to assess the impact of HLA genetics on the capacity of mounting protective vaccination responses in the future.	yes
2021	Association of Blood Groups with the Severity and Outcome of COVID-19 Infection in Children.	The objective of this study was to find out the association of ABO blood groups with the severity and outcome of corona virus disease 2019 (COVID-19) in children. It included all laboratory-confirmed cases of COVID-19 and post-COVID multisystem inflammatory syndrome in children (MIS-C)/ Kawasaki disease (KD) like illness, admitted from March to September, 2020 to The Children's Hospital, Lahore. Out of 66 children, 45 (68.2%) were COVID-19 and 21 (31.8%) MIS-C/KD temporally associated with SARS-C0V-2. The mean age was 7.9 ± 4.2 years. Majority of children had mild to moderate illness 38 (57.6%), while 23 (34.8%) had severe or critical disease. Among all patients, 24 (36.4%) had some underlying comorbidity. Blood group A was significantly associated with severe and critical disease (p=0.030). COVID-19 in children had generally a good outcome, but children with blood group A were more susceptible to severe/critical disease. Key Words: Coronavirus disease 2019, ABO blood groups, Children, Severity, Outcome.	yes

2021	Identification of immune correlates of fatal outcomes in critically ill COVID-19 patients.	Prior studies have demonstrated that immunologic dysfunction underpins severe illness in COVID-19 patients, but have lacked an in-depth analysis of the immunologic drivers of death in the most critically ill patients. We performed immunophenotyping of viral antigen-specific and unconventional T cell responses, neutralizing antibodies, and serum proteins in critically ill patients with SARS-CoV-2 infection, using influenza infection, SARS-CoV-2-convalescent health care workers, and healthy adults as controls. We identify mucosal-associated invariant T (MAIT) cell activation as an independent and significant predictor of death in COVID-19 (HR = 5.92, 95% CI = 2.49-14.1). MAIT cell activation correlates with several other mortality-associated immunologic measures including broad activation of CD8+ T cells and non-Vδ2 γδT cells, and elevated levels of cytokines and chemokines, including GM-CSF, CXCL10, CCL2, and IL-6. MAIT cell activation is also a predictor of disease severity in influenza (ECMO/death HR = 4.43, 95% CI = 1.08-18.2). Single-cell RNA-sequencing reveals a shift from focused IFNα-driven signals in COVID-19 ICU patients who survive to broad pro-inflammatory responses in fatal COVID-19 -a feature not observed in severe influenza. We conclude that fatal COVID-19 infection is driven by uncoordinated inflammatory responses that drive a hierarchy of T cell activation, elements of which can serve as prognostic indicators and potential targets for immune intervention.	yes
2021	COVID-19 induces proatherogenic alterations in moderate to severe non-comorbid patients: A single-center observational study.	Patients with COVID-19 can be asymptomatic or present mild to severe symptoms, leading to respiratory and cardiovascular complications and death. Type 2 diabetes mellitus (T2DM) and obesity are considered risk factors for COVID-19 poor prognosis. In parallel, COVID-19 severe patients exhibit dyslipidemia and alterations in neutrophil to lymphocyte ratio (NLR) associated with disease severity and mortality. To investigate whether such alterations are caused by the infection or results from preexisting comorbidities, this work analyzed dyslipidemia and the hemogram profile of COVID-19 patients according to the severity and compared with patients without T2DM or obesity comorbidities. Dyslipidemia, with a marked decrease in HDL levels, and increased NLR accompanied the disease severity, even in non-T2DM and non-obese patients, indicating that COVID-19 causes the observed alterations. Because decreased hemoglobin is involved in COVID-19 severity, and hemoglobin concentration is associated with metabolic diseases, the erythrogram of patients was also evaluated. We verified a drop in hemoglobin and erythrocyte number in severe patients, independently of T2DM and obesity, which may explain in part the need for artificial ventilation in severe cases. Thus, the control of such parameters (especially HDL levels, NLR, and hemoglobin concentration) could be a good strategy to prevent COVID-19 complications and death.	yes
2021	SARS-CoV-2 Impairs Dendritic Cells and Regulates DC-SIGN Gene Expression in Tissues.	The current spreading coronavirus SARS-CoV-2 is highly infectious and pathogenic. In this study, we screened the gene expression of three host receptors (ACE2, DC-SIGN and L-SIGN) of SARS coronaviruses and dendritic cells (DCs) status in bulk and single cell transcriptomic datasets of upper airway, lung or blood of COVID-19 patients and healthy controls. In COVID-19 patients, DC-SIGN gene expression was interestingly decreased in lung DCs but increased in blood DCs. Within DCs, conventional DCs (cDCs) were depleted while plasmacytoid DCs (pDCs) were augmented in the lungs of mild COVID-19. In severe cases, we identified augmented types of immature DCs (CD22 + or ANXA1 + DCs) with MHCII downregulation. In this study, our observation indicates that DCs in severe cases stimulate innate immune	yes

		responses but fail to specifically present SARS-CoV-2. It provides insights into the profound modulation of DC function in severe COVID-19.	
2021	Seasonal coronavirus-specific B cells with limited SARS-CoV-2 cross-reactivity dominate the IgG response in severe COVID-19.	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus disease 2019 (COVID-19). Little is known about the interplay between preexisting immunity to endemic seasonal coronaviruses and the development of a SARS-CoV-2-specific IgG response. We investigated the kinetics, breadth, magnitude, and level of cross-reactivity of IgG antibodies against SARS-CoV-2 and heterologous seasonal and epidemic coronaviruses at the clonal level in patients with mild or severe COVID-19 as well as in disease control patients. We assessed antibody reactivity to nucleocapsid and spike antigens and correlated this IgG response to SARS-CoV-2 neutralization. Patients with COVID-19 mounted a mostly type-specific SARS-CoV-2 response. Additionally, IgG clones directed against a seasonal coronavirus were boosted in patients with severe COVID-19. These boosted clones showed limited cross-reactivity and did not neutralize SARS-CoV-2. These findings indicate a boost of poorly protective CoV-specific antibodies in patients with COVID-19 that correlated with disease severity, revealing "original antigenic sin."	no
2021	Blood fibrocytes are associated with severity and prognosis in COVID-19 pneumonia.	Increased blood fibrocytes are associated with a poor prognosis in fibrotic lung diseases. We aimed to determine whether the percentage of circulating fibrocytes could be predictive of severity and prognosis during coronavirus disease 2019 (COVID-19) pneumonia. Blood fibrocytes were quantified by flow cytometry as CD45 + /CD15 - /CD34 + /collagen-1 + cells in patients hospitalized for COVID-19 pneumonia. In a subgroup of patients admitted in an intensive care unit (ICU), fibrocytes were quantified in blood and bronchoalveolar lavage (BAL). Serum amyloid P (SAP), transforming growth factor-β1 (TGF-β1), CXCL12, CCL2, and FGF2 concentrations were measured. We included 57 patients in the hospitalized group (median age = 59 yr [23-87]) and 16 individuals as healthy controls. The median percentage of circulating fibrocytes was higher in the patients compared with the controls (3.6% [0.2-9.2] vs. 2.1% [0.9-5.1], P = 0.04). Blood fibrocyte count was lower in the six patients who died compared with the survivors (1.6% [0.2-4.4] vs. 3.7% [0.6-9.2], P = 0.02). Initial fibrocyte count was higher in patients showing a complete lung computed tomography (CT) resolution at 3 mo. Circulating fibrocyte count was decreased in the ICU group (0.8% [0.1-2.0]), whereas BAL fibrocyte count was 6.7% (2.2-15.4). Serum SAP and TGF-β1 concentrations were increased in hospitalized patients. SAP was also increased in ICU patients. CXCL12 and CCL2 were increased in ICU patients and negatively correlated with circulating fibrocyte count. We conclude that circulating fibrocytes were increased in patients hospitalized for COVID-19 pneumonia, and a lower fibrocyte count was associated with an increased risk of death and a slower resolution of lung CT opacities.	yes

2021	Different Profiles of Antibodies and Cytokines Were Found Between Severe and Moderate COVID-19 Patients.	Our objective was to determine the antibody and cytokine profiles in different COVID-19 patients. COVID-19 patients with different clinical classifications were enrolled in this study. The level of IgG antibodies, IgA, IgM, IgE, and IgG subclasses targeting N and S proteins were tested using ELISA. Neutralizing antibody titers were determined by using a toxin neutralization assay (TNA) with live SARS-CoV-2. The concentrations of 8 cytokines, including IL-2, IL-4, IL-6, IL-10, CCL2, CXCL10, IFN-γ, and TNF-α, were measured using the Protein Sample Ella-Simple ELISA system. The differences in antibodies and cytokines between severe and moderate patients were compared by t-tests or Mann-Whitney tests. A total of 79 COVID-19 patients, including 49 moderate patients and 30 severe patients, were enrolled. Compared with those in moderate patients, neutralizing antibody and IgG-S antibody titers in severe patients were significantly higher. The concentration of IgG-N antibody was significantly higher than that of IgG-S antibody in COVID-19 patients. There was a significant difference in the distribution of IgG subclass antibodies between moderate patients and severe patients. The positive ratio of anti-S protein IgG3 is significantly more than anti-N protein IgG3, while the anti-S protein IgG4 positive rate is significantly less than the anti-N protein IgG4 positive rate. IL-2 was lower in COVID-19 patients than in healthy individuals, while IL-4, IL-6, CCL2, IFN-γ, and TNF-α were higher in COVID-19 patients than in healthy individuals. IL-6 was significantly higher in severe patients than in moderate patients. The antibody level of anti-S protein was positively correlated with the titer of neutralizing antibody, but there was no relationship between cytokines and neutralizing antibody. Our findings show the severe COVID-19 patients' antibody levels were stronger than those of moderate patients, and a cytokine storm is associated with COVID-19 severity. There was a difference in immunoglobulin type between anti-S protein antibodies and anti-N protein antibodies in COVID-19 patients. And clarified the value of the profile in critical prevention.	yes
2021	Integrated analysis of plasma and single immune cells uncovers metabolic changes in individuals with COVID-19.	A better understanding of the metabolic alterations in immune cells during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may elucidate the wide diversity of clinical symptoms experienced by individuals with coronavirus disease 2019 (COVID-19). Here, we report the metabolic changes associated with the peripheral immune response of 198 individuals with COVID-19 through an integrated analysis of plasma metabolite and protein levels as well as single-cell multiomics analyses from serial blood draws collected during the first week after clinical diagnosis. We document the emergence of rare but metabolically dominant T cell subpopulations and find that increasing disease severity correlates with a bifurcation of monocytes into two metabolically distinct subsets. This integrated analysis reveals a robust interplay between plasma metabolites and cell-type-specific metabolic reprogramming networks that is associated with disease severity and could predict survival.	m

2021	Clinical value of blood markers to assess the severity of coronavirus disease 2019.	Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is threatening the world with the symptoms of seasonal influenza. This study was conducted to investigate the patient characteristics and clinical value of blood markers to assess the severity of coronavirus disease 2019 (COVID-19). 187 patients, diagnosed with COVID-19 (non-severe and severe cases) and admitted to hospital between January 27th and March 8th of 2020, were enrolled in the present study. A higher proportion of clinical symptoms, including cough, expectoration, myalgia, and fatigue were observed in the non-severe group. The level of white blood cell count, neutrophils, CRP, IL-6 and IL-8 were significantly increased, while the platelet count was remarkedly decreased in the severe group. The risk model based on lymphocyte, IL-6, IL-8, CRP and platelet counts had the highest area under the receiver operator characteristic curve (AUROC). The baseline of IL-6, IL-8 and CRP was positively correlated with other parameters except in the cases of lymphocyte, hemoglobin and platelet counts. The baseline of the platelet count was negatively correlated with other parameters except in the lymphocyte and hemoglobin counts. Additionally, there was no connection between the severity of COVID-19 and cultures of blood, sputum or catheter secretion. The present study suggested that high leucocyte and low platelets counts were independent predictive markers of the severity of COVID-19.	yes
2021	Impact of blood type on thrombosis and disease severity in adult COVID-19 patients.	NA	yes
2021	Differential plasmacytoid dendritic cell phenotype and type I Interferon response in asymptomatic and severe COVID-19 infection.	SARS-CoV-2 fine-tunes the interferon (IFN)-induced antiviral responses, which play a key role in preventing coronavirus disease 2019 (COVID-19) progression. Indeed, critically ill patients show an impaired type I IFN response accompanied by elevated inflammatory cytokine and chemokine levels, responsible for cell and tissue damage and associated multi-organ failure. Here, the early interaction between SARS-CoV-2 and immune cells was investigated by interrogating an in vitro human peripheral blood mononuclear cell (PBMC)-based experimental model. We found that, even in absence of a productive viral replication, the virus mediates a vigorous TLR7/8-dependent production of both type I and III IFNs and inflammatory cytokines and chemokines, known to contribute to the cytokine storm observed in COVID-19. Interestingly, we observed how virus-induced type I IFN secreted by PBMC enhances anti-viral response in infected lung epithelial cells, thus, inhibiting viral replication. This type I IFN was released by plasmacytoid dendritic cells (pDC) via an ACE-2-indipendent but Neuropilin-1-dependent mechanism. Viral sensing regulates pDC phenotype by inducing cell surface expression of PD-L1 marker, a feature of type I IFN producing cells. Coherently to what observed in vitro, asymptomatic SARS-CoV-2 infected subjects displayed a similar pDC phenotype associated to a very high serum type I IFN level and induction of anti-viral IFN-stimulated genes in PBMC. Conversely, hospitalized patients with severe COVID-19 display very low frequency of circulating pDC with an inflammatory phenotype and high levels of chemokines and pro-inflammatory cytokines in serum. This study further shed light on the early events resulting from the interaction between SARS-CoV-2 and immune cells occurring in vitro and confirmed ex vivo. These observations can improve our understanding on the contribution of pDC/type I IFN axis in the	no

		regulation of the anti-viral state in asymptomatic and severe COVID-19 patients.	
2021	Type I, II, and III Interferon Signatures Correspond to Coronavirus Disease 2019 Severity.	We analyzed plasma levels of interferons (IFNs) and cytokines, and expression of IFN-stimulated genes in peripheral blood mononuclear cells in patients with coronavirus disease 2019 of varying disease severity. Patients hospitalized with mild disease exhibited transient type I IFN responses, while intensive care unit patients had prolonged type I IFN responses. Type II IFN responses were compromised in intensive care unit patients. Type III IFN responses were induced in the early phase of infection, even in convalescent patients. These results highlight the importance of early type I and III IFN responses in controlling coronavirus disease 2019 progression.	no
2021	The impact of COVID-19 pandemic on glycemic control in patients with diabetes mellitus in Turkey: a multi-center study from Kocaeli.	The aim of this study is to determine the impact of the COVID-19 pandemic on the management and disease control of the patients with diabetes mellitus in Kocaeli. This study was carried out in six leading central hospitals in five major districts of Kocaeli. The study was conducted between June 2020 and November 2020. The patients who had previous admissions to these clinics within 6 months prior to the pandemic were enrolled in the study. A total of 283 patients were enrolled in the study, among them 151 (53%) patients were female, 268 (95%) had type 2 DM and remaining 5% had type 1 DM. The median weight of the patients was similar between the previous and last visits (84 kg vs 83 kg, p = 0,88). Laboratory parameters of previous and current visits revealed that mean fasting plasma glucose (FPG) and HbA1c levels were not significantly changed. The number of the patients who had controlled blood pressure was significantly decreased. The number of those who had neuropathic complains and the severity of dyslipidemia significantly increased during pandemic period. Our study demonstrated that despite decreased compliance with diet and exercise, and difficulty in accessing medication, there was no significant change in weight, FPG and HbA1c levels in diabetic patients. Since cultural differences, education level and socioeconomic opportunities differ between societies, national and international studies will be more	no

		accurate to evaluate the effects of epidemics on the course of chronic diseases.	
2021	Immunometabolic signatures predict risk of progression to sepsis in COVID-19.	Viral sepsis has been proposed as an accurate term to describe all multisystemic dysregulations and clinical findings in severe and critically ill COVID-19 patients. The adoption of this term may help the implementation of more accurate strategies of early diagnosis, prognosis, and in-hospital treatment. We accurately quantified 110 metabolites using targeted metabolomics, and 13 cytokines/chemokines in plasma samples of 121 COVID-19 patients with different levels of severity, and 37 non-COVID-19 individuals. Analyses revealed an integrated host-dependent dysregulation of inflammatory cytokines, neutrophil activation chemokines, glycolysis, mitochondrial metabolism, amino acid metabolism, polyamine synthesis, and lipid metabolism typical of sepsis processes distinctive of a mild disease. Dysregulated metabolites and cytokines/chemokines showed differential correlation patterns in mild and critically ill patients, indicating a crosstalk between metabolism and hyperinflammation. Using multivariate analysis, powerful models for diagnosis and prognosis of COVID-19 induced sepsis were generated, as well as for mortality prediction among septic patients. A metabolite panel made of kynurenine/tryptophan ratio, IL-6, LysoPC a C18:2, and phenylalanine discriminated non-COVID-19 from sepsis patients with an area under the curve (AUC (95%CI)) of 0.991 (0.986-0.995), with sensitivity of 0.978 (0.963-0.992) and specificity of 0.920 (0.890-0.949). The panel that included C10:2, IL-6, NLR, and C5 discriminated mild patients from sepsis patients with an AUC (95%CI) of 0.965 (0.952-0.977), with sensitivity of 0.993(0.984-1.000) and specificity of 0.851 (0.815-0.887). The panel with citric acid, LysoPC a C28:1, neutrophil-lymphocyte ratio (NLR) and kynurenine/tryptophan ratio discriminated severe patients from sepsis patients with an AUC (95%CI) of 0.829 (0.800-0.858), with sensitivity of 0.738 (0.695-0.781) and specificity of 0.781 (0.735-0.827). Septic patients who survived were different from those that did not survive with a model consisting of hippuric acid, along with the presence of Type II diabetes, with an AUC (95%CI) of 0.831 (0.788-0.874), with sensitivity of 0.765 (0.697-0.832) and specificity of 0.817 (0.770-0.865).	yes

2021	What Is the Role of Therapeutic Plasma Exchange as an Adjunctive Treatment in Severe COVID-19: A Systematic Review.	Since the COVID-19 pandemic outbreak, multiple promising treatment modalities have been tested, however, only several of them were proven to be effective. Therapeutic plasma exchange (TPE) has been recently discussed as a possible supportive treatment for severe cases. To investigate a possible role of TPE in severe COVID-19 we used a structured systematic search strategy to retrieve all relevant publications in the field. We screened in PubMed, EMBASE, Web of Science, Cochrane Library and clinicaltrials.gov for data published until the 4 June 2021. We identified 18 papers, enrolling 384 patients, 220 of whom received TPE. The number of TPE sessions ranged from 1 to 9 and the type of replacement fluid varied markedly between studies (fresh frozen plasma or 5% albumin solution, or convalescent plasma). Biochemical improvement was observed in majority of studies as far as C-reactive protein (CRP), interleukin-6 (IL-6), ferritin, lactate dehydrogenase (LDH), D-dimer concentrations and lymphocyte count are concerned. The improvement at a laboratory level was associated with enhancement of respiratory function. Adverse effects were limited to five episodes of transient hypotension and one femoral artery puncture and thrombophlebitis. Although the effect of therapeutic plasma exchange on mortality remains unclarified, the procedure seems to improve various secondary end-points such as PaO 2 /FiO 2 ratio or biomarkers of inflammation. Therapeutic plasma exchange appears to be a safe treatment modality in COVID-19 patients in terms of side effects.	no
2021	Acute Inflammatory Mediators in Young Adult Patients with COVID-19 in Mexico.	Young adults (18-40 years old) are an active population with high risk of infection and transmission of COVID-19. They are considered a low-risk population due to its low 1.0% case fatality rate (CFR). Despite their high clinical usefulness to prevent fatal cases, inflammatory and coagulation biomarkers studies are limited. For this reason, we performed a retrospective cohort study with COVID-19 patients in Hermosillo, Mexico, to assess inflammation, coagulopathy profile, and severity outcomes in young adults. We analyzed blood samples to determine the neutrophil/lymphocyte ratio (NLR), neutrophil/monocyte ratio (NMR), lymphocyte/monocyte ratio (LMR), platelet/lymphocyte ratio (PLR), and C-reactive protein (C-RP). We included epidemiological features and comorbidities, and compared them to the severity status. Only 359 COVID-19-confirmed young adults were included in the ambulatory (44.8%), hospitalized (42.9%), and death (12%) severity groups. Laboratory results showed an increase in NMR, LMR, and C-RP associated with the aggravated patients. Additionally, obesity, arterial hypertension, and type-2 diabetes mellitus (T2DM) were associated with the COVID-19 severity outcome. We found that 9.1% and 30.3% of young adults presented the novel COVID-19-associated coagulopathy (CAC) and the risk of CAC, respectively. These parameters can be considered independent biomarkers reflecting an enhanced inflammatory process related to the COVID-19 prognosis.	no

2021	Severe COVID-19 Patients Show an Increase in Soluble TNFR1 and ADAM17, with a Relationship to Mortality.	Overproduction of inflammatory cytokines is a keystone event in COVID-19 pathogenesis; TNF and its receptors (TNFR1 and TNFR2) are critical pro-inflammatory molecules. ADAM17 releases the soluble (sol) forms of TNF, TNFR1, and TNFR2. This study evaluated TNF, TNFRs, and ADAM17 at the protein, transcriptional, and gene levels in COVID-19 patients with different levels of disease severity. In total, 102 patients were divided into mild, moderate, and severe condition groups. A group of healthy donors (HD; $n = 25$) was included. Our data showed that solTNFR1 and solTNFR2 were elevated among the COVID-19 patients ($p < 0.0001$), without increasing the transcriptional level. Only solTNFR1 was higher in the severe group as compared to the mildly ill ($p < 0.01$), and the level was higher in COVID-19 patients who died than those that survived ($p < 0.0001$). The solTNFR1 level had a discrete negative correlation with C-reactive protein ($p = 0.006$, Rho = -0.33). The solADAM17 level was higher in severe as compared to mild disease conditions ($p < 0.01$), as well as in COVID-19 patients who died as compared to those that survived ($p < 0.001$). Additionally, a potential association between polymorphism TNFRSF1A :rs767455 and a severe degree of disease was suggested. These data suggest that solTNFR1 and solADAM17 are increased in severe conditions. solTNFR1 should be considered a potential target in the development of new therapeutic options.	no
2021	High Thermal Amplitude Red Blood Cell Agglutinating Cold Type Autoantibodies in a Case of Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia and Multiorgan Failure.	A 48-year-old man diagnosed with multiorgan failure and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia developed anemia and polyclonal cold agglutinins that reacted at 37 °C. He recovered after a 2-month hospitalization where he received intensive care support. Cold agglutinins resolved after 2 weeks of supportive care. As red blood cell (RBC) cryptic antigens and warm type autoimmune hemolysis have been recently described in coronavirus disease 2019 (COVID-19) patients, we believe this mechanism may also give rise of clinically detectable cold immunoglobulin M (IgM) autoantibodies. Given the thermal amplitude of this particular agglutinin we believe it is possible that in vivo RBC agglutination could contribute to disease severity.	no
2021	Increase in blood glucose level and incidence of diabetic ketoacidosis in children with type 1 diabetes mellitus in the Daegu-Gyeongbuk area during the coronavirus disease 2019 (COVID-19) pandemic: a retrospective cross-sectional study.	The coronavirus disease 2019 (COVID-19) outbreak in the Daegu-Gyeongbuk area in 2020 has caused difficulties in the daily life and hospital care of children with type 1 diabetes mellitus (T1DM). We detected an increase in blood sugar levels in these children and the number of patients hospitalized with more severe diabetic ketoacidosis (DKA) compared to those before COVID-19. This single-center study was conducted at Kyungpook National University Children's Hospital. The following patient groups were included; 45 returning patients diagnosed with T1DM and undergoing insulin treatment for more than 2 years and 20 patients newly diagnosed with T1DM before and after COVID-19 were selected by age matching. Returning patients before and after the outbreak were selected, and changes in hemoglobin A1c (HbA1c) levels were retrospectively reviewed. The HbA1c levels and severity of symptoms in newly diagnosed patients during hospitalization were examined. HbA1c levels in returning patients with T1DM were significantly increased after COVID-19 (before, 7.70%±1.38% vs. after, 8.30%±2.05%; p=0.012). There were 10 and 10 newly diagnosed patients before and after COVID-19, respectively. The proportion of patients with drowsiness and dyspnea at the time of admission was higher after COVID-19 than before (before, 2 of 10 vs. after, 4 of 10). The HbA1c levels were higher in newly diagnosed patients hospitalized after COVID-19 than before (before, 11.15% vs. after, 13.60%;	no

		p=0.036). Due to COVID-19 in the Daegu-Gyeongbuk area, there was an increase in blood glucose levels in children with T1DM and in the incidence of severe DKA in newly diagnosed diabetes mellitus patients.	
2021	Clinical Characteristics and Outcomes of Hypertensive Patients Infected with COVID-19: A Retrospective Study.	Hypertension has been reported as the most prevalent comorbidity in patients with coronavirus disease 2019 (COVID-19). This retrospective study aims to compare the clinical characteristics and outcomes in COVID-19 patients with or without hypertension. A total of 944 hospitalized patients with laboratory-confirmed COVID-19 were included from January to March 2020. Information from the medical record, including clinical features, radiographic and laboratory results, complications, treatments, and clinical outcomes, were extracted for the analysis. A total of 311 (32.94%) patients had comorbidity with hypertension. In COVID-19 patients with hypertension, the coexistence of type 2 diabetes (56.06% vs 43.94%), coronary heart disease (65.71% vs 34.29%), poststroke syndrome (68.75% vs 31.25%) and chronic kidney diseases (77.78% vs 22.22%) was significantly higher, while the coexistence of hepatitis B infection (13.04% vs 86.96%) was significantly lower than in COVID-19 patients without hypertension. Computed tomography (CT) chest scans show that COVID-19 patients with hypertension have higher rates of pleural effusion than those without hypertension (56.60% vs 43.40%). In addition, the levels of blood glucose [5.80 (IQR, 5.05-7.50) vs 5.39 (IQR, 4.81-6.60)], erythrocyte sedimentation rate (ESR) [28 (IQR, 17.1-55.6) vs 21.8 (IQR, 11.5-44.1), P=0.008], C-reactive protein (CRP) [17.92 (IQR, 3.11-46.6) vs 3.15 (IQR, 3.11-23.4), P=0.013] and serum amyloid A (SAA) [99.28 (IQR, 8.85-300) vs 15.97 (IQR, 5.97-236.1), P=0.005] in COVID-19 patients with hypertension were significantly higher than in patients without hypertension. It is common for patients with COVID-19 to have the coexistence of hypertension, type 2 diabetes, coronary heart disease and so on, which may exacerbate the severity of COVID-19. Therefore, optimal management of hypertension and other comorbidities is essential for better clinical outcomes.	no

2021	Type I interferon autoantibodies are associated with systemic immune alterations in patients with COVID-19.	Neutralizing autoantibodies against type I interferons (IFNs) have been found in some patients with critical coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, the prevalence of these antibodies, their longitudinal dynamics across the disease severity scale, and their functional effects on circulating leukocytes remain unknown. Here, in 284 patients with COVID-19, we found type I IFN–specific autoantibodies in peripheral blood samples from 19% of patients with critical disease and 6% of patients with severe disease. We found no type I IFN autoantibodies in individuals with moderate disease. Longitudinal profiling of over 600,000 peripheral blood mononuclear cells using multiplexed single-cell epitope and transcriptome sequencing from 54 patients with COVID-19 and 26 non–COVID-19 controls revealed a lack of type I IFN–stimulated gene (ISG-I) responses in myeloid cells from patients with critical disease. This was especially evident in dendritic cell populations isolated from patients with critical disease producing type I IFN–specific autoantibodies. Moreover, we found elevated expression of the inhibitory receptor leukocyte-associated immunoglobulin-like receptor 1 (LAIR1) on the surface of monocytes isolated from patients with critical disease early in the disease course. LAIR1 expression is inversely correlated with ISG-I expression response in patients with COVID-19 but is not expressed in healthy controls. The deficient ISG-I response observed in patients with critical COVID-19 with and without type I IFN–specific autoantibodies supports a unifying model for disease pathogenesis involving ISG-I suppression through convergent mechanisms.	no
2021	Association Between S100b Levels and COVID-19 Pneumonia: A Case Control Study.	Extracellular S100b effects are mediated by the receptor for advanced glycation end products (RAGE), which is the S100b membrane receptor. RAGE belongs to the immunoglobulin superfamily of cell surface molecules and serves as a multiligand receptor and is expressed in high abundance by alveolar type I (AT-I) cells in adult pulmonary tissue. This study aimed to provide an insight into the association between the severity of COVID-19 disease and serum S100b levels during admission to the emergency department (ED). A total of 64 patients (34 mild cases; 30 severe cases) were diagnosed with COVID-19 pneumonia and 30 healthy volunteers were admitted to study. Serum S100b levels were measured by using enzymle linked immunoassay method from blood serum samples. Serum S100b levels showed a significantly higher mean value in mild and severe disease cohorts than in healthy controls ($p=0.036$ and $p=0.028$ respectively). Receiver operating characteristic (ROC) analysis indicated greater area under the curve (AUC) for serum S100b levels of the COVID-19 patients (AUC=0.663, 95% CI=0.541-0.785; $p=0.014$). In addition, serum S100b concentration was measured as 151.7 ng/ml at 79.3% sensitivity and 51.7% specificity ($p=0.014$). Serum S100b protein levels can serve as a valuable clinical marker in establishing diagnosis of patients. Though not useful in identifying different stages of COVID-19 infection, serum S100b concentration along with other known markers can be utilized to reliably predict clinical severity along with other clinical parameters.	no

2021	Cardiac pathology 6 months after hospitalization for COVID-19 and association with the acute disease severity.	Coronavirus disease 2019 (COVID-19) may cause myocardial injury and myocarditis, and reports of persistent cardiac pathology after COVID-19 have raised concerns of long-term cardiac consequences. We aimed to assess the presence of abnormal cardiovascular resonance imaging (CMR) findings in patients recovered from moderate-to-severe COVID-19, and its association with markers of disease severity in the acute phase. Fifty-eight (49%) survivors from the prospective COVID MECH study, underwent CMR median 175 [IQR 105-217] days after COVID-19 hospitalization. Abnormal CMR was defined as left ventricular ejection fraction (LVEF) <50% or myocardial scar by late gadolinium enhancement. CMR indices were compared to healthy controls (n = 32), and to circulating biomarkers measured during the index hospitalization. Abnormal CMR was present in 12 (21%) patients, of whom 3 were classified with major pathology (scar and LVEF <50% or LVEF <40%). There was no difference in the need of mechanical ventilation, length of hospital stay, and vital signs between patients with vs without abnormal CMR after 6 months. Severe acute respiratory syndrome coronavirus 2 viremia and concentrations of inflammatory biomarkers during the index hospitalization were not associated with persistent CMR pathology. Cardiac troponin T and N-terminal pro-B-type natriuretic peptide concentrations on admission, were higher in patients with CMR pathology, but these associations were not significant after adjusting for demographics and established cardiovascular disease. CMR pathology 6 months after moderate-to-severe COVID-19 was present in 21% of patients and did not correlate with severity of the disease. Cardiovascular biomarkers during COVID-19 were higher in patients with CMR pathology, but with no significant association after adjusting for confounders. COVID MECH Study ClinicalTrials.gov Identifier: NCT04314232.	no
2021	Risk factors for mortality in patients over 70 years old with COVID-19 in Wuhan at the early break: retrospective case series.	Elderly patients with COVID-19 were shown to have a high case-fatality rate. We aimed to explore the risk factors associated with death in patients over 70 years old (yr). In this retrospective study, we enrolled consecutively hospitalized patients over 70 yr with COVID-19 between January 20 and February 15, 2020 in Renmin Hospital of Wuhan University. Epidemiological, demographic, and clinical data were collected. Clinical subtypes, including mild, moderate, severe, and critical types, were used to evaluate the severity of disease. Patients were classified into two groups: survivor and non-survivor groups. Clinical data were compared between the two groups. Univariable and multivariable Cox regression methods were used to explore the risk factors. A total of 147 patients were enrolled. The case-fatality rate was 28.6%. Multivariable Cox proportional hazard regression showed that clinical subtypes, including the severe type (HR = 2.983, 95% CI: 1.231-7.226, P = 0.016) and the critical type (HR = 3.267, 95%CI: 1.009-10.576, P = 0.048), were associated with increasing risk of death when compared with the general type. Blood urea nitrogen greater than 9.5 mmol/L (HR = 2.805, 95% CI: 1.141-6.892, P = 0.025) on admission was an independent risk factor for death among laboratory findings. The patients over 70 yr with COVID-19 had a high case-fatality rate. The risk factors, including clinical subtypes and blood urea nitrogen greater than 9.5 mmol/L, could help physicians to identify elderly patients with poor clinical outcomes at an early stage.	no

2021	Clinical characteristics and ABO blood groups in COVID-19 patients, Saudi Arabia.	This study assessed the proportion of ABO blood groups and clinical characteristics among Saudi patients with coronavirus disease 2019 (COVID-19) in Jazan, Saudi Arabia.This retrospective cohort study included 404 Saudi adults with COVID-19, confirmed by the real-time reverse transcription-polymerase chain reaction. The participants were selected randomly between July 1, 2020, and July 31, 2020, from the Health Electronic Surveillance Network system, which contains the primary data on COVID-19 infections in Jazan.Blood type O (62.4%) represented the highest proportion in COVID-19 Saudi patients followed by the other blood groups which distributed as follows: blood type A (25.5%), blood type B (10.1%), and blood type AB (2%). Men, and people aged 18-44 years, represented the higher percentage than women and those of a younger age. The majority of the patients with COVID-19 had clinical symptoms (88.4%), and the remainder (11.6%) were asymptomatic. Ninety four percent of the patients had mild COVID-19 symptoms and self-isolated at home. Only 6.4% of the cases were severe and admitted to hospital. There was no significant association between a specific ABO blood group and COVID-19 clinical symptoms (P=.950), incubation period (P=.780), disease duration (P=.430), and disease severity (P=.340). Old age and diabetes were the significant predictors of COVID-19 severity and hospital admission (P=.010).Blood group O represented the highest proportion of COVID-19 Saudi patients as it is the most common blood group in Saudi individuals in Jazan. However, no specific blood group was associated with COVID-19 severity and hospital admission. Old age and diabetes mellitus were shown to be significant predictors of severe COVID-19 and hospital admission.	yes
2021	Cardiac adipose tissue volume and IL-6 level at admission are complementary predictors of severity and short-term mortality in COVID-19 diabetic patients.	COVID-19 diabetic adults are at increased risk of severe forms irrespective of obesity. In patients with type-II diabetes, fat distribution is characterized by visceral and ectopic adipose tissues expansion, resulting in systemic inflammation, which may play a role in driving the COVID-19 cytokine storm. Our aim was to determine if cardiac adipose tissue, combined to interleukin-6 levels, could predict adverse short-term outcomes, death and ICU requirement, in COVID-19 diabetic patients during the 21 days after admission. Eighty one consecutive patients with type-II diabetes admitted for COVID-19 were included. Interleukin-6 measurement and chest computed tomography with total cardiac adipose tissue index (CATi) measurement were performed at admission. The primary outcome was death during the 21 days following admission while intensive care requirement with or without early death (ICU-R) defined the secondary endpoint. Associations of CATi and IL-6 and threshold values to predict the primary and secondary endpoints were determined. Of the enrolled patients (median age 66 years [IQR: 59-74]), 73% male, median body mass index (BMI) 27 kg/m 2 [IQR: 24-31]) 20 patients had died from COVID-19, 20 required intensive care and 41 were in conventional care at day 21 after admission. Increased CATi and IL-6 levels were both significantly related to increased early mortality (respectively OR = 6.15, p = 0.002; OR = 18.2, p < 0.0001) and ICU-R (respectively OR = 3.27, p = 0.01; OR = 4.86, p = 0.002). These associations remained significant independently of age, sex, BMI as well as troponin-T level and pulmonary lesion extension in CT. We combined CATi and IL-6 levels as a multiplicative interaction score (CATi*IL-6). The cut-point for this score was ≥ 6386 with a sensitivity of 0.90 and a specificity of 0.87 (AUC = 0.88) and an OR of 59.6 for early mortality (p < 0.0001). Cardiac adipose tissue index and IL-6 determination at admission could help physicians to better identify diabetic patients with a potentially	no

		severe and lethal short term course irrespective of obesity. Diabetic patients with high CATi at admission, a fortiori associated with high IL-6 levels could be a relevant target population to promptly initiate anti-inflammatory therapies.	
2021	Upregulation of pulmonary tissue factor, loss of thrombomodulin and immunothrombosis in SARS-CoV-2 infection.	SARS-CoV-2 infection is associated with thrombotic and microvascular complications. The cause of coagulopathy in the disease is incompletely understood. A single-center cross-sectional study including 66 adult COVID-19 patients (40 moderate, 26 severe disease), and 9 controls, performed between 04/2020 and 10/2020. Markers of coagulation, endothelial cell function [angiopoietin-1,-2, P-selectin, von Willebrand Factor Antigen (WF:Ag), von Willebrand Factor Ristocetin Cofactor, ADAMTS13, thrombomodulin, soluble Endothelial cell Protein C Receptor (sEPCR), Tissue Factor Pathway Inhibitor], neutrophil activation (elastase, citrullinated histones) and fibrinolysis (tissue-type plasminogen activator, plasminogen activator inhibitor-1) were evaluated using ELISA. Tissue Factor (TF) was estimated by antithrombin-FVIIa complex (AT/FVIIa) and microparticles-TF (MP-TF). We correlated each marker and determined its association with severity. Expression of pulmonary TF, thrombomodulin and EPCR was determined by immunohistochemistry in 9 autopsies. Comorbidities were frequent in both groups, with older age associated with severe disease. All patients were on prophylactic anticoagulants. Three patients (4.5%) developed pulmonary embolism. Mortality was 7.5%. Patients presented with mild alterations in the coagulogram (compensated state). Biomarkers of endothelial cell, neutrophil activation and fibrinolysis were elevated in severe vs moderate disease; AT/FVIIa and MP-TF levels were higher in severe patients. Logistic regression revealed an association of D -dimers, angiopoietin-1, vWF:Ag, thrombomodulin, white blood cells, absolute neutrophil count (ANC) and hemoglobin levels with severity, with ANC and vWF:Ag identified as independent factors. Notably, postmortem specimens demonstrated epithelial expression of TF in the lung of fatal COVID-19 cases with loss of	no

		thrombomodulin staining, implying in a shift towards a procoagulant state. Coagulation dysregulation has multifactorial etiology in SARS-Cov-2 infection. Upregulation of pulmonary TF with loss of thrombomodulin emerge as a potential link to immunothrombosis, and therapeutic targets in the disease. John Hopkins University School of Medicine.	

2021	Helicobacter pylori - 2021.	Összefoglaló. A Helicobacter pylori továbbra is a világ legelterjedtebb fertőzése: prevalenciája a fejlődő országokban 70-80%, a fejlett országokban csökkenő tendenciát mutat. A dél-magyarországi véradókban a prevalencia 32%-ra csökkent. A migráció a befogadó ország számára a fertőzés fokozott kockázatával jár. A szövettani diagnózisban az immunhisztokémiai vizsgálat pontosabb a hagyományos Giemsa-festésnél. A mesterséges intelligencia érzékenysége a hagyományos endoszkópiáéval összehasonlítva 87%, pontossága 86%. Az újgenerációs szekvenálással lehetséges egy biopsziás mintából több antibiotikumérzékenység meghatározása. A Helicobacter pylori kezelésének európai regisztere kimutatta, hogy 2013 és 2018 között a bizmutalapú négyes vagy a 14 napos egyidejű négyes kezelések hatásosabbak, mint a hagyományos hármas kezelés, de elterjedésük igen lassú folyamat, jelentős földrajzi különbségekkel. Az új típusú koronavírus (SARS-CoV-2) felléphet Helicobacter pylori fertőzésben is, egymás kóros hatását felerősítve. A diagnosztikai módszerek korlátozottak. Protonpumpagátlók szedése növeli a COVID-19-fertőzés kockázatát és annak súlyos kimenetelét. Előzetesen ismert peptikus fekély, vérzés, illetve antikoguláns kezelés előtt az eradikáció a vírusos fertőzés lezajlása után indokolt. A probiotikumoknak az eradikációra gyakorolt hatásáról 20, közepes minőségű metaanalízis született, így a konszenzusokban foglalt álláspontok sem egyértelműek: a jövőben ezt tisztázni kell. Orv Hetil. 2021; 162(32): 1275-1282. Summary. Helicobacter pylori is still the most widespread infection in the world: its overall prevalence is 70-80% in developing regions, but fortunately it is decreasing in the Western world. The prevalence in blood donors from South-Eastern Hungary decreased from 63% in the 1990's to 32% in 2019. Migration constitutes an increased risk of infection for the destination countries. Immunohistochemistry has proven to be more accurate in histological diagnosis than the conventional Giemsa stain. The sensitivity and accuracy of artificial intelligence as compared to videoendoscopy were 87% and 86%, respectively. The European Register on the management of Helicobacter pylori infection revealed that concomitant quadruple and 14-day bismuth-based therapies are more efficient than triple combinations, although their incorporation in practice is a long-lasting process, with large geographical variations. The novel type of coronavirus (SARS-CoV-2) can also occur in Helicobacter pylori-infected patients, mutually enhancing their pathogenetic effects. Diagnostic possibilities are limited in this setting. The use of proton pump inhibitors increases the risk of viral infection and the severity of the disease. Eradication treatment seems justified in patients with previously known peptic ulcers or gastrointestinal bleeding, or before starting anticoagulant treatment, but must be postponed after resolution of viral infection. The effect of probiotics on eradication was addressed by 20, medium-to-low quality meta-analyses and so, the recommendations of the guidelines are equivocal, which must be clarified in the future with higher quality studies. Orv Hetil. 2021; 162(32): 1275-1282.	no

2021	Monocytes and Macrophages in COVID-19.	COVID-19 is a contagious viral disease caused by SARS-CoV-2 that led to an ongoing pandemic with massive global health and socioeconomic consequences. The disease is characterized primarily, but not exclusively, by respiratory clinical manifestations ranging from mild common cold symptoms, including cough and fever, to severe respiratory distress and multi-organ failure. Macrophages, a heterogeneous group of yolk-sac derived, tissue-resident mononuclear phagocytes of complex ontogeny present in all mammalian organs, play critical roles in developmental, homeostatic and host defense processes with tissue-dependent plasticity. In case of infection, they are responsible for early pathogen recognition, initiation and resolution of inflammation, as well as repair of tissue damage. Monocytes, bone-marrow derived blood-resident phagocytes, are recruited under pathological conditions such as viral infections to the affected tissue to defend the organism against invading pathogens and to aid in efficient resolution of inflammation. Given their pivotal function in host defense and the potential danger posed by their dysregulated hyperinflammation, understanding monocyte and macrophage phenotypes in COVID-19 is key for tackling the disease's pathological mechanisms. Here, we outline current knowledge on monocytes and macrophages in homeostasis and viral infections and summarize concepts and key findings on their role in COVID-19. While monocytes in the blood of patients with moderate COVID-19 present with an inflammatory, interferon-stimulated gene (ISG)-driven phenotype, cellular dysfunction epitomized by loss of HLA-DR expression and induction of S100 alarmin expression is their dominant feature in severe disease. Pulmonary macrophages in COVID-19 derived from infiltrating inflammatory monocytes are in a hyperactivated state resulting in a detrimental loop of pro-inflammatory cytokine release and recruitment of cytotoxic effector cells thereby exacerbating tissue damage at the site of infection.	no
2021	Genetic Screening for TLR7 Variants in Young and Previously Healthy Men With Severe COVID-19.	Loss-of-function TLR7 variants have been recently reported in a small number of males to underlie strong predisposition to severe COVID-19. We aimed to determine the presence of these rare variants in young men with severe COVID-19. We prospectively studied males between 18 and 50 years-old without predisposing comorbidities that required at least high-flow nasal oxygen to treat COVID-19. The coding region of TLR7 was sequenced to assess the presence of potentially deleterious variants. TLR7 missense variants were identified in two out of 14 patients (14.3%). Overall, the median age was 38 (IQR 30-45) years. Both variants were not previously reported in population control databases and were predicted to be damaging by in silico predictors. In a 30-year-old patient a maternally inherited variant [c.644A>G; p.(Asn215Ser)] was identified, co-segregating in his 27-year-old brother who also contracted severe COVID-19. A second variant [c.2797T>C; p.(Trp933Arg)] was found in a 28-year-old patient, co-segregating in his 24-year-old brother who developed mild COVID-19. Functional testing of this variant revealed decreased type I and II interferon responses in peripheral mononuclear blood cells upon stimulation with the TLR7 agonist imiquimod, confirming a loss-of-function effect. This study supports a rationale for the genetic screening for TLR7 variants in young men with severe COVID-19 in the absence of other relevant risk factors. A diagnosis of TLR7 deficiency could not only inform on treatment options for the patient, but also enables pre-symptomatic testing of at-risk male relatives with the possibility of instituting early preventive and therapeutic interventions.	yes

2021	The association of ABO blood group with the asymptomatic COVID-19 cases in India.	The COVID-19 pandemic resulted in multiple waves of infection worldwide. The large variations in case fatality rate among different geographical regions suggest that the human susceptibility against this virus varies substantially. Several studies from different parts of the world showed a significant association of ABO blood group and COVID-19 susceptibility. It was demonstrated that individuals with blood group O are at the lower risk of coronavirus infection. To establish the association of ABO blood group in SARS-CoV-2 susceptibility, we for the first time analysed SARS-CoV-2 neutralising antibodies among 509 individuals, collected from three major districts of Eastern Uttar Pradesh region of India. Interestingly, we found neutralising antibodies in a significantly higher percentage of people with blood group AB (0.36) followed by B (0.31), A (0.22) and lowest in people with blood group O (0.11). We further estimated that people with blood group AB are at comparatively higher risk of infection than other blood groups. Thus, among the asymptomatic SARS-CoV-2 recovered people blood group AB has highest, whilst individuals with blood group O has lowest risk of infection.	yes
2021	Early Prediction of COVID-19 Ventilation Requirement and Mortality from Routinely Collected Baseline Chest Radiographs, Laboratory, and Clinical Data with Machine Learning.	Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China, in late 2019 and created a global pandemic that overwhelmed healthcare systems. COVID-19, as of July 3, 2021, yielded 182 million confirmed cases and 3.9 million deaths globally according to the World Health Organization. Several patients who were initially diagnosed with mild or moderate COVID-19 later deteriorated and were reclassified to severe disease type. The aim is to create a predictive model for COVID-19 ventilatory support and mortality early on from baseline (at the time of diagnosis) and routinely collected data of each patient (CXR, CBC, demographics, and patient history). Four common machine learning algorithms, three data balancing techniques, and feature selection are used to build and validate predictive models for COVID-19 mechanical requirement and mortality. Baseline CXR, CBC, demographic, and clinical data were retrospectively collected from April 2, 2020, till June 18, 2020, for 5739 patients with confirmed PCR COVID-19 at King Abdulaziz Medical City in Riyadh. However, of those patients, only 1508 and 1513 have met the inclusion criteria for ventilatory support and mortalilty endpoints, respectively. In an independent test set, ventilation requirement predictive model with top 20 features selected with reliefF algorithm from baseline radiological, laboratory, and clinical data using support vector machines and random undersampling technique attained an AUC of 0.87 and a balanced accuracy of 0.81. For mortality endpoint, the top model yielded an AUC of 0.83 and a balanced accuracy of 0.80 using all features with balanced random forest. This indicates that with only routinely collected data our models can predict the outcome with good performance. The predictive ability of combined data consistently outperformed each data set individually for intubation and mortality. For the ventilator support, chest X-ray severity annotations alone performed better than comorbidity, complete blood count, age, or gender with an AUC of 0.85 and balanced accuracy of 0.79. For mortality, comorbidity alone achieved an AUC of 0.80 and a balanced accuracy of 0.72, which is higher than models that use either chest radiograph, laboratory, or demographic features only. The experimental results demonstrate the practicality of the proposed COVID-19 predictive tool for hospital resource planning and patients' prioritization in the current COVID-19 pandemic crisis.	yes

2021	Advanced glycation end products (AGEs) and its receptor, RAGE, modulate age-dependent COVID-19 morbidity and mortality. A review and hypothesis.	Coronavirus Disease 2019 (COVID-19), caused by the novel virus SARS-CoV-2, is often more severe in older adults. Besides age, other underlying conditions such as obesity, diabetes, high blood pressure, and malignancies, which are also associated with aging, have been considered risk factors for COVID-19 mortality. A rapidly expanding body of evidence has brought up various scenarios for these observations and hyperinflammatory reactions associated with COVID-19 pathogenesis. Advanced glycation end products (AGEs) generated upon glycation of proteins, DNA, or lipids play a crucial role in the pathogenesis of age-related diseases and all of the above-mentioned COVID-19 risk factors. Interestingly, the receptor for AGEs (RAGE) is mainly expressed by type 2 epithelial cells in the alveolar sac, which has a critical role in SARS-CoV-2-associated hyper inflammation and lung injury. Here we discuss our hypothesis that AGEs, through their interaction with RAGE amongst other molecules, modulates COVID-19 pathogenesis and related comorbidities, especially in the elderly.	no
2021	Analyses of ABO blood groups with susceptibility and symptomatic variations of COVID-19 infection, a questionnaire-based survey.	Coronavirus disease 2019 (COVID-19) is a novel respiratory disease that has led to a global pandemic and created a havoc. The COVID-19 disease severity varies among individuals, depending on fluctuating symptoms. Many infectious diseases such as hepatitis B and dengue hemorrhagic fever have been associated with ABO blood groups. The aim of this study was to explore whether ABO blood groups might serve as a risk or a protective factor for COVID-19 infection. Moreover, the symptomatic variations of COVID-19 infection among the individuals with different blood groups were also analyzed. An online questionnaire-based survey was conducted in which 305 partakers were included, who had successfully recovered from coronavirus infection. The ABO blood groups of 1294 healthy individuals were also taken as a control. The results of the current study demonstrated that antibody A containing blood groups (blood group B, p-value: 0.049 and blood group O, p-value: 0.289) had a protective role against COVID-19 infection. The comparison of symptomatic variations among COVID-19-infected subjects showed that blood group O subjects had lower chances of experiencing severe symptoms relating to respiratory distress, while subjects with AB blood group were more prone to develop symptoms, but the differences in both groups were found to be statistically non-significant. In conclusion, subjects who do not have anti-A antibodies in their serum (i.e., subjects with group A and AB) are more likely to be infected with COVID-19. The current data showed that there was no significant association of signs and symptoms variations of COVID-19 infection among individuals with different blood groups.	yes

2021	Severe COVID-19 Is Characterized by an Impaired Type I Interferon Response and Elevated Levels of Arginase Producing Granulocytic Myeloid Derived Suppressor Cells.	COVID-19 ranges from asymptomatic in 35% of cases to severe in 20% of patients. Differences in the type and degree of inflammation appear to determine the severity of the disease. Recent reports show an increase in circulating monocytic-myeloid-derived suppressor cells (M-MDSC) in severe COVID 19 that deplete arginine but are not associated with respiratory complications. Our data shows that differences in the type, function and transcriptome of granulocytic-MDSC (G-MDSC) may in part explain the severity COVID-19, in particular the association with pulmonary complications. Large infiltrates by Arginase 1 + G-MDSC (Arg + G-MDSC), expressing NOX-1 and NOX-2 (important for production of reactive oxygen species) were found in the lungs of patients who died from COVID-19 complications. Increased circulating Arg + G-MDSC depleted arginine, which impaired T cell receptor and endothelial cell function. Transcriptomic signatures of G-MDSC from patients with different stages of COVID-19, revealed that asymptomatic patients had increased expression of pathways and genes associated with type I interferon (IFN), while patients with severe COVID-19 had increased expression of genes associated with arginase production, and granulocyte degranulation and function. These results suggest that asymptomatic patients develop a protective type I IFN response, while patients with severe COVID-19 have an increased inflammatory response that depletes arginine, impairs T cell and endothelial cell function, and causes extensive pulmonary damage. Therefore, inhibition of arginase-1 and/or replenishment of arginine may be important in preventing/treating severe COVID-19.	no
2021	High triglyceride to HDL-cholesterol ratio as a biochemical marker of severe outcomes in COVID-19 patients.	Coronavirus disease 2019 (COVID-19) patients with severe complications have shown comorbidities with cardiovascular-disease, hypertension and type 2 diabetes mellitus; clinical disorders that share the common metabolic alterations of insulin resistance and dyslipidaemia. A high triglyceride to high density lipoprotein cholesterol (Tg/HDL c) ratio has been associated with reduced insulin sensitivity, metabolic syndrome and adverse cardiovascular events. Our aim in this study was to determine the association between different components of the lipid profile and particularly the Tg/HDL c ratio with severe complications like the requirement of invasive mechanical ventilation in COVID-19 patients. We collected demographic, clinical and biochemical data to conduct a cohort study in 43 adult patients with confirmed COVID-19 diagnosis by quantitative polymerase chain reaction (qPCR) at baseline and in the subsequent 15 days. Patients were subjected to a very similar treatment scheme with the JAK1/2 inhibitor ruxolitinib. Descriptive statistics, variable association and logistic regression were applied to identify predictors of disease severity among elements and calculations from the lipid profile. Patients were aged 57 ± 14 years; 55.8% were male from which 75% required hospitalization and 44.2% were female who 58% were hospitalized. The most common comorbidities were type 2 diabetes mellitus (58%) and hypertension (40%). Hospitalized and critical care patients showed lower HDL c blood levels and increased Tg/HDL c ratio than those with outpatient management and mild/asymptomatic COVID-19. Tg/HDL c ratio correlated with variables of disease severity such as lactate dehydrogenase (LDH) levels ($r = 0.356$; $p < 0.05$); National Early Warning Score 2 (NEWS 2) ($r = 0.495$; $p < 0.01$); quick sequential organ failure assessment (qSOFA) ($r = 0.538$; $p < 0.001$); increased need of oxygen support ($r = 0.447$; $p < 0.01$) and requirement of mechanical ventilation ($r = 0.378$; $p < 0.05$). Tg/HDL c ratio had a negative correlation with partial oxygen saturation/fraction of inspired oxygen	no

		(SaO 2/FiO2) ratio (r = -0.332;p < 0.05). Linear regression analysis showed that Tg/HDL c ratio can predict increases in inflammatory factors like LDH (p < 0.01); ferritin (p < 0.01) and D-dimer (p < 0.001). Logistic regression model indicated that ≥7.45 Tg/HDL c ratio predicts requirement of invasive mechanical ventilation (OR 11.815, CI 1.832-76.186, p < 0.01). The Tg/HDLc ratio can be used as an early biochemical marker of COVID-19 severe prognosis with requirement of invasive mechanical ventilation.	
2021	The potential role of neopterin in Covid-19: a new perspective.	Neopterin (NPT) is a member of pteridines group, synthesized by macrophages when stimulated by interferon gamma (INF-γ). NPT is regarded as a macrophage stimulation indicator, marker of cellular immune activation and T helper 1 (Th1) type 1 immune response. Here, we aimed to provide a view point on the NPT features and role in Covid-19. Serum NPT level is regarded as an independent prognostic factor for Covid-19 severity, with levels starting to increase from the 3rd day of SARS-CoV-2 infection, being associated with severe dyspnea, longer hospitalization period and complications. Also, early raise of NPT reflects monocytes/macrophages activation before antibody immune response, despite the NPT level may also remain high in Covid-19 patients or at the end of incubation period before the onset of clinical symptoms. On the other hand, NPT attenuates the activity of macrophage foam cells and is linked to endothelial inflammation through inhibition of adhesion molecules and monocytes migration. However, NPT also exerts anti-inflammatory and antioxidant effects by suppressing NF-κB signaling and NLRP3 inflammasomes. NPT can be viewed as a protective compensatory mechanism to counterpoise hyper-inflammation, oxidative stress, and associated organ damage.	no

2021	Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: A prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine.	Dialysis and kidney transplant patients are vulnerable populations for COVID-19 related disease and mortality. We conducted a prospective study exploring the eight week time course of specific cellular (interferon-γ release assay and flow cytometry) or/and humoral immune responses (ELISA) to SARS-CoV-2 boost vaccination in more than 3100 participants including medical personnel, dialysis patients and kidney transplant recipients using mRNA vaccines BNT162b2 or mRNA-1273. SARS-CoV-2-vaccination induced seroconversion efficacy in dialysis patients was similar to medical personnel (> 95%), but markedly impaired in kidney transplant recipients (42%). T-cellular immunity largely mimicked humoral results. Major risk factors of seroconversion failure were immunosuppressive drug number and type (belatacept, MMF-MPA, calcineurin-inhibitors) as well as vaccine type (BNT162b2 mRNA). Seroconversion rates induced by mRNA-1273 compared to BNT162b2 vaccine were 97% to 88% ($p < 0.001$) in dialysis and 49% to 26% in transplant patients, respectively. Specific IgG directed against the new binding domain of the spike protein (RDB) were significantly higher in dialysis patients vaccinated by mRNA-1273 (95%) compared to BNT162b2 (85%, $p < 0.001$). Vaccination appeared safe and highly effective demonstrating an almost complete lack of symptomatic COVID-19 disease after boost vaccination as well as ceased disease incidences during third pandemic wave in dialysis patients. Dialysis patients exhibit a remarkably high seroconversion rate of 95% after boost vaccination, while humoral response is impaired in the majority of transplant recipients. Immunosuppressive drug number and type as well as vaccine type (BNT162b2) are major determinants of seroconversion failure in both dialysis and transplant patients suggesting immune monitoring and adaption of vaccination protocols.	no
2021	Soluble HLA-G is upregulated in serum of patients with severe COVID-19.	Soluble HLA-G (sHLA-G) molecules are considered potent immunomodulators, and their dysregulated expression has been implicated in several pathological conditions, including coronavirus disease 19 (COVID-19). Therefore, a case-control study (103 COVID-19 patients and 105 controls) was performed to determine sHLA-G role in severity of COVID-19. Results revealed that median levels of sHLA-G were significantly increased in serum of patients compared to controls (19.3 vs. 12.7 ng/mL; $p < 0.001$). When patients and controls were stratified by age group, gender, body mass index, chronic disease, or ABO and Rh blood groups, the sHLA-G level did not show a significant difference in each stratum. Logistic regression analysis demonstrated that the up-regulated expression of sHLA-G was associated with an elevated risk of developing COVID-19. Receiver operating characteristic curve analysis showed that sHLA-G was a very good predictor of COVID-19, and at a cut-off value of 15.4 ng/mL, the sensitivity and specificity of sHLA-G were 79.6 and 79.0%, respectively. Spearman rank correlation analysis revealed that sHLA-G was positively correlated with age, erythrocyte sedimentation rate, white blood cell count, and random blood glucose, while a negative correlation was recorded with vitamin D. In conclusion, up-regulated expression of sHLA-G was indicated in patients with severe COVID-19.	no

2021	COVID-19 in Children: Expressions of Type I/II/III Interferons, TRIM28, SETDB1, and Endogenous Retroviruses in Mild and Severe Cases.	Children with the new coronavirus disease 2019 (COVID-19) have milder symptoms and a better prognosis than adult patients. Several investigations assessed type I, II, and III interferon (IFN) signatures in SARS-CoV-2 infected adults, however no data are available for pediatric patients. TRIM28 and SETDB1 regulate the transcription of multiple genes involved in the immune response as well as of human endogenous retroviruses (HERVs). Exogenous viral infections can trigger the activation of HERVs, which in turn can induce inflammatory and immune reactions. Despite the potential cross-talks between SARS-CoV-2 infection and TRIM28, SETDB1, and HERVs, information on their expressions in COVID-19 patients is lacking. We assessed, through a PCR real time Taqman amplification assay, the transcription levels of six IFN-I stimulated genes, IFN-II and three of its sensitive genes, three IFN-lIIs, as well as of TRIM28, SETDB1, pol genes of HERV-H, -K, and -W families, and of env genes of Syncytin (SYN)1, SYN2, and multiple sclerosis-associated retrovirus (MRSV) in peripheral blood from COVID-19 children and in control uninfected subjects. Higher expression levels of IFN-I and IFN-II inducible genes were observed in 36 COVID-19 children with mild or moderate disease as compared to uninfected controls, whereas their concentrations decreased in 17 children with severe disease and in 11 with multisystem inflammatory syndrome (MIS-C). Similar findings were found for the expression of TRIM-28, SETDB1, and every HERV gene. Positive correlations emerged between the transcriptional levels of type I and II IFNs, TRIM28, SETDB1, and HERVs in COVID-19 patients. IFN-III expressions were comparable in each group of subjects. This preserved induction of IFN-λs could contribute to the better control of the infection in children as compared to adults, in whom IFN-III deficiency has been reported. The upregulation of IFN-I, IFN-II, TRIM28, SETDB1, and HERVs in children with mild symptoms, their declines in severe cases or with MIS-C, and the positive correlations of their transcription in SARS-CoV-2-infected children suggest that they may play important roles in conditioning the evolution of the infection.	no
2021	Outcomes of renal replacement therapy in the critically ill with COVID-19.	To describe outcomes of critically ill patients with COVID-19, particularly the association of renal replacement therapy to mortality. A single-center prospective observational study was carried out. ICU of a tertiary care center. Consecutive adults with COVID-19 admitted to the ICU. Renal replacement therapy. Demographic data, medical history, illness severity, type of oxygen therapy, laboratory data and use of renal replacement therapy to generate a logistic regression model describing independent risk factors for mortality. Of the total of 166 patients, 51% were mechanically ventilated and 26% required renal replacement therapy. The overall hospital mortality rate was 36%, versus 56% for those requiring renal replacement therapy, and 68% for those with both mechanical ventilation and renal replacement therapy. The logistic regression model identified four independent risk factors for mortality: age (adjusted OR 2.8 [95% CI 1.8-4.4] for every 10-year increase), mechanical ventilation (4.2 [1.7-10.6]), need for continuous venovenous hemofiltration (2.3 [1.3-4.0]) and C-reactive protein (1.1 [1.0-1.2] for every 10mg/L increase). In our cohort, acute kidney injury requiring renal replacement therapy was associated to a high mortality rate similar to that associated to the need for mechanical ventilation, while multiorgan failure necessitating both techniques implied an extremely high mortality risk.	no

2021	ABO phenotype and clinical correlates of COVID-19 severity in hospitalized patients.	This study investigates the association between ABO blood phenotype and COVID-19 severity, measured by intensive care unit admission, need for intubation, hospitalization length and death. It further explores clinical predictors of COVID-19 severity within a primarily Hispanic demographic in San Diego County. We retrospectively reviewed 942 total patients, 473 with available blood type, hospitalized at five Scripps Health hospitals with COVID-19. No significant association was found between ABO phenotype and COVID-19 severity on multivariate analysis, while a diagnosis of anemia and male sex was associated with all severity outcomes on exploratory analysis. Our results provide relevant clinical correlates of COVID-19 severity and help better elucidate the association between ABO phenotype and COVID-19.	yes
2021	High Neutrophil/Lymphocyte Ratios in Symptomatic Pediatric COVID-19 Patients.	To investigate the symptoms and laboratory results of children hospitalised with the diagnosis of COVID-19, aiming to reveal the characteristics of symptomatic cases. A descriptive cross-sectional study. Department of Pediatrics, Kastamonu Training and Research Hospital, Kastamonu, Turkey from March to December 2020. Seventy-nine children, hospitalised with the diagnosis of COVID-19, were included in the study and were divided into two groups as symptomatic and asymptomatic. The demographic data, laboratory results and clinics of the patients of the two groups were compared. The mean age of participants was 10.43 ± 5.91 (0-17) years, and 57% (n=45) of them were girls. Five patients in the symptomatic group had comorbidities (2 allergic asthma, cerebral palsy, type-1 diabetes mellitus and anorexia nervosa). The most common symptom was fever (36.7%, n=29). It was noteworthy that everyone with an NLR >3.13 (high-NLR) was symptomatic. Significantly more patients in the high-NLR group were symptomatic compared with the low-NLR group (p=0.005). On the other hand, symptomatic children had significantly higher levels of C-reactive protein (2.8 (IQR: 1.2-10.0) mg/L vs. 1.4 (IQR: 0.4-2.0) mg/L, p=0.011); and procalcitonin (0.05 (IQR: 0.02-0.10) ng/mL vs. 0.01 (IQR: 0.00-0.03) ng/mL, p<0.001) than those without symptoms. One of the children with cerebral palsy died from pneumonia during the study. C-reactive protein, procalcitonin and NLR levels were found to be significantly higher in symptomatic children. NLR can be suggested as a potential marker associated with disease severity in COVID-19 patients, which needs to be supported by other studies. Key Words: COVID-19, Children, Neutrophil / lymphocyte ratio, C-reactive protein, Procalcitonin.	no
2021	Blood system ABO antigens as risk factor for severity of SARS-CoV-2 infection.	Whether there is an influence of the ABO blood system on SARS-CoV-2 infection is unknown. To analyze if there is an association between the ABO system antigens and susceptibility to and severity of SARS-CoV-2 infection. The frequency of ABO system antigens was compared in 73 confirmed cases of SARS-CoV-2 infection and 52 clinically healthy donors. Infection severity was assessed by comparing the frequency of antigens by disease severity and mortality. The risk of suffering from SARS-CoV-2 infection increases in subjects with A vs. non-A antigen (OR = 1.45; 95 % CI: 1.061-1.921). Blood phenotype O reduces the risk of SARS-CoV-2 infection (OR = 0.686; 95 % CI: 0.522-0.903). No differences were found regarding disease severity. In critically ill patients, the risk of mortality increased in subjects with A vs. non-A antigen (OR = 3.34; 95 % CI: 1.417-8.159). Blood group A is a risk factor for SARS-CoV-2 infection, but not for disease severity, although in critically ill patients it is a risk factor for mortality.	yes

2021	The Impact of COVID-19 Pandemic on Prevalence of Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes: A Single-Centre Study in Central Pennsylvania.	We conducted this study to investigate whether the COVID-19 pandemic impacted the rate of DKA and previously identified risk factors in children presenting with T1D. We performed an extension of a retrospective analysis of all paediatric patients (age ≤ 18) newly diagnosed with T1D within a tertiary care referral centre between 01/01/2017 and 09/14/2020. Demographics, insurance coverage and clinical documents 30 days before their T1D diagnosis were abstracted to assess for symptoms at diagnosis, laboratory values (blood glucose, HbA 1c , venous pH and bicarbonate) and any healthcare encounters within 30 days of their diagnosis of T1D. 412 patients with T1D [171 F:241 M; 370 pre-COVID era:42 post-COVID era] were included. The percentages of DKA diagnoses at admission were very similar between the pre-COVID and post-COVID groups (47% vs. 48%), as were the severity (13% vs. 14% mild DKA; 33% vs. 31% moderate or severe DKA). There were no fluctuations in the rate of DKA among paediatric patients newly diagnosed with T1D throughout the coronavirus pandemic in central Pennsylvania.	no
2021	Does ABO Blood Groups Affect Outcomes in Hospitalized COVID-19 Patients?	Blood group type A has been associated with increased susceptibility for coronavirus disease 2019 (COVID-19) infection when compared to group O. The aim of our study was to examine outcomes in hospitalized COVID-19 patients among blood groups A and O. This is an observational study. Kruskal-Wallis and Chi-square tests were used to compare continuous and categorical variables. Multivariable logistic regression models were used to examine association of blood groups with rates of mortality and severity of disease. All adult patients (> 18 years) admitted with COVID-19 infection between March 1, 2020 and March 10, 2021 at a large community hospital in Northeast Georgia were included. We compared mortality, severity of disease (use of mechanical ventilation, vasopressor, and acute renal failure), rates of venous thromboembolism and inflammatory markers between the blood groups. We used multivariable logistic regression model to adjust for demographical and clinical characteristics, use of COVID-19 medications and severity. A total of 3,563 of 5,204 admitted patients had information on blood groups. Of these, 1,301 (36.5%) were group A, 377 (10.6 %) were group B, 133 (3.7%) were group AB and 1,752 (49.2%) were group O. On adjusted analysis, there were no significant differences in rates of intensive care unit (ICU) admissions, mechanical ventilation, vasopressors, acute renal failure, venous thromboembolism and readmission rate between the blood groups A and O. In-hospital mortality was also not statistically different among the blood groups A and O (17.5% vs. 20.1%; P = 0.07). On adjusted analysis, in-hospital mortality was not lower in blood groups O (odds ratio (OR): 1.06; 95% confidence interval (CI): 0.80 - 1.40, P = 0.70). Once hospitalized with COVID-19 infection, blood groups A and O are not associated with increased severity or in-hospital mortality.	yes

2021	Assessment and Management of Diabetic Patients During the COVID-19 Pandemic.	COVID-19 has become a great challenge across the globe, particularly in developing and densely populated countries, such as India. COVID-19 is extremely infectious and is transmitted via respiratory droplets from infected persons. DM, hypertension, and cardiovascular disease are highly prevalent comorbidities associated with COVID-19. It has been observed that COVID-19 is associated with high blood-glucose levels, mainly in people with type 2 diabetes mellitus (T2DM). Several studies have shown DM to be a significant risk factor affecting the severity of various kinds of infection. Dysregulated immunoresponse found in diabetic patients plays an important role in exacerbating severity. DM is among the comorbidities linked with mortality and morbidity in COVID-19 patients. Chronic conditions like obesity, cardiovascular disorders, and hypertension, together with changed expression of ACE2, dysregulated immunoresponse, and endothelial dysfunction, may put diabetic patients at risk of greater COVID-19 severity. Therefore, it is important to study specific characteristics of COVID-19 in diabetic people and treat these comorbidities along with COVID-19 infection, mainly among old individuals who are already suffering from serious and critical infections. This review will be helpful in understanding the mechanisms involved in COVID-19 and DM, the role of ACE2 in COVID-19 pathogenesis, management of DM, and associated complications in COVID-19 patients.	no
2021	Discovering common pathogenetic processes between COVID-19 and diabetes mellitus by differential gene expression pattern analysis.	Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the newly discovered coronavirus, SARS-CoV-2. Increased severity of COVID-19 has been observed in patients with diabetes mellitus (DM). This study aimed to identify common transcriptional signatures, regulators and pathways between COVID-19 and DM. We have integrated human whole-genome transcriptomic datasets from COVID-19 and DM, followed by functional assessment with gene ontology (GO) and pathway analyses. In peripheral blood mononuclear cells (PBMCs), among the upregulated differentially expressed genes (DEGs), 32 were found to be commonly modulated in COVID-19 and type 2 diabetes (T2D), while 10 DEGs were commonly downregulated. As regards type 1 diabetes (T1D), 21 DEGs were commonly upregulated, and 29 DEGs were commonly downregulated in COVID-19 and T1D. Moreover, 35 DEGs were commonly upregulated in SARS-CoV-2 infected pancreas organoids and T2D islets, while 14 were commonly downregulated. Several GO terms were found in common between COVID-19 and DM. Prediction of the putative transcription factors involved in the upregulation of genes in COVID-19 and DM identified RELA to be implicated in both PBMCs and pancreas. Here, for the first time, we have characterized the biological processes and pathways commonly dysregulated in COVID-19 and DM, which could be in the next future used for the design of personalized treatment of COVID-19 patients suffering from DM as comorbidity.	no

2021	Assessment of severity and mortality of COVID-19 with anti-A1 and anti-B IgM isohaemagglutinins, a reflection of the innate immune status.	The relationship between the innate immune system that creates the polysaccharide antibody response and COVID-19 is not fully understood. In this study, it was aimed to determine the predictive values of isohaemagglutinins in COVID-19 severity/mortality. Approximately 15 440 patients diagnosed with COVID-19 were examined, and a total of 286 patients with anti-B and anti-A1 IgM isohaemagglutinins test results were randomly enrolled in the study. These patients were stratified into two groups according to anti-A1 (n: 138 blood type B or O) and anti-B (n: 148 blood type A) IgM isohaemagglutinins. Anti-A1 or/and anti-B IgM, biochemical parameters, symptoms, chronic diseases, hospitalisation status, intubation status, admission to intensive care unit (ICU) and exitus status were recorded and evaluated for all patients. Anti-A1 IgM and anti-B IgM were significantly lower in ICU patients (7.5 ± 9.9 vs 18.0 ± 20.4 and 5.5 ± 6.3 vs 19.3 ± 33.6 titres, respectively; P < .01) and in exitus patients (3.8 ± 3.6 vs 16.7 ± 18.7 and 3.5 ± 4.7 vs 16.9 ± 29.6 titres respectively; P < .01). In the ROC analysis performed to differentiate between exitus and discharge within groups, the sensitivity of anti-B IgM and anti-A1 IgM at cut-off ≤4 was 88.9% and 79.6%, specificity 66.0% and 73.4%, and AUC 0.831 and 0.861, respectively (P < .01). Anti-A1 IgM decreased the mortality risk 0.811 times per unit while anti-B IgM decreased 0.717 times (P < .01). Anti-B and anti-A1 isohaemagglutinins, which are an expression of the innate immune system, can be used to predict the severity and mortality of COVID-19 disease.	no
2021	Type 2 Diabetes Coagulopathy Proteins May Conflict With Biomarkers Reflective of COVID-19 Severity.	Detailed proteomic analysis in a cohort of patients with differing severity of COVID-19 disease identified biomarkers within the complement and coagulation cascades as biomarkers for disease severity has been reported; however, it is unclear if these proteins differ sufficiently from other conditions to be considered as biomarkers. A prospective, parallel study in T2D (n = 23) and controls (n = 23). A hyperinsulinemic clamp was performed and normoglycemia induced in T2D [4.5 ± 0.07 mmol/L (81 ± 1.2 mg/dl)] for 1-h, following which blood glucose was decreased to ≤2.0 mmol/L (36 mg/dl). Proteomic analysis for the complement and coagulation cascades were measured using Slow Off-rate Modified Aptamer (SOMA)-scan. Thirty-four proteins were measured. At baseline, 4 of 18 were found to differ in T2D versus controls for platelet degranulation [Neutrophil-activating peptide-2 (p = 0.014), Thrombospondin-1 (p = 0.012), Platelet factor-4 (p = 0.007), and Kininogen-1 (p = 0.05)], whilst 3 of 16 proteins differed for complement and coagulation cascades [Coagulation factor IX (p < 0.05), Kininogen-1 (p = 0.05), and Heparin cofactor-2 (p = 0.007)]; STRING analysis demonstrated the close relationship of these proteins to one another. Induced euglycemia in T2D showed no protein changes versus baseline. At hypoglycemia, however, four proteins changed in controls from baseline [Thrombospondin-1 (p < 0.014), platelet factor-4 (p < 0.01), Platelet basic protein (p < 0.008), and Vitamin K-dependent protein-C (p < 0.00003)], and one protein changed in T2D [Vitamin K-dependent protein-C, (p < 0.0002)]. Seven of 34 proteins suggested to be biomarkers of COVID-19 severity within the platelet degranulation and complement and coagulation cascades differed in T2D versus controls, with further changes occurring at hypoglycemia, suggesting that validation of these biomarkers is critical. It is unclear if these protein changes in T2D may predict worse COVID-19 disease for these patients. https://clinicaltrials.gov/, identifier NCT03102801.	no

2021	Sequential dosing of convalescent COVID-19 plasma with significant temporal clinical improvements in a persistently SARS-COV-2 positive patient.	The current global pandemic, SARS-CoV-2 infection, is still extending across the world affecting millions of lives to the date. While new successful vaccines are available with promising outcomes to minimize the spread and to reduce the severity of the disease, optimal therapeutic options still remain elusive. COVID-19 convalescent plasma (CCP) is an investigational treatment option which studies suggesting signals of efficacy and favorable outcomes only for patients treated very early in course of the disease. Benefits of the use of CCP later in the disease remain highly debated and therefore are not common practice. We hereby report a case of severe SARS-CoV-2 infection in a young male patient with prolonged COVID-19 positivity who received repeat doses of CCP treatments later in the disease with temporal clinical improvement. This patient's case highlights the need of further studies evaluating efficacy of repeated dosing of CCP. This also suggests a potential of successful use of CCP later in the disease in selected COVID-19 patients.	no
2021	COVID-19-induced acute renal tubular injury associated with elevation of serum inflammatory cytokine.	Severe acute respiratory syndrome Coronavirus 2 has rapidly spread worldwide, with acute kidney injury (AKI) as one of the manifestations with unknown causal mechanisms. We aimed to investigate tubular injury by assessing tubular markers and their association with the severity of Coronavirus disease 2019 (COVID-19). We examined the associations between laboratory markers and urinary levels of N-acetyl-β-D-glucosaminidase (uNAG), β2-microglobulin (u β2MG), α1-microglobulin (u α1MG), and liver-type fatty acid binding protein (L-FABP). We studied 18 COVID-19 patients without previous chronic kidney disease and analyzed the relationship between the urinary biomarkers and inflammatory markers in patients with severe (n = 7) or non-severe (n = 11) COVID-19, defined by requirements of supplemental oxygen. Fourteen patients (78%) showed abnormal urinalysis findings and two (11%) developed AKI. Patients with severe COVID-19 had significantly higher levels of proteinuria, uNAG, uβ2MG, uα 1MG, and L-FABP than those with non-severe disease. Serum levels of interleukin-6 (IL-6) were significantly higher on admission in all severe COVID-19 cases and correlated with the levels of L-FABP, uβ2MG, uα1MG, uNAG, and proteinuria. Moreover, the changes in serum IL-6 (ΔIL-6) levels from baseline to 7 days after admission significantly correlated with ΔL-FABP and Δuβ2MG. Levels of tubular injury markers, especially L-FABP and uβ2MG, were significantly associated with IL-6 levels even in patients with no evident AKI. This suggests that L-FABP and uβ2MG could be useful as early detective biomarkers for COVID-19 associated renal injury.	no

2021	The Impact of COVID-19 Lockdown on Metabolic Control and Access to Healthcare in People with Diabetes: the CONFI-DIAB Cross-Sectional Study.	The COVID-19 pandemic led to an international health crisis and restrictions. While the phenotype associated with COVID-19 severity in people with diabetes has rapidly been explored, the impact of restrictive measures, including lockdown, and tertiary care disruption on metabolic control and access to healthcare remained unknown. The aim of our study was to provide a comprehensive assessment on the overall management of diabetes during lockdown, including glucose control, weight changes, health care consumption and use of alternative forms of care such as telemedicine services, in a large sample of patients with type 1 (T1DM) or type 2 diabetes mellitus (T2DM). A prioritization of a care self-administered questionnaire was sent at the end of the first COVID-19 lockdown to all patients with diabetes routinely followed by diabetologists from the University Hospital of Nancy (France). This observational cross-sectional single-center study focused on data from patients with diabetes who returned the questionnaire along with medical records. The primary outcome was the change in HbA1c levels between the 6 months preceding and the 6 weeks following the lockdown. Data are expressed as numbers (%) or medians (quartiles). This study is registered with ClinicalTrials.gov (NCT04485351). We analyzed data from 870 patients with diabetes: 549 T2DM (63.1%), 520 males (59.8%), age 65.0 (57.0, 72.0), body mass index 28.6 (25.1, 32.9) and diabetes duration 20.0 (10.0, 30.0) years. HbA1c levels pre- and post-lockdown were respectively 7.7% (7.1, 8.4) and 7.4% (6.8, 8.2), translating into a significant reduction of - 0.1% (- 0.6, 0.15) ($p < 0.0001$). Stratified analyses suggested a consistent significant reduction of HbA1c independently of diabetes type. HbA1c reduction was significantly different according to weight changes: - 0.3% (- 0.8, 0.0), - 0.1% (- 0.5, 0.1) and - 0.1% (- 0.5, 0.3) for patients who lost, had stable or gained weight, respectively ($p = 0.0029$). Respectively, 423 (49.4%) and 790 (92.3%) patients did not consult their general practitioner and diabetologist. Blood tests were undergone by 379 (44.8%) patients, 673 (78.3%) did refill their prescriptions, and 269 (32.1%) used teleconsultation services. Despite the implementation of a lockdown and disruption in healthcare, no deterioration, rather an improvement, in metabolic control was observed in a large sample of patients with T1DM and T2DM.	no

2021	Pre-existing asthma as a comorbidity does not modify cytokine responses and severity of COVID-19.	A significant portion of COVID-19 sufferers have asthma. The impacts of asthma on COVID-19 progression are still unclear but a modifying effect is plausible as respiratory viruses are acknowledged to be an important trigger for asthma exacerbations and a different, potentially type-2 biased, immune response might occur. In this study, we compared the blood circulating cytokine response to COVID-19 infection in patients with and without asthma. Plasma samples and clinical information were collected from 80 patients with mild (25), severe (36) or critical (19) COVID-19 and 29 healthy subjects at the John Radcliffe Hospital, Oxford, UK. The concentrations of 51 circulating proteins in the plasma samples were measured with Luminex and compared between groups. Total 16 pre-existing asthma patients were found (3 in mild, 10 in severe, and 3 in critical COVID-19). The prevalence of asthma in COVID-19 severity groups did not suggest a clear correlation between asthma and COVID-19 severity. Within the same COVID-19 severity group, no differences were observed between patients with or without asthma on oxygen saturation, CRP, neutrophil counts, and length of hospital stay. The mortality in the COVID-19 patients with asthma (12.5%) was not higher than that in patients without asthma (17.2%). No significant difference was found between asthmatic and non-asthmatic in circulating cytokine response in different COVID-19 severity groups, including the cytokines strongly implicated in COVID-19 such as CXCL10, IL-6, CCL2, and IL-8. Pre-existing asthma was not associated with an enhanced cytokine response after COVID-19 infection, disease severity or mortality.	no
2021	Clinical characteristics, risk factors, and cardiac manifestations of cancer patients with COVID-19.	Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been associated with cardiovascular features, which may be deteriorated in patients with cancer. However, cardiac outcomes of cancer patients with COVID-19 have not been closely examined. We retrospectively assessed 1,244 patients with COVID-19 from February 1 to August 31, 2020 (140 cancer and 1,104 noncancer patients). Demographic and clinical data were obtained and compared between cancer and noncancer groups. Including the cardiac biomarkers, we also analyzed laboratory findings between these two groups. Risk factors for in-hospital mortality were identified by multivariable Cox regression models. For cancer group, 56% were in severe and critical status with more diabetes and immune deficiency, whereas the proportion was 10% for noncancer group. Patients with cancer had increased levels of leukocyte, neutrophil count, and blood urea nitrogen (BUN) (all $P < 0.01$), whereas lymphocyte count was significantly lower ($P < 0.001$). The most common solid tumor types were gastrointestinal cancer (26%), lung cancer (21%), and breast and reproductive cancer (both 19%). There is a rising for cardiac biomarkers, including pro-B-type natriuretic peptide (Pro-BNP), sensitive troponin I (cTnI), myoglobin (MYO), creatine kinase-MB (CK-MB), as well as D-Dimer in COVID-19 cancer population, especially in deceased subjects with cancer. The 30-day in-hospital mortality in cancer group was dramatically raised than that in noncancer group (12.9% vs. 4.0%, $P < 0.01$). In multivariable Cox regression models, fever, disease severity status, and underlying diseases were risk factors for mortality. COVID-19 patients with cancer relate to deteriorating conditions and poor cardiac outcomes accompanied by a high in-hospital mortality, which warrants more aggressive treatment. NEW & NOTEWORTHY Our study indicates that the 30-day mortality is higher in COVID-19 patients with cancer; more COVID-19 patients with cancer are in severe and critical status; age, respiratory rate,	no

		neutrophil count, AST, BUN, MYO, Pro-BNP, disease severity status, underlying diseases, and fever are risk factors for in-hospital mortality among COVID-19 cancer cases; COVID-19 patients with cancer display severely impaired myocardium, damaged heart function, and imbalanced homeostasis of coagulation; what is more, those with both cancer and CVD have more significantly increased Pro-BNP and D-Dimer level.	
2021	Prolonged SARS-CoV-2 RNA virus shedding and lymphopenia are hallmarks of COVID-19 in cancer patients with poor prognosis.	Patients with cancer are at higher risk of severe coronavirus infectious disease 2019 (COVID-19), but the mechanisms underlying virus-host interactions during cancer therapies remain elusive. When comparing nasopharyngeal swabs from cancer and noncancer patients for RT-qPCR cycle thresholds measuring acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 1063 patients (58% with cancer), we found that malignant disease favors the magnitude and duration of viral RNA shedding concomitant with prolonged serum elevations of type 1 IFN that anticorrelated with anti-RBD IgG antibodies. Cancer patients with a prolonged SARS-CoV-2 RNA detection exhibited the typical immunopathology of severe COVID-19 at the early phase of infection including circulation of immature neutrophils, depletion of nonconventional monocytes, and a general lymphopenia that, however, was accompanied by a rise in plasmablasts, activated follicular T-helper cells, and non-naive Granzyme B + FasL + , Eomes high TCF-1 high , PD-1 + CD8 + Tc1 cells. Virus-induced lymphopenia worsened cancer-associated lymphocyte loss, and low lymphocyte counts correlated with chronic SARS-CoV-2 RNA shedding, COVID-19 severity, and a higher risk of cancer-related death in the first and second surge of the pandemic. Lymphocyte loss correlated with significant changes in metabolites from the polyamine and biliary salt pathways as well as increased blood DNA from Enterobacteriaceae and Micrococcaceae gut family members in long-term viral carriers. We surmise that cancer therapies may exacerbate the paradoxical association between lymphopenia and COVID-19-related immunopathology, and that the	no

		prevention of COVID-19-induced lymphocyte loss may reduce cancer-associated death.	
2021	A serum proteome signature to predict mortality in severe COVID-19 patients.	Here, we recorded serum proteome profiles of 33 severe COVID-19 patients admitted to respiratory and intensive care units because of respiratory failure. We received, for most patients, blood samples just after admission and at two more later time points. With the aim to predict treatment outcome, we focused on serum proteins different in abundance between the group of survivors and non-survivors. We observed that a small panel of about a dozen proteins were significantly different in abundance between these two groups. The four structurally and functionally related type-3 cystatins AHSG, FETUB, histidine-rich glycoprotein, and KNG1 were all more abundant in the survivors. The family of inter-α-trypsin inhibitors, ITIH1, ITIH2, ITIH3, and ITIH4, were all found to be differentially abundant in between survivors and non-survivors, whereby ITIH1 and ITIH2 were more abundant in the survivor group and ITIH3 and ITIH4 more abundant in the non-survivors. ITIH1/ITIH2 and ITIH3/ITIH4 also showed opposite trends in protein abundance during disease progression. We defined an optimal panel of nine proteins for mortality risk assessment. The prediction power of this mortality risk panel was evaluated against two recent COVID-19 serum proteomics studies on independent cohorts measured in other laboratories in different countries and observed to perform very well in predicting mortality also in these cohorts. This panel may not be unique for COVID-19 as some of the proteins in the panel have previously been annotated as mortality markers in aging and in other diseases caused by different pathogens, including bacteria.	no

2021	COVID-19 Severity in Obesity: Leptin and Inflammatory Cytokine Interplay in the Link Between High Morbidity and Mortality.	Obesity is one of the foremost risk factors in coronavirus infection resulting in severe illness and mortality as the pandemic progresses. Obesity is a well-known predisposed chronic inflammatory condition. The dynamics of obesity and its impacts on immunity may change the disease severity of pneumonia, especially in acute respiratory distress syndrome, a primary cause of death from SARS-CoV-2 infection. The adipocytes of adipose tissue secret leptin in proportion to individuals' body fat mass. An increase in circulating plasma leptin is a typical characteristic of obesity and correlates with a leptin-resistant state. Leptin is considered a pleiotropic molecule regulating appetite and immunity. In immunity, leptin functions as a cytokine and coordinates the host's innate and adaptive responses by promoting the Th1 type of immune response. Leptin induced the proliferation and functions of antigen-presenting cells, monocytes, and T helper cells, subsequently influencing the pro-inflammatory cytokine secretion by these cells, such as TNF-α, IL-2, or IL-6. Leptin scarcity or resistance is linked with dysregulation of cytokine secretion leading to autoimmune disorders, inflammatory responses, and increased susceptibility towards infectious diseases. Therefore, leptin activity by leptin long-lasting super active antagonist's dysregulation in patients with obesity might contribute to high mortality rates in these patients during SARS-CoV-2 infection. This review systematically discusses the interplay mechanism between leptin and inflammatory cytokines and their contribution to the fatal outcomes in COVID-19 patients with obesity.	no
2021	Association between Hyperglycemia at Hospital Presentation and Hospital Outcomes in COVID-19 Patients with and without Type 2 Diabetes: A Retrospective Cohort Study of Hospitalized Inner-City COVID-19 Patients.	This study aimed to determine the relationships among hyperglycemia (HG), the presence of type 2 diabetes (T2D), and the outcomes of COVID-19. Demographic data, blood glucose levels (BG) measured on admission, and hospital outcomes of COVID-19 patients hospitalized at Boston University Medical Center from 1 March to 4 August 2020 were extracted from the hospital database. HG was defined as BG > 200 mg/dL. Patients with type 1 diabetes or BG < 70 mg/dL were excluded. A total of 458 patients with T2D and 976 patients without T2D were included in the study. The mean ± SD age was 56 ± 17 years and 642 (45%) were female. HG occurred in 193 (42%) and 42 (4%) of patients with and without T2D, respectively. Overall, the in-hospital mortality rate was 9%. Among patients without T2D, HG was statistically significantly associated with mortality, ICU admission, intubation, acute kidney injury, and severe sepsis/septic shock, after adjusting for potential confounders ($p < 0.05$). However, only ICU admission and acute kidney injury were associated with HG among patients with T2D ($p < 0.05$). Among the 235 patients with HG, the presence of T2D was associated with decreased odds of mortality, ICU admission, intubation, and severe sepsis/septic shock, after adjusting for potential confounders, including BG ($p < 0.05$). In conclusion, HG in the subset of patients without T2D could be a strong indicator of high inflammatory burden, leading to a higher risk of severe COVID-19.	no

2021	Diverse Humoral Immune Responses in Younger and Older Adult COVID-19 Patients.	We sought to discover links between antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and patient clinical variables, cytokine profiles, and antibodies to endemic coronaviruses. Serum samples from 30 patients of younger (26 to 39 years) and older (69 to 83 years) age groups and with varying clinical severities ranging from outpatient to mechanically ventilated were collected and used to probe a novel multi-coronavirus protein microarray. This microarray contained variable-length overlapping fragments of SARS-CoV-2 spike (S), envelope (E), membrane (M), nucleocapsid (N), and open reading frame (ORF) proteins created through in vitro transcription and translation (IVTT). The array also contained SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), human coronavirus OC43 (HCoV-OC43), and HCoV-NL63 proteins. IgG antibody responses to specific epitopes within the S1 protein region spanning amino acids (aa) 500 to 650 and within the N protein region spanning aa 201 to 300 were found to be significantly higher in older patients and further significantly elevated in those older patients who were ventilated. Additionally, there was a noticeable overlap between antigenic regions and known mutation locations in selected emerging SARS-CoV-2 variants of current clinical consequence (B.1.1.7, B1.351, P.1, CAL20.C, and B.1.526). Moreover, the older age group displayed more consistent correlations of antibody reactivity with systemic cytokine and chemokine responses than the younger adult group. A subset of patients, however, had little or no response to SARS-CoV-2 antigens and disproportionately severe clinical outcomes. Further characterization of these slow-low-responding individuals with cytokine analysis revealed significantly higher interleukin-10 (IL-10), IL-15, and interferon gamma-induced protein 10 (IP-10) levels and lower epidermal growth factor (EGF) and soluble CD40 ligand (sCD40L) levels than those of seroreactive patients in the cohort. IMPORTANCE As numerous viral variants continue to emerge in the coronavirus disease 2019 (COVID-19) pandemic, determining antibody reactivity to SARS-CoV-2 epitopes becomes essential in discerning changes in the immune response to infection over time. This study enabled us to identify specific areas of antigenicity within the SARS-CoV-2 proteome, allowing us to detect correlations of epitopes with clinical metadata and immunological signals to gain holistic insight into SARS-CoV-2 infection. This work also emphasized the risk of mutation accumulation in viral variants and the potential for evasion of the adaptive immune responses in the event of reinfection. We additionally highlighted the correlation of antigenicity between structural proteins of SARS-CoV-2 and endemic HCoVs, raising the possibility of cross-protection between homologous lineages. Finally, we identified a subset of patients with minimal antibody reactivity to SARS-CoV-2 infection, prompting discussion of the potential consequences of this alternative immune response.	no

2021	The Systematic Effect of Mesenchymal Stem Cell Therapy in Critical COVID-19 Patients: A Prospective Double Controlled Trial.	The aim of this clinical trial was to control the cytokine storm by administering mesenchymal stem cells (MSCs) to critically-ill COVID-19 patients, to evaluate the healing effect, and to systematically investigate how the treatment works. Patients with moderate and critical COVID-19 clinical manifestations were separated as Group 1 (moderate cases, n = 10, treated conventionally), Group 2 (critical cases, n = 10, treated conventionally), and Group 3 (critical cases, n = 10, treated conventionally plus MSCs transplantation therapy of three consecutive doses on treatment days 0, 3, and 6, (as 3 × 10 6 cells/kg, intravenously). The treatment mechanism of action was investigated with evaluation markers of the cytokine storm, via biochemical parameters, levels of proinflammatory and anti-inflammatory cytokines, analyses of tissue regeneration via the levels of growth factors, apoptosis markers, chemokines, matrix metalloproteinases, and granzyme-B, and by the assessment of the immunomodulatory effects via total oxidant/antioxidant status markers and the levels of lymphocyte subsets. In the assessment of the overall mortality rates of all the cases, six patients in Group-2 and three patients in Group-3 died, and there was no loss in Group-1. Proinflammatory cytokines IFNγ, IL-6, IL-17A, IL-2, IL-12, anti-inflammatory cytokines IL-10, IL-13, IL-1ra, and growth factors TGF-β, VEGF, KGF, and NGF levels were found to be significant in Group-3. When Group-2 and Group-3 were compared, serum ferritin, fibrinogen and CRP levels in Group-3 had significantly decreased. CD45 +, CD3 +, CD4 +, CD8 +, CD19 +, HLA-DR +, and CD16 + / CD56 + levels were evaluated. In the statistical comparison of the groups, significance was only determined in respect of neutrophils. The results demonstrated the positive systematic and cellular effects of MSCs application on critically ill COVID-19 patients in a versatile way. This effect plays an important role in curing and reducing mortality in critically ill patients.	no
2021	Unbiased Analysis of Temporal Changes in Immune Serum Markers in Acute COVID-19 Infection With Emphasis on Organ Failure, Anti-Viral Treatment, and Demographic Characteristics.	Identification of novel immune biomarkers to gauge the underlying pathology and severity of COVID-19 has been difficult due to the lack of longitudinal studies. Here, we analyzed serum collected upon COVID-19 admission (t1), 48 hours (t2), and seven days later (t3) using Olink proteomics and correlated to clinical, demographics, and therapeutic data. Older age positively correlated with decorin, pleiotrophin, and TNFRS21 but inversely correlated with chemokine (both C-C and C-X-C type) ligands, monocyte attractant proteins (MCP) and TNFRS14. The burden of pre-existing conditions was positively correlated with MCP-4, CAIX, TWEAK, TNFRS12A, and PD-L2 levels. Individuals with COVID-19 demonstrated increased expression of several chemokines, most notably from the C-C and C-X-C family, as well as MCP-1 and MCP-3 early in the course of the disease. Similarly, deceased individuals had elevated MCP-1 and MCP-3 as well as Gal-9 serum levels. LAMP3, GZMB, and LAG3 at admission correlated with mortality. Only CX3CL13 and MCP-4 correlated positively with APACHE score and length of stay, while decorin, MUC-16 and TNFRSF21 with being admitted to the ICU. We also identified several organ-failure-specific immunological markers, including those for respiratory (IL-18, IL-15, Gal-9) or kidney failure (CD28, VEGF). Treatment with hydroxychloroquine, remdesivir, convalescent plasma, and steroids had a very limited effect on the serum variation of biomarkers. Our study identified several potential targets related to COVID-19 heterogeneity (MCP-1, MCP-3, MCP-4, TNFR superfamily members, and programmed death-ligand), suggesting a potential role of these molecules in the pathology of COVID-19.	no

2021	Distinctive Biomarker Features in the Endotheliopathy of COVID-19 and Septic Syndromes.	Endotheliopathy is a key element in COVID-19 pathophysiology, contributing to both morbidity and mortality. Biomarkers distinguishing different COVID-19 phenotypes from sepsis syndrome remain poorly understood. To characterize circulating biomarkers of endothelial damage in different COVID-19 clinical disease stages compared with sepsis syndrome and normal volunteers. Patients with COVID-19 pneumonia (n=49) were classified into moderate, severe, or critical (life-threatening) disease. Plasma samples were collected within 48 to 72h of hospitalization to analyze endothelial activation markers, including soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1), von Willebrand Factor (VWF), A disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13 (ADAMTS-13) activity, thrombomodulin (TM), and soluble TNF receptor I (sTNFRI); heparan sulfate (HS) for endothelial glycocalyx degradation; C5b9 deposits on endothelial cells in culture and soluble C5b9 for complement activation; circulating dsDNA for neutrophil extracellular traps (NETs) presence, and α2-antiplasmin and PAI-1 as parameters of fibrinolysis. We compared the level of each biomarker in all three COVID-19 groups and healthy donors as controls (n=45). Results in critically ill COVID-19 patients were compared with other intensive care unit (ICU) patients with septic shock (SS, n=14), sepsis (S, n=7), and noninfectious systemic inflammatory response syndrome (NI-SIRS, n=7). All analyzed biomarkers were increased in COVID-19 patients versus controls ($P<0.001$), except for ADAMTS-13 activity that was normal in both groups. The increased expression of sVCAM-1, VWF, sTNFRI, and HS was related to COVID-19 disease severity ($P<0.05$). Several differences in these parameters were found between ICU groups: SS patients showed significantly higher levels of VWF, TM, sTNFRI, and NETS compared with critical COVID-19 patients and ADAMTS-13 activity was significantly lover in SS, S, and NI-SIRS versus critical COVID-19 ($P<0.001$). Furthermore, α2-antiplasmin activity was higher in critical COVID-19 versus NI-SIRS ($P<0.01$) and SS ($P<0.001$), whereas PAI-1 levels were significantly lower in COVID-19 patients compared with NI-SIRS, S, and SS patients ($P<0.01$). COVID-19 patients present with increased circulating endothelial stress products, complement activation, and fibrinolytic dysregulation, associated with disease severity. COVID-19 endotheliopathy differs from SS, in which endothelial damage is also a critical feature of pathobiology. These biomarkers could help to stratify the severity of COVID-19 disease and may also provide information to guide specific therapeutic strategies to mitigate endotheliopathy progression.	no

2021	Lung distribution of gas and blood volume in critically ill COVID-19 patients: a quantitative dual-energy computed tomography study.	Critically ill COVID-19 patients have pathophysiological lung features characterized by perfusion abnormalities. However, to date no study has evaluated whether the changes in the distribution of pulmonary gas and blood volume are associated with the severity of gas-exchange impairment and the type of respiratory support (non-invasive versus invasive) in patients with severe COVID-19 pneumonia. This was a single-center, retrospective cohort study conducted in a tertiary care hospital in Northern Italy during the first pandemic wave. Pulmonary gas and blood distribution was assessed using a technique for quantitative analysis of dual-energy computed tomography. Lung aeration loss (reflected by percentage of normally aerated lung tissue) and the extent of gas:blood volume mismatch (percentage of non-aerated, perfused lung tissue-shunt; aerated, non-perfused dead space; and non-aerated/non-perfused regions) were evaluated in critically ill COVID-19 patients with different clinical severity as reflected by the need for non-invasive or invasive respiratory support. Thirty-five patients admitted to the intensive care unit between February 29th and May 30th, 2020 were included. Patients requiring invasive versus non-invasive mechanical ventilation had both a lower percentage of normally aerated lung tissue (median [interquartile range] 33% [24-49%] vs. 63% [44-68%], $p < 0.001$); and a larger extent of gas:blood volume mismatch (43% [30-49%] vs. 25% [14-28%], $p = 0.001$), due to higher shunt (23% [15-32%] vs. 5% [2-16%], $p = 0.001$) and non-aerated/non perfused regions (5% [3-10%] vs. 1% [0-2%], $p = 0.001$). The PaO 2 /FiO 2 ratio correlated positively with normally aerated tissue ($\rho = 0.730$, $p < 0.001$) and negatively with the extent of gas-blood volume mismatch ($\rho = -0.633$, $p < 0.001$). In critically ill patients with severe COVID-19 pneumonia, the need for invasive mechanical ventilation and oxygenation impairment were associated with loss of aeration and the extent of gas:blood volume mismatch.	no
2021	Lewis and ABO histo-blood types and the secretor status of patients hospitalized with COVID-19 implicate a role for ABO antibodies in susceptibility to infection with SARS-CoV-2.	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) targets the respiratory and gastric epithelium, causing coronavirus disease 2019 (COVID-19). Tissue antigen expression variations influence host susceptibility to many infections. This study aimed to investigate the closely linked Lewis (FUT3) and ABO histo-blood types, including secretor (FUT2) status, to infections with SARS-CoV-2 and the corresponding severity of COVID-19. Patients (Caucasians, n = 338) were genotyped for ABO, FUT3, and FUT2, and compared to a reference population of blood donors (n = 250,298). The association between blood types and severity of COVID-19 was addressed by dividing patients into four categories: hospitalized individuals in general wards, patients admitted to the intensive care unit with and without intubation, and deceased patients. Comorbidities were considered in subsequent analyses. Patients with blood type Lewis (a-b-) or O were significantly less likely to be hospitalized (odds ratio [OR] 0.669, confidence interval [CI] 0.446-0.971, OR 0.710, CI 0.556-0.900, respectively), while type AB was significantly more prevalent in the patient cohort (OR 1.519, CI 1.014-2.203). The proportions of secretors/nonsecretors, and Lewis a+ or Lewis b+ types were consistent between patients and controls. The analyzed blood groups were not associated with the clinical outcome as defined. Blood types Lewis (a-b-) and O were found to be protective factors, whereas the group AB is suggested to be a risk factor for COVID-19. The antigens investigated may not be prognostic for disease severity, but a role for ABO isoagglutinins in SARS-CoV-2 infections is strongly suggested.	yes

2021	Autoantibodies against ACE2 and angiotensin type-1 receptors increase severity of COVID-19.	The renin-angiotensin system (RAS) plays a major role in COVID-19. Severity of several inflammation-related diseases has been associated with autoantibodies against RAS, particularly agonistic autoantibodies for angiotensin type-1 receptors (AA-AT1) and autoantibodies against ACE2 (AA-ACE2). Disease severity of COVID-19 patients was defined as mild, moderate or severe following the WHO Clinical Progression Scale and determined at medical discharge. Serum AA-AT1 and AA-ACE2 were measured in COVID-19 patients (n = 119) and non-infected controls (n = 23) using specific solid-phase, sandwich enzyme-linked immunosorbent assays. Serum LIGHT (TNFSF14; tumor necrosis factor ligand superfamily member 14) levels were measured with the corresponding assay kit. At diagnosis, AA-AT1 and AA-ACE2 levels were significantly higher in the COVID-19 group relative to controls, and we observed significant association between disease outcome and serum AA-AT1 and AA-ACE2 levels. Mild disease patients had significantly lower levels of AA-AT1 ($p < 0.01$) and AA-ACE2 ($p < 0.001$) than moderate and severe patients. No significant differences were detected between males and females. The increase in autoantibodies was not related to comorbidities potentially affecting COVID-19 severity. There was significant positive correlation between serum levels of AA-AT1 and LIGHT (TNFSF14; r Pearson = 0.70, $p < 0.001$). Both AA-AT1 (by agonistic stimulation of AT1 receptors) and AA-ACE2 (by reducing conversion of Angiotensin II into Angiotensin 1-7) may lead to increase in AT1 receptor activity, enhance proinflammatory responses and severity of COVID-19 outcome. Patients with high levels of autoantibodies require more cautious control after diagnosis. Additionally, the results encourage further studies on the possible protective treatment with AT1 receptor blockers in COVID-19.	no
2021	The landscape of antibody binding in SARS-CoV-2 infection.	The search for potential antibody-based diagnostics, vaccines, and therapeutics for pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has focused almost exclusively on the spike (S) and nucleocapsid (N) proteins. Coronavirus membrane (M), ORF3a, and ORF8 proteins are humoral immunogens in other coronaviruses (CoVs) but remain largely uninvestigated for SARS-CoV-2. Here, we use ultradense peptide microarray mapping to show that SARS-CoV-2 infection induces robust antibody responses to epitopes throughout the SARS-CoV-2 proteome, particularly in M, in which 1 epitope achieved excellent diagnostic accuracy. We map 79 B cell epitopes throughout the SARS-CoV-2 proteome and demonstrate that antibodies that develop in response to SARS-CoV-2 infection bind homologous peptide sequences in the 6 other known human CoVs. We also confirm reactivity against 4 of our top-ranking epitopes by enzyme-linked immunosorbent assay (ELISA). Illness severity correlated with increased reactivity to 9 SARS-CoV-2 epitopes in S, M, N, and ORF3a in our population. Our results demonstrate previously unknown, highly reactive B cell epitopes throughout the full proteome of SARS-CoV-2 and other CoV proteins.	no

2021	Early multidrug treatment of SARS-CoV-2 infection (COVID-19) and reduced mortality among nursing home (or outpatient/ambulatory) residents.	The outbreak of COVID-19 from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread all over the world with tremendous morbidity and mortality in the elderly. In-hospital treatment addresses the multifaceted nature of the illness including initial viral replication, cytokine storm, and endothelial injury with thrombosis. We identified nine reports of early treatment outcomes in COVID-19 nursing home patients. Multi-drug therapy including hydroxychloroquine with one or more anti-infectives, corticosteroids, and antithrombotic anti-blood clotting agents can be extended to seniors in the nursing home setting without hospitalization. Data from nine studies found hydroxychloroquine-based multidrug regimens were associated with a statistically significant > 60% reduction in mortality. Going forward, we conclude that early empiric treatment for the elderly with COVID-19 in the nursing home setting (or similar congregated settings with elderly residents/patients e.g. LTF or ALF) has a reasonable probability of success and acceptable safety. This group remains our highest at-risk group and warrants acute treatment focus prior to symptoms worsening. Given the rapidity and severity of SARS-CoV-2 outbreaks in nursing homes, in-center treatment of acute COVID-19 patients is a reasonable strategy to reduce the risks of hospitalization and death. If elderly high-risk patients in such congregated nursing home type settings are allowed to worsen with no early treatment, they may be too sick and fragile to benefit from in-hospital therapeutics and are at risk for pulmonary failure, life-ending micro-thrombi of the lungs, kidneys etc. The issue is timing of therapeutics, and we argue that early treatment before hospitalization, is the right time and can potentially save lives, especially among our higher-risk elderly populations hit hardest by severe illness and death from COVID-19. We must reiterate, we are talking about 'early' treatment before the disease is far along in the disease sequelae where the patient then needs hospitalization and aggressive interventions. We are referring to the initial days e.g. day one, post infection when symptoms emerge or there is strong clinical suspicion. This early therapeutic option deserves serious and urgent consideration by the medical establishment and respective decision-makers. Doctors must be allowed their clinical discretion in how they optimally treat their patients. Doctors must be brave and trust their skilled judgements and do all to save the lives of their patients. We therefore hypothesize that early outpatient ambulatory treatment, once initiated as soon as symptoms begin in high-risk positive persons, would significantly reduce hospitalizations and prevent deaths. Specifically, the provision of early multi-drug sequenced therapy with repurposed drugs will reduce hospitalization and death in elderly patients being cared for in long-term-care facilities. The most important implications of our hypothesis are: 1) hospitalizations and deaths would be reduced 2) transmission would be reduced due to the mitigation of symptoms and 3) recovery following infection and treatment provides for natural exposure immunity that is broad based, durable, and robust (helping towards natural immunity within the population). The end result is reduced strain on hospitals and systems that would allow for other non-COVID illnesses to receive care.	no

2021	Type 1 inflammatory endotype relates to low compliance, lung fibrosis, and severe complications in COVID-19.	Coronavirus disease 2019 (COVID-19) is an acute respiratory disease; approximately 5% of patients developing severe COVID-19. It is known that cytokine release is associated with disease severity, but the relationship between the different clinical phenotypes and inflammatory endotypes is not well understood. This study investigated the association between inflammatory biomarker-based endotypes and severe COVID-19 phenotypes. Interleukin (IL) -6, C-reactive protein (CRP), C-X-C motif chemokine (CXCL) 9, IL-18, C-C motif chemokine (CCL) 3, CCL17, IL-10, and vascular endothelial growth factor (VEGF) were measured in 57 COVID-19 patients, and their association with clinical characteristics was examined using a cluster analysis. Significantly higher blood levels of the eight inflammatory markers were noted in patients who developed acute respiratory distress syndrome (ARDS) than in those who did not develop ARDS (non-ARDS). Using a cluster analysis, the patient groups were classified into four clusters, of which two had patients with high IL-6 and CRP levels. In the cluster with high levels of Type 1 (T1) inflammatory markers such as CXCL9 and IL-18, 85% of the patients had ARDS, 65% of the patients developed acute kidney injury (AKI), and 78% of the patients developed pulmonary fibrosis. In the cluster with high levels of T1 inflammatory markers, the patients frequently suffered from tissue damage, manifested as ARDS and AKI. Our findings identified distinct T1 inflammatory endotypes of COVID-19 and suggest the importance of controlling inflammation by monitoring T1 biomarkers and treating accordingly to limit the severity of the disease.	no
2021	Blood group type A secretors are associated with a higher risk of COVID-19 cardiovascular disease complications.	The SARS-CoV-2 virus causes COVID-19, an infection capable of causing severe disease and death but which can also be asymptomatic or oligosymptomatic. We investigated whether ABO blood group or secretor status was associated with COVID-19 severity. We investigated secretor status because expression of ABO glycans on secreted proteins and non-erythroid cells are controlled by a fucosyltransferase (FUT2), and inactivating FUT2 mutations result in a non-secretor phenotype which protects against some viral infections. Data combined from healthcare records and our own laboratory tests (n = 275) of hospitalized SARS-CoV-2 polymerase chain reaction positive patients confirmed higher than expected numbers of blood group A individuals compared to O (RR = 1.24, CI 95% [1.05, 1.47], p = 0.0111). There was also a significant association between group A and COVID-19-related cardiovascular complications (RR = 2.56, CI 95% [1.43, 4.55], p = 0.0011) which is independent of gender. Molecular analysis revealed that group A non-secretors are significantly less likely to be hospitalized than secretors. Testing of convalescent plasma donors, among whom the majority displayed COVID-19 symptoms and only a small minority required hospitalization, group A non-secretors were slightly over-represented. Our findings showed that group A non-secretors are not resistant to infection by SARS-CoV-2, but are more likely to experience a less severe form of associated disease.	yes

2021	C-type lectins and extracellular vesicles in virus-induced NETosis.	Dysregulated formation of neutrophil extracellular traps (NETs) is observed in acute viral infections. Moreover, NETs contribute to the pathogenesis of acute viral infections, including those caused by the dengue virus (DV) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Furthermore, excessive NET formation (NETosis) is associated with disease severity in patients suffering from SARS-CoV-2-induced multiple organ injuries. Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and other members of C-type lectin family (L-SIGN, LSECtin, CLEC10A) have been reported to interact with viral glycans to facilitate virus spreading and exacerbates inflammatory reactions. Moreover, spleen tyrosine kinase (Syk)-coupled C-type lectin member 5A (CLEC5A) has been shown as the pattern recognition receptor for members of flaviviruses, and is responsible for DV-induced cytokine storm and Japanese encephalomyelitis virus (JEV)-induced neuronal inflammation. Moreover, DV activates platelets via CLEC2 to release extracellular vesicles (EVs), including microvesicles (MVs) and exosomes (EXOs). The DV-activated EXOs (DV-EXOs) and MVs (DV-MVs) stimulate CLEC5A and Toll-like receptor 2 (TLR2), respectively, to enhance NET formation and inflammatory reactions. Thus, EVs from virus-activated platelets (PLT-EVs) are potent endogenous danger signals, and blockade of C-type lectins is a promising strategy to attenuate virus-induced NETosis and intravascular coagulopathy.	no
2021	Potential association of COVID-19 and ABO blood group: An Indian study.	Coronavirus disease 2019 (COVID-19) transmits from person to person mainly through respiratory droplets and coughing. Infection severity ranges from asymptomatic and mild infection to those with moderate and severe symptoms which may lead to multiple organ failure and mortality. Infection severity largely depends on individual's immune response, age and co-morbidities. Present study categorized COVID-19 infected patients based on their infection severity and linked COVID-19 severity with age, gender and ABO blood group types. Clinical details of 383 COVID-19 patients were collected from Rajiv Gandhi Super Specialty hospital (RGSSH), India; divided into three groups; mild, moderate and severe patients, based on their symptoms. Present analysis revealed that age plays major role in infection severity, as the symptoms are more severe in patients above 45 years. Infection rate was higher in males compared to females. Most patients with A(+ve) and B(+ve) blood group were severely affected compared to those of blood group type O(+ve) and AB(+ve). O(+ve) blood group was least represented in severe patients. Present findings could be helpful in generating awareness amongst the population regarding susceptibility towards the COVID-19 infection. This supportive information would help clinicians and health workers to propose new strategies and tactical solution against COVID-19 infection.	yes

2021	Angiotensin-converting enzyme-1 gene insertion/deletion polymorphism may be associated with COVID-19 clinical severity: a prospective cohort study.	Angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism may play a role in the pathogenesis of coronavirus-19 disease (COVID-19). Investigate the relationship between ACE I/D polymorphism and the clinical severity of COVID-19. Prospective cohort study. Tertiary care hospital. The study included COVID-19 patients with asymptomatic, mild, and severe disease with clinical data and whole blood samples collected from 1 April 2020 to 1 July 2020. ACE I/D genotypes were determined by polymerase chain reaction and agarose gel electrophoresis. ACE DD, DI and II genotypes frequencies. 90 cases, 30 in each disease severity group. Age and the frequency of general comorbidity increased significantly from the asymptomatic disease group to the severe disease group. Advanced age, diabetes mellitus and presence of ischemic heart disease were independent risk factors for severe COVID-19 [OR and 95 % CI: 1.052 (1.021-1.083), 5.204 (1.006-26.892) and 5.922 (1.109-31.633), respectively]. The ACE II genotype was the dominant genotype (50%) in asymptomatic patients, while the DD genotype was the dominant genotype (63.3 %) in severe disease. The ACE II geno-type was protective against severe COVID-19 [OR and 95% CI: .323 (.112-.929)]. All nine patients (8.9%) who died had severe disease. The clinical severity of COVID-19 infection may be associated with the ACE I/D polymorphism. Small sample size and single center. None.	no
2021	Histo-blood group A is a risk factor for severe COVID-19.	Evaluate the impact of ABO histo-blood group type on COVID-19 severity. ABO histo-blood type has been associated with different outcomes in infectious diseases. It has also shown a higher proportion of type A patients with SARS-CoV-2. In this observational study, extracted from an ongoing clinical trial on the efficacy of convalescent plasma transfused in COVID-19 patients, we describe the impact of ABO blood type on the risk of developing severe COVID-19. Seventy-two consecutive patients (37 type A, 23 type O, 11 type B, 1 type AB) with severe (respiratory failure) COVID-19 were included. Control group was composed of 160 individuals randomly selected from the same populational basis. Blood group A was overrepresented (51.39%) in the patient group in relation to the control group (30%), whereas blood group O was less represented (31.94%) in patient than in control group (48%). Odds ratio (A vs. O) was 2.581 (1.381-4.817), CI 95%; $p = 0.004$. Also, blood group A patients appeared to have more severe disease, given by the scores of the Sequential Organ Failure Assessment and Simplified Acute Physiologic Score 3 ($p = 0.036$ and $p = 0.058$, respectively). Histo-blood type A is associated with a higher risk of developing severe COVID-19 in relation to blood type O.	yes

2021	Side Effects and Perceptions Following COVID-19 Vaccination in Jordan: A Randomized, Cross-Sectional Study Implementing Machine Learning for Predicting Severity of Side Effects.	Since the coronavirus disease 2019 (COVID-19) was declared a pandemic, there was no doubt that vaccination is the ideal protocol to tackle it. Within a year, a few COVID-19 vaccines have been developed and authorized. This unparalleled initiative in developing vaccines created many uncertainties looming around the efficacy and safety of these vaccines. This study aimed to assess the side effects and perceptions following COVID-19 vaccination in Jordan. A cross-sectional study was conducted by distributing an online survey targeted toward Jordan inhabitants who received any COVID-19 vaccines. Data were statistically analyzed and certain machine learning (ML) tools, including multilayer perceptron (MLP), eXtreme gradient boosting (XGBoost), random forest (RF), and K-star were used to predict the severity of side effects. A total of 2213 participants were involved in the study after receiving Sinopharm, AstraZeneca, Pfizer-BioNTech, and other vaccines (38.2%, 31%, 27.3%, and 3.5%, respectively). Generally, most of the post-vaccination side effects were common and non-life-threatening (e.g., fatigue, chills, dizziness, fever, headache, joint pain, and myalgia). Only 10% of participants suffered from severe side effects; while 39% and 21% of participants had moderate and mild side effects, respectively. Despite the substantial variations between these vaccines in the presence and severity of side effects, the statistical analysis indicated that these vaccines might provide the same protection against COVID-19 infection. Finally, around 52.9% of participants suffered before vaccination from vaccine hesitancy and anxiety; while after vaccination, 95.5% of participants have advised others to get vaccinated, 80% felt more reassured, and 67% believed that COVID-19 vaccines are safe in the long term. Furthermore, based on the type of vaccine, demographic data, and side effects, the RF, XGBoost, and MLP gave both high accuracies (0.80, 0.79, and 0.70, respectively) and Cohen's kappa values (0.71, 0.70, and 0.56, respectively). The present study confirmed that the authorized COVID-19 vaccines are safe and getting vaccinated makes people more reassured. Most of the post-vaccination side effects are mild to moderate, which are signs that body's immune system is building protection. ML can also be used to predict the severity of side effects based on the input data; predicted severe cases may require more medical attention or even hospitalization.	yes
2021	Mild COVID-19 despite autoantibodies against type I IFNs in autoimmune polyendocrine syndrome type 1.	Autoantibodies against IFN-α and IFN-ω (type I IFNs) were recently reported as causative for severe COVID-19 in the general population. Autoantibodies against IFN-α and IFN-ω are present in almost all patients with autoimmune polyendocrine syndrome type 1 (APS-1) caused by biallelic deleterious or heterozygous dominant mutations in AIRE. We therefore hypothesized that autoantibodies against type I IFNs also predispose patients with APS-1 to severe COVID-19. We prospectively studied 6 patients with APS-1 between April 1, 2020 and April 1, 2021. Biobanked pre-COVID-19 sera of APS-1 subjects were tested for neutralizing autoantibodies against IFN-α and IFN-ω. The ability of the patients' sera to block recombinant human IFN-α and IFN-ω was assessed by assays quantifying phosphorylation of signal transducer and activator of transcription 1 (STAT1) as well as infection-based IFN-neutralization assays. We describe 4 patients with APS-1 and preexisting high titers of neutralizing autoantibodies against IFN-α and IFN-ω who contracted SARS-CoV-2, yet developed only mild symptoms of COVID-19. None of the patients developed dyspnea, oxygen requirement, or high temperature. All infected patients with APS-1 were females and younger than 26 years of age. Clinical	yes

		penetrance of neutralizing autoantibodies against type I IFNs for severe COVID-19 is not complete.	
2021	ABO blood group and COVID-19: an updated systematic literature review and meta-analysis.	Following the first reports in the literature, the association between the ABO blood group and SARS-CoV-2 infection has been investigated by a number of studies, although with varying results. The main object of this systematic review was to assess the relationship between the ABO blood group and the occurrence and severity of COVID-19. A systematic literature search using appropriate MeSH terms was performed through Medline and PubMed. The outcomes considered were the prevalence of the blood group O vs non-O types in SARS-CoV-2 infected and non-infected subjects, and the severity of SARS-CoV-2 infection according to ABO group. The methodological quality of the studies included in the analysis was assessed with the Newcastle-Ottawa Scale, and the overall quality of the available evidence using the GRADE system. Benchmarks used to evaluate the effect size were odd ratios (ORs) for case control studies and risk ratios (RRs) for cohort studies. Twenty-one studies were included in the analysis. Overall, individuals with group O had a lower infection rate compared to individuals of non-O group (OR: 0.81; 95% CI: 0.75, 0.86). However, the difference in the effect size was significantly lower in cohort studies compared to case control studies. No evidence was found indicating an effect of the O type on the disease severity in the infected patients. We have found low/very low evidence that group O individuals are less susceptible to SARS-CoV-2 infection compared to those in the non-O group. No evidence was found indicating an effect of the O type on disease severity in SARS-CoV-2 infection.	yes

2021	Antibodies Against Angiotensin II Receptor Type 1 and Endothelin A Receptor Are Associated With an Unfavorable COVID19 Disease Course.	Lung histopathology demonstrates vasculopathy in a subset of deceased COVID19 patients, which resembles histopathology observed in antibody-mediated lung transplant rejection. Autoantibodies against angiotensin II type 1 receptor (AT1R) and Endothelin receptor Type A (ETAR) have been demonstrated in antibody-mediated rejection and may also be associated with severe COVID19 infection. Objective To assess AT1R and ETAR auto-antibodies in COVID19 patients and controls, and explore their association with disease course. 65 hospitalized patients with COVID19 infection were included. Clinical and laboratory findings were retrospectively assessed. Patients with unfavorable disease course, admitted at the intensive care unit and/or deceased during hospital admission (n=33) were compared to admitted COVID19 patients with favorable disease course (n=32). The presence of antinuclear antibodies (ANA) and auto-antibodies against AT1R or ETAR in peripheral blood were compared between COVID19 with unfavorable and favorable disease course and age matched controls (n=20). The presence of ANA was not significantly different between COVID19 patients with unfavorable (n=7/33; 21%) and favorable disease course (n=6/32; 19%) (p= 0.804) and controls (n=3/20; 15%). Auto-antibodies against AT1R were significantly increased in unfavorable disease course (median 14.59 U/mL, IQR 11.28 - 19.89) compared to favorable disease course (median 10.67 U/mL, IQR 8.55 - 13.0, p< 0.01). ETAR antibody titers were also significantly increased in unfavorable disease course (median 7.21, IQR 5.0 - 10.45) as compared to favorable disease course (median 4.0, IQR 3.0 - 6.0, p <0.05). Auto-antibodies against AT1R and ETAR are significantly increased in COVID19 patients with an unfavorable disease course.	yes
2021	Circulating Type I Interferon Levels and COVID-19 Severity: A Systematic Review and Meta-Analysis.	Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, resulting in a range of clinical manifestations and outcomes. Laboratory and immunological alterations have been considered as potential markers of disease severity and clinical evolution. Type I interferons (IFN-I), mainly represented by IFN-α and β, are a group of cytokines with an important function in antiviral responses and have played a complex role in COVID-19. Some studies have demonstrated that IFN-I levels and interferon response is elevated in mild cases, while other studies have noted this in severe cases. The involvement of IFN-I on the pathogenesis and outcomes of SARS-CoV-2 infection remains unclear. In this study, we summarize the available evidence of the association of plasma protein levels of type I IFN with the severity of COVID-19. The PRISMA checklist guided the reporting of the data. A systematic search of the MEDLINE (PubMed), EMBASE, and Web of Science databases was performed up to March of 2021, looking for articles that evaluated plasma protein levels of IFN-I in mild, severe, or critical COVID-19 patients. Comparative meta-analyses with random effects were performed to compare the standardized mean differences in plasma protein levels of IFN-I of mild versus severe and mild versus critical patients. Meta-regressions were performed to test the moderating role of age, sex, time that the IFN-I was measured, and limit of detection of the assay used in the difference between the means. There was no significant difference in plasma levels of IFN-α when comparing between mild and severe patients (SMD = -0.236, 95% CI -0.645 to 0.173, p = 0.258, I2 = 82.11), nor when comparing between patients mild and critical (SMD = 0.203, 95% CI -0.363 to 0.770, p = 0.481, I2 = 64.06). However, there was a significant difference between healthy individuals and patients with mild disease (SMD = 0.447, 95% CI 0.085	yes

		to 0.810, p = 0.016, I2 = 62.89). Peripheral IFN-α cannot be used as a severity marker as it does not determine the clinical status presented by COVID-19 patients.	
2021	Predicting outcomes of COVID-19 from admission biomarkers: a prospective UK cohort study.	COVID-19 has an unpredictable clinical course, so prognostic biomarkers would be invaluable when triaging patients on admission to hospital. Many biomarkers have been suggested using large observational datasets but sample timing is crucial to ensure prognostic relevance. The DISCOVER study prospectively recruited patients with COVID-19 admitted to a UK hospital and analysed a panel of putative prognostic biomarkers on the admission blood sample to identify markers of poor outcome. Consecutive patients admitted to hospital with proven or clinicoradiological suspected COVID-19 were consented. Admission bloods were extracted from the clinical laboratory. A panel of biomarkers (interleukin-6 (IL-6), soluble urokinase plasminogen activator receptor (suPAR), Krebs von den Lungen 6, troponin, ferritin, lactate dehydrogenase, B-type natriuretic peptide, procalcitonin) were performed in addition to routinely performed markers (C reactive protein (CRP), neutrophils, lymphocytes, neutrophil:lymphocyte ratio). Age, National Early Warning Score (NEWS2), CURB-65 and radiographic severity score on initial chest radiograph were included as comparators. All biomarkers were tested in logistic regression against a composite outcome of non-invasive ventilation, intensive care admission or death, with area under the curve (AUC) (figures calculated). 187 patients had 28-day outcomes at the time of analysis. CRP (AUC: 0.69, 95% CI: 0.59 to 0.78), lymphocyte count (AUC: 0.62, 95% CI: 0.53 to 0.72) and other routine markers did not predict the primary outcome. IL-6 (AUC: 0.77, 0.65 to 0.88) and suPAR (AUC: 0.81, 0.72 to 0.88) showed some promise, but simple clinical features alone such as NEWS2 score (AUC: 0.70, 0.60 to 0.79) or age (AUC: 0.70, 0.62 to 0.77) performed nearly as well. Admission blood biomarkers have only moderate predictive value for predicting COVID-19 outcomes, while simple clinical features such as age and NEWS2 score outperform many biomarkers. IL-6 and suPAR had the best performance, and further	yes

		studies should focus on the additive value of these biomarkers to routine care.	
2021	Clinical Course of COVID-19 in Identical Twins.	The rapid outbreak of coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to infection with variable clinical presentations and a wide clinical spectrum. The disease was first reported in Wuhan, China in 2019 and has rapidly spread worldwide. Despite reports of dynamic changes in disease progression, clinical predictors of disease severity have been difficult to identify. The following case describing identical twins with laboratory confirmed COVID-19 who had very different disease courses. These patients resided in the same home and shared many of the same comorbidities, including type 2 diabetes mellitus, hypertension and morbid obesity. Although twin 1 had higher inflammatory markers, white blood cell (WBC) and an arguably more complicated medical history in comparison to their identical twin, the patient experienced a milder and shorter disease course. This case highlights the need for identifying proper disease markers and predictors early in the clinical course in order to direct future management guidelines and timely treatment.	yes

2021	Increased Serum Levels of Soluble TNF-α Receptor Is Associated With ICU Mortality in COVID-19 Patients.	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) has infected over 112M patients and resulted in almost 2.5M deaths worldwide. The major clinical feature of severe COVID-19 patients requiring ventilation is acute respiratory distress syndrome (ARDS) possibly associated with a cytokine storm. To elucidate serum levels of TNF-α and soluble TNF-Receptor 1 (sTNFR1) in patients with severe and mild COVID-19 disease as determinants of disease severity. We determined serum TNF-α and sTNFR1 concentrations in 46 patients with laboratory-confirmed COVID-19 (17 patients with severe disease within the intensive care unit [ICU] and 29 non-severe, non-ICU patients) and 15 healthy controls upon admission using ELISA. Subjects were recruited between March-May 2020 at the Masih Daneshvari Hospital Tehran, Iran. Serum levels of sTNFRI were significantly higher in ICU patients (P<0.0001) and non-ICU patients (P=0.0342) compared with healthy subjects. Serum sTNFR1 were significantly higher in ICU patients than in non-ICU patients (P<0.0001). Serum TNF-α levels were greater in ICU and non-ICU patients than in the healthy subjects group (p<0.0001). The sTNFRI concentration in ICU (r=0.79, p=0.0002) and non-ICU (r=0.42, p=0.02) patients positively correlated with age although serum sTNFRI levels in ICU patients were significantly higher than in older healthy subjects. The sTNFRI concentration in ICU patients negatively correlated with ESR. The study demonstrates higher sTNFRI in ICU patients with severe COVID-19 disease and this be a biomarker of disease severity and mortality. Future studies should examine whether lower levels of systemic sTNFR1 at admission may indicate a better disease outcome.	yes

2021	Dynamic and features of SARS-CoV-2 infection in Gabon.	In a context where SARS-CoV-2 population-wide testing is implemented, clinical features and antibody response in those infected have never been documented in Africa. Yet, the information provided by analyzing data from population-wide testing is critical to understand the infection dynamics and devise control strategies. We described clinical features and assessed antibody response in people screened for SARS-CoV-2 infection. We analyzed data from a cohort of 3464 people that we molecularly screened for SARS-CoV-2 infection in our routine activity. We recorded people SARS-CoV-2 diagnosis, age, gender, blood types, white blood cells (WBC), symptoms, chronic disease status and time to SARS-CoV-2 RT-PCR conversion from positive to negative. We calculated the age-based distribution of SARS-CoV-2 infection, analyzed the proportion and the spectrum of COVID-19 severity. Furthermore, in a nested sub-study, we screened 83 COVID-19 patients and 319 contact-cases for anti-SARS-CoV-2 antibodies. Males and females accounted for respectively 51% and 49% of people screened. The studied population median and mean age were both 39 years. 592 out of 3464 people (17.2%) were diagnosed with SARS-CoV-2 infection with males and females representing, respectively, 53% and 47%. The median and mean ages of SARS-CoV-2 infected subjects were 37 and 38 years respectively. The lowest rate of infection (8%) was observed in the elderly (aged > 60). The rate of SARS-Cov-2 infection in both young (18-35 years old) and middle-aged adults (36-60 years old) was around 20%. The analysis of SARS-CoV-2 infection age distribution showed that middle-aged adults accounted for 54.7% of SARS-CoV-2 positive persons, followed respectively by young adults (33.7%), children (7.7%) and elderly (3.8%). 68% (N = 402) of SARS-CoV-2 infected persons were asymptomatic, 26.3% (N = 156) had influenza-like symptoms, 2.7% (N = 16) had influenza-like symptoms associated with anosmia and ageusia, 2% (N = 11) had dyspnea and 1% (N = 7) had respiratory failure, which resulted in death. Data also showed that 12% of SARS-CoV-2 infected subjects, had chronic diseases. Hypertension, diabetes, and asthma were the top concurrent chronic diseases representing respectively 58%, 25% and 12% of recorded chronic diseases. Half of SARS-CoV-2 RT-PCR positive patients were cured within 14 days following the initiation of the anti-COVID-19 treatment protocol. 78.3% of COVID-19 patients and 55% of SARS-CoV-2 RT-PCR confirmed negative contact-cases were positive for anti-SARS-CoV-2 antibodies. Patients with severe-to-critical illness have higher leukocytes, higher neutrophils and lower lymphocyte counts contrarily to asymptomatic patients and patients with mild-to-moderate illness. Neutrophilic leukopenia was more prevalent in asymptomatic patients and patients with mild-to-moderate disease for 4 weeks after diagnosis (27.1-42.1%). In Patients with severe-to-critical illness, neutrophilic leukocytosis or neutrophilia (35.6-50%) and lymphocytopenia (20-40%) were more frequent. More than 60% of participants were blood type O. It is also important to note that infection rate was slightly higher among A and B blood types compared with type O. In this African setting, young and middle-aged adults are most likely driving community transmission of COVID-19. The rate of critical disease is relatively low. The high rate of anti-SARS-CoV-2 antibodies observed in SARS-CoV-2 RT-PCR negative contact cases suggests that subclinical infection may have been overlooked in our setting.	no

2021	Antiphospholipid antibodies in COVID-19: a meta-analysis and systematic review.	Many studies reported high prevalence of antiphospholipid antibodies (aPL) in patients with COVID-19 raising questions about its true prevalence and its clinical impact on the disease course. We conducted a meta-analysis and a systematic review to examine the prevalence of aPL and its clinical impact in patients with COVID-19. 21 studies with a total of 1159 patients were included in our meta-analysis. Among patients hospitalised with COVID-19, the pooled prevalence rate of one or more aPL (IgM or IgG or IgA of anticardiolipin (aCL) or anti-ß2 glycoprotein (anti-ß2 GPI) or antiphosphatidylserine/prothrombin, or lupus anticoagulant (LA)) was 46.8% (95% CI 36.1% to 57.8%). The most frequent type of aPL found was LA, with pooled prevalence rate of 50.7% (95% CI 34.8% to 66.5%). Critically ill patients with COVID-19 had significantly higher prevalence of aCL (IgM or IgG) (28.8% vs 7.10%, p<0.0001) and anti-ß2 GPI (IgM or IgG) (12.0% vs 5.8%, p<0.0001) as compared with non-critically ill patients. However, there was no association between aPL positivity and mean levels of C reactive protein (mean difference was 32 (95% CI -15 to 79), p=0.18), D-dimer (mean difference was 34 (95% CI -194 to 273), p=0.77), mortality (1.46 (95% CI 0.29 to 7.29), p=0.65), invasive ventilation (1.22 (95% CI 0.51 to 2.91), p=0.65) and venous thromboembolism (1.38 (95% CI 0.57 to 3.37), p=0.48). aPLs were detected in nearly half of patients with COVID-19, and higher prevalence of aPL was found in severe disease. However, there was no association between aPL positivity and disease outcomes including thrombosis, invasive ventilation and mortality. However, further studies are required to identify the clinical and pathological role of aPL in COVID-19.	no
2021	COVID-19 clinical course and blood groups: Turkish population-based study	SARS-CoV-2 enters the cell through the binding of the S glycoprotein on the surface of the virus to the angiotensin- converting enzyme 2 (ACE-2) in the host cells and also SARS-CoV S protein binding to ACE-2 was inhibited by anti-A antibodies. The aim of the study was to investigate the relationship between blood groups and the course of COVID-19 in Turkey. Laboratory confirmed COVID-19 patients aged 18 and over (n = 39.850) were randomized in age and sex- matched groups according to blood groups. Advanced age, male sex and blood group A were found to be related with increased rate of intensive care unit (ICU) admission (OR = 1.089, 95% CI: 1.085–1.093 for age; OR = 1.963, 95% CI: 1.737–2.218 for male sex; OR = 1.216, 95% CI: 1.023–1.446 for blood group A). When blood group O individuals were compared to non-O individuals, no significant difference was observed regarding the rate of hospital and ICU admission, mechanical ventilation (MV) support, length of hospital and ICU stay, and case fatality rate (CFR). The CFR in patients with blood group A, B, O, and AB were 2.6%, 2.2%, 3.1%, and 2.3%, respectively. There were no significant differences between Rh-negative and positive patients regarding the rate of hospital and ICU admission (p = 0.280 and p = 0.741, respectively), also the rate of MV support and CFR was similar (p = 0.933 and p = 0.417). Our study revealed that ABO and Rh blood groups do not have any impact on the rate of hospital admission, hospital and ICU stay, MV support, and CFR.	yes

2021	Systemic Inflammation May Induce Cardiac Injury in COVID-19 Patients Including Children and Adolescents Without Underlying Cardiovascular Diseases: A Systematic Review.	Coronavirus disease 2019(COVID-19) is an ongoing global pandemic with a daily increasing number of affected individuals and a relatively high mortality rate. COVID-19 patients that develop cardiac injury are at increased risk of a worse clinical course with higher rates of mortality. Increasing amounts of evidence suggest that a system-wide inflammatory response and a cytokine storm mediated type syndrome plays a crucial role in disease progression. This systematic review investigates the possible role of hyperinflammation in inducing cardiac injury as one of the severe complications of COVID-19. A systematic literature search was performed using PubMed, Embase and Scopus databases to identify relevant clinical studies that investigated cardiovascular injury manifestations and reported inflammatory and cardiac biomarkers in COVID-19 patients. Only 29 studies met our inclusion criteria and the majority of these studies demonstrated significantly elevated inflammatory and cardiac blood markers. It was evident that underlying cardiovascular diseases may increase the risk of developing cardiac injury. However, many COVID-19 patients included in this review, developed different types of cardiac injury without having any underlying cardiovascular diseases. Furthermore, many of these patients were either children or adolescents. Therefore, age and comorbidities may not always be the two main risk factors that dictate the severity and outcome of COVID-19. Further investigations are required to understand the underlying mechanisms of pathogenicity as an urgent requirement to develop the appropriate treatment and prevention strategies. These strategies may specifically target hyperinflammation as a suspected driving factor for some of the severe complications of COVID-19.	no

2021	SARS-CoV-2 seroprevalence, and IgG concentration and pseudovirus neutralising antibody titres after infection, compared by HIV status: a matched case-control observational study.	Most cohorts show similar or lower COVID-19 incidence among people living with HIV compared with the general population. However, incidence might be affected by lower testing rates among vulnerable populations. We aimed to compare SARS-CoV-2 IgG seroprevalence, disease severity, and neutralising antibody activity after infection among people with and without HIV receiving care in a county hospital system over a 3-month period. In this matched case-control observational study, remnant serum samples were collected between Aug 1 and Oct 31, 2020, from all people living with HIV who underwent routine outpatient laboratory testing in a municipal health-care system (San Francisco General Hospital, CA, USA). Samples from people living with HIV were date of collection-matched (same day) and age-matched (±5 years) to samples from randomly selected adults (aged 18 years or older) without HIV receiving care for chronic conditions at the same hospital. We compared seroprevalence by HIV status via mixed-effects logistic regression models, accounting for the matched structure of the data (random effects for the matched group), adjusting for age, sex, race or ethnicity, and clinical factors (ie, history of cardiovascular or pulmonary disease, and type 2 diabetes). Severe COVID-19 was assessed in participants with past SARS-CoV-2 (IgG or PCR) infection by chart review and compared with multivariable mixed-effects logistic regression, adjusting for age and sex. SARS-CoV-2 IgG, neutralising antibody titres, and antibody avidity were measured in serum of participants with previous positive PCR tests and compared with multivariable mixed-effects models, adjusting for age, sex, and time since PCR-confirmed SARS-CoV-2 infection. 1138 samples from 955 people living with HIV and 1118 samples from 1062 people without HIV were tested. SARS-CoV-2 IgG seroprevalence was 3·7% (95% CI 2·4 to 5·0) among people with HIV compared with 7·4% (5·7 to 9·2) among people without HIV (adjusted odds ratio 0·50, 95% CI 0·30 to 0·83). Among 31 people with HIV and 70 people without HIV who had evidence of past infection, the odds of severe COVID-19 were 5·52 (95% CI 1·01 to 64·48) times higher among people living with HIV. Adjusting for time since PCR-confirmed infection, SARS-CoV-2 IgG concentrations were lower (percentage change -53%, 95% CI -4 to -76), pseudovirus neutralising antibody titres were lower (-67%, -25 to -86), and avidity was similar (7%, -73 to 87) among people living with HIV compared with those without HIV. Although fewer infections were detected by SARS-CoV-2 IgG testing among people living with HIV than among those without HIV, people with HIV had more cases of severe COVID-19. Among people living with HIV with past SARS-CoV-2 infection, lower IgG concentrations and pseudovirus neutralising antibody titres might reflect a diminished serological response to infection, and the similar avidity could be driven by similar time since infection. US National Institute of Allergy and Infectious Diseases, US National Institutes of Health.	no

2021	Predicting COVID-19 Severity with a Specific Nucleocapsid Antibody plus Disease Risk Factor Score.	Effective methods for predicting COVID-19 disease trajectories are urgently needed. Here, enzyme-linked immunosorbent assay (ELISA) and coronavirus antigen microarray (COVAM) analysis mapped antibody epitopes in the plasma of COVID-19 patients (n = 86) experiencing a wide range of disease states. The experiments identified antibodies to a 21-residue epitope from nucleocapsid (termed Ep9) associated with severe disease, including admission to the intensive care unit (ICU), requirement for ventilators, or death. Importantly, anti-Ep9 antibodies can be detected within 6 days post-symptom onset and sometimes within 1 day. Furthermore, anti-Ep9 antibodies correlate with various comorbidities and hallmarks of immune hyperactivity. We introduce a simple-to-calculate, disease risk factor score to quantitate each patient's comorbidities and age. For patients with anti-Ep9 antibodies, scores above 3.0 predict more severe disease outcomes with a 13.42 likelihood ratio (96.7% specificity). The results lay the groundwork for a new type of COVID-19 prognostic to allow early identification and triage of high-risk patients. Such information could guide more effective therapeutic intervention. IMPORTANCE The COVID-19 pandemic has resulted in over two million deaths worldwide. Despite efforts to fight the virus, the disease continues to overwhelm hospitals with severely ill patients. Diagnosis of COVID-19 is readily accomplished through a multitude of reliable testing platforms; however, prognostic prediction remains elusive. To this end, we identified a short epitope from the SARS-CoV-2 nucleocapsid protein and also a disease risk factor score based upon comorbidities and age. The presence of antibodies specifically binding to this epitope plus a score cutoff can predict severe COVID-19 outcomes with 96.7% specificity.	
2021	The influence of HLA genotype on the severity of COVID-19 infection.	The impact of COVID-19 varies markedly, not only between individual patients but also between different populations. We hypothesised that differences in human leukocyte antigen (HLA) genes might influence this variation. Using next generation sequencing, we analysed the class I and class II classical HLA genes of 147 individuals of European descent experiencing variable clinical outcomes following COVID-19 infection. Forty-nine of these patients were admitted to hospital with severe respiratory disease. They had no significant pre-existing comorbidities. We compared the results to those obtained from a group of 69 asymptomatic hospital workers who evidence of COVID exposure based on blood antibody testing. Allele frequencies in both the severe and asymptomatic groups were compared to local and national healthy controls with adjustments made for age and sex. With the inclusion of hospital staff who had reported localised symptoms only (limited to loss of smell/taste, n = 13) or systemic symptoms not requiring hospital treatment (n = 16), we carried out ordinal logistic regression modelling to determine the relative influence of age, BMI, sex and the presence of specific HLA genes on symptomatology. We found a significant difference in the allele frequency of HLA-DRB1*04:01 in the severe patient compared to the asymptomatic staff group (5.1% vs. 16.7%, P = .003 after adjustment for age and sex). There was a significantly lower frequency of the haplotype DQA1*01:01-DQB1*05:01-DRB1*01:01 in the asymptomatic group compared to the background population (P = .007). Ordinal logistic regression modelling confirmed the significant influence of DRB1*04:01 on the clinical severity of COVID-19 observed in the cohorts. These alleles are found in greater frequencies in the North Western European population. This regional study provides evidence that HLA genotype influences clinical outcome	no

		in COVID-19 infection. Validation studies must take account of the complex genetic architecture of the immune system across different geographies and ethnicities.	
2021	ABO blood groups, COVID-19 infection and mortality.	A recent study showed that the ABO gene, chr 9q34.2, which determines blood type, may affect COVID-19 disease severity, although this result has not been reproducible. A UK study of 2200 COVID-19 patients found no relationship of ABO blood type to disease severity. A Danish study identified ABO blood group as a risk factor for SARS-CoV-2 infection but not for hospitalization or death from COVID-19. In the current study, we wished to analyze the relationship of ABO blood group and the ABO genetic locus to COVID-19 test positivity and mortality in subjects from the UK Biobank (UKB). ABO blood type is from UKB data field 23165. Blood type was imputed for genotyped UK Biobank participants using three SNPs (rs505922, rs8176719, and rs8176746) in the ABO gene on chromosome 9q34.2. We analyzed the chromosome 9 snp rs657152 to assess the relationship of the ABO locus to COVID-19 test positivity and mortality. COVID-19 test results (negative or positive) were not related to blood group in males ($p = 0.977$, two tailed Fisher exact test) or females ($p = 0.548$). COVID-19 outcomes (alive or died) were not related to blood group in males ($p = 0.102$, two tailed Fisher exact test) or females ($p = 0.226$). We found no significant relationship of rs657152 to COVID-19 test positivity or mortality. We were not able to confirm that ABO blood group influences risk of COVID-19 infection or outcome.	yes
2021	Severe COVID-19 in an APS1 patient with interferon autoantibodies treated with plasmapheresis.	NA	no

2021	Trans-ancestry analysis reveals genetic and nongenetic associations with COVID-19 susceptibility and severity.	COVID-19 presents with a wide range of severity, from asymptomatic in some individuals to fatal in others. Based on a study of 1,051,032 23andMe research participants, we report genetic and nongenetic associations with testing positive for SARS-CoV-2, respiratory symptoms and hospitalization. Using trans-ancestry genome-wide association studies, we identified a strong association between blood type and COVID-19 diagnosis, as well as a gene-rich locus on chromosome 3p21.31 that is more strongly associated with outcome severity. Hospitalization risk factors include advancing age, male sex, obesity, lower socioeconomic status, non-European ancestry and preexisting cardiometabolic conditions. While non-European ancestry was a significant risk factor for hospitalization after adjusting for sociodemographics and preexisting health conditions, we did not find evidence that these two primary genetic associations explain risk differences between populations for severe COVID-19 outcomes.	yes
2021	The Impact of COVID-19 Pandemic Lockdown on the Incidence of New-Onset Type 1 Diabetes and Ketoacidosis Among Saudi Children.	Overburdened healthcare systems during the coronavirus disease (COVID-19) pandemic led to suboptimal chronic disease management, including that of pediatric type 1 diabetes mellitus (T1DM). The pandemic also caused delayed detection of new-onset diabetes in children; this increased the risk and severity of diabetic ketoacidosis (DKA). We therefore investigated the frequency of new-onset pediatric T1DM and DKA in Saudi Arabia during the COVID-19 pandemic and compared it to the same period in 2019. We conducted a multicenter retrospective cohort study, including patients aged 1-14 years admitted with new-onset T1DM or DKA during the COVID-19 pandemic (March-June 2020) and the same period in 2019. We assessed factors including age, sex, anthropometric measures, nationality, duration of diabetes, diabetes management, HbA1c levels, glycemic control, cause of admission, blood gas levels, etiology of DKA, DKA complications, length of hospital stay, and COVID-19 test status. During the lockdown, 106 children, compared with 154 in 2019, were admitted to 6 pediatric diabetes centers. Among the admissions, DKA was higher in 2020 than in 2019 (83% vs. 73%; P =0.05; risk ratio=1.15; 95% confidence interval, 1.04-1.26), after adjusting for age and sex. DKA frequency among new-onset T1DM and HbA1c levels at diagnosis were higher in 2020 than in 2019 (26% vs. 13.4% [P =<0.001] and 12.1 ± 0.2 vs. 10.8 ± 0.25 [P <0.001], respectively). Females and older patients had a higher risk of DKA. The lockdown implemented in Saudi Arabia has significantly impacted children with T1DM and led to an increased DKA frequency, including children with new-onset T1DM, potentially owing to delayed presentation.	yes
2021	A novel application of delayed-type hipersensitivity reaction to measure cellular immune response in SARS-CoV-2 exposed individuals.	To understand the anti-virus adaptive immune response occurring during SARS-Cov-2 infection is necessary to have methods to investigate cellular and humoral components. The goal of this study has been to investigate the utility of a specific spike-DTH test using a coronavirus recombinant protein in COVID-19 patients. DTH studies were performed by intradermal injection of a commercial recombinant spike protein from SARS-CoV-2 along with conventional serology studies. Fifty-one COVID-19 patients were studied showing 84,3% of concordance with spike-DTH and anti-RBD-IgG. Spike-DTH was superior to identify seven more COVID-19 individuals. A high specificity was found with no positive spike DTH reactions in the non-sick individuals. The skin test also showed more stable results over time while specific anti-RBD-IgG decreased gradually. Clinical severity groups also showed a progressive gradient of larger positive spike-DTH.	yes

		Specific spike DTH test seems to be an easy method to study cell immune response.	
2021	Neutralizing Autoantibodies to Type I IFNs in >10% of Patients with Severe COVID-19 Pneumonia Hospitalized in Madrid, Spain.	In a recent study, autoantibodies neutralizing type I interferons (IFNs) were present in at least 10% of cases of critical COVID-19 pneumonia. These autoantibodies neutralized most type I IFNs but rarely IFN-beta. We aimed to define the prevalence of autoantibodies neutralizing type I IFN in a cohort of patients with severe COVID-19 pneumonia treated with IFN-beta-1b during hospitalization and to analyze their impact on various clinical variables and outcomes. We analyzed stored serum/plasma samples and clinical data of COVID-19 patients treated subcutaneously with IFN-beta-1b from March to May 2020, at the Infanta Leonor University Hospital in Madrid, Spain. The cohort comprised 47 COVID-19 patients with severe pneumonia, 16 of whom (34%) had a critical progression requiring ICU admission. The median age was 71 years, with 28 men (58.6%). Type I IFN-alpha- and omega-neutralizing autoantibodies were found in 5 of 47 patients with severe pneumonia or critical disease (10.6%), while they were not found in any of the 118 asymptomatic controls ($p = 0.0016$). The autoantibodies did not neutralize IFN-beta. No demographic, comorbidity, or clinical differences were seen between individuals with or without autoantibodies. We found a significant correlation between the presence of neutralizing autoantibodies and higher C-reactive protein levels ($p = 5.10e-03$) and lower lymphocyte counts ($p = 1.80e-02$). No significant association with response to IFN-beta-1b therapy ($p = 0.34$) was found. Survival analysis suggested that neutralizing autoantibodies may increase the risk of death (4/5, 80% vs 12/42, 28.5%). Autoantibodies neutralizing type I IFN underlie severe/critical COVID-19 stages in at least 10% of cases, correlate with increased C-RP and lower lymphocyte counts, and confer a trend towards increased risk of death. Subcutaneous IFN-beta treatment of hospitalized patients did not seem to improve clinical outcome. Studies of earlier, ambulatory IFN-beta treatment are warranted.	no

2021	Longitudinal Peripheral Blood Transcriptional Analysis Reveals Molecular Signatures of Disease Progression in COVID-19 Patients.	Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with some patients developing severe illness or even death. Disease severity has been associated with increased levels of proinflammatory cytokines and lymphopenia. To elucidate the atlas of peripheral immune response and pathways that might lead to immunopathology during COVID-19 disease course, we performed a peripheral blood RNA sequencing analysis of the same patient's samples collected from symptom onset to full recovery. We found that PBMCs at different disease stages exhibited unique transcriptome characteristics. We observed that SARS-CoV-2 infection caused excessive release of inflammatory cytokines and lipid mediators as well as an aberrant increase of low-density neutrophils. Further analysis revealed an increased expression of RNA sensors and robust IFN-stimulated genes expression but a repressed type I IFN production. SARS-CoV-2 infection activated T and B cell responses during the early onset but resulted in transient adaptive immunosuppression during severe disease state. Activation of apoptotic pathways and functional exhaustion may contribute to the reduction of lymphocytes and dysfunction of adaptive immunity, whereas increase in IL2 , IL7 , and IL15 may facilitate the recovery of the number and function of lymphocytes. Our study provides comprehensive transcriptional signatures of peripheral blood response in patients with moderate COVID-19.	no

2021	[Coronavirus disease 2019 in Northeastern Sichuan: clinical characteristics and treatment analysis of 59 cases].	To analyze the epidemiological, clinical characteristics and treatment of coronavirus disease 2019 (COVID-19) in Northeastern Sichuan, and summarize experience in time to provide reference for clinical diagnosis and treatment. A retrospective study was conducted. Fifty-nine patients with COVID-19 admitted to Bazhong Central Hospital and Dazhou Central Hospital from January 27th to February 9th, 2020 were selected as the subjects. The data of demography, epidemiology, laboratory examination, chest CT and related clinical treatment were collected. According to the severity of the disease, the patients were divided into three types: mild, general and severe types, and the differences of the above indices among different clinical types were compared. (1) General information and epidemiology: 31 cases (52.5%) were male, 28 cases (47.5%) were female, the average age was (42.0±16.4) years old, and the patients over 40 years old accounted for the largest proportion (35 cases, 59.3%). The proportion of clinical type was 72.9% (43 cases) in general type, and 62.7% (37 cases) were imported type. With the increase of disease severity, the average age of patients also showed a significant increase trend [the age of the mild, general and severe patients were (30.9±13.6), (42.7±15.3), (55.8±18.9) years old, $P < 0.01$]. The proportion of patients with more than one basic disease in severe patients was significantly higher than those in mild and general patients [66.7% (4/6) vs. 20.0% (2/10), 9.3% (4/43), both $P < 0.05$]. In the distribution of clinical symptoms, the proportion of severe patients with chest distress/dyspnea was significantly higher than those in mild and general patients [66.7% (4/6) vs. 10.0% (1/10), 11.6% (5/43), both $P < 0.05$]. (2) Laboratory examination index: the total number of white blood cell count (WBC), neutrophils count (NEU), C-reactive protein (CRP) in severe patients were higher than those in mild patients and general patients [WBC (×10 9 /L): 7.21±4.35 vs. 5.85±1.69, 5.43±2.04; NEU (×10 9 /L): 6.09±4.43 vs. 3.95±1.45, 3.54±1.83; CRP (mg/L): 16.00 (8.20, 46.43) vs. 5.00 (0.00, 16.13), 15.00 (3.13, 28.58)], the albumin (Alb) level in severe patients was lower than those in mild and general patients (g/L: 38.00±5.35 vs. 49.23±5.27, 39.81±2.15, both $P < 0.05$), while the hemoglobin (Hb) level in mild patients was higher than that in severe and general patients (g/L: 155.2±12.1 vs. 141.3±6.8, 131.1±11.7, both $P < 0.05$). (3) Chest imaging: the CT manifestations of typical cases were single or multiple ground glass shadows. With the progress of the disease, the focus gradually increased, the scope gradually expanded, and multiple solid shadows of lung lobes were involved. (4) Treatment: all patients received at least 2 kinds of antiviral therapy, and the application rate of Interferon and Ribavirin in severe patients were higher than those in mild and general patients [100.0% (6/6) vs. 80.0% (8/10), 97.7% (42/43); 83.3% (5/6) vs. 0% (0/10), 20.9% (9/43); all $P < 0.05$]. (5) Prognosis: until March 6th 2020, 50 patients (84.8%) were discharged from the hospital after rehabilitation, and the remaining 9 patients were still under treatment, none deaths. The proportion of severe patients with chest distress/dyspnea is higher, the older the patients are and the more basic diseases are, the more likely they are to develop into severe type. High resolution chest CT could be considered for suspected cases or even fever patients, which may show the progress of the disease.	no

2021	The role of chest CT quantitative pulmonary inflammatory index in the evaluation of the course and treatment outcome of COVID-19 pneumonia.	To explore the clinical application value of chest CT quantitative pulmonary inflammation index (PII) in the evaluation of the course and treatment outcome of COVID-19 pneumonia. One hundred and eighteen patients with COVID-19 pneumonia diagnosed by RT-PCR were analyzed retrospectively. The correlation between chest CT PII, clinical symptoms and laboratory examinations during the entire hospitalization period was compared. The average age of the patients was 46.0 ± 15 (range: 1-74) years. Of the 118 patients, 62 are male (52.5%) and 56 are female (47.5%). Among them, 116 patients recovered and were discharged, 2 patients died, and the median length of hospital stay was 22 (range: 9-41) days. On admission, 76.3% of the patients presented with fever, and the laboratory studies showed a decrease in lymphocyte (LYM) count and an increase in lactate dehydrogenase (LDH) levels, C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR). Within the studies' chest CTs, the median number of involved lung lobes was 4 (range: 0-5) and the median number of involved lung segments was 9 (range 0-20). The left lower lobe and the right lower lobe were the most likely areas to be involved (89.0% and 83.9%), and 84.7% of the patients had inflammatory changes in both lungs. The main manifestations on chest CT were ground glass opacities (31.4%), ground glass opacities and consolidation (20.3%), ground glass opacities and reticular patterns (32.2%), mixed type (13.6%), and white lungs (1.7%); common accompanying signs included linear opacities (55.9%), air bronchograms (46.6%), thick small vessel shadows (36.4%), and pleural hypertrophy (13.6%). The chest CT at discharge showed complete absorption of lesions in 19 cases (16.1%), but not in the remaining 99 cases. Lesions remained in a median of 3 lung lobes (range: 0-5). Residual lesions remained in a median of 5 lung segments (range: 0-20). The residual lesions mainly presented as ground glass opacities (61.0%), and the main accompanying sign was linear opacities (59.3%). Based on chest CT, the median maximum PII of lungs was 30.0% (range: 0-97.5%), and the median PII after discharge in the patients excluding the two deaths was 12.5% (range: 0-53.0%). PII was significantly negatively correlated with the LYM count and significantly positively correlated with body temperature, LDH, CRP, and ESR. There was no significant correlation between the PII and the white blood cell count, but the grade of PII correlated well with the clinical classification. PII can be used to monitor the severity and the treatment outcome of COVID-19 pneumonia, provide help for clinical classification, assist in treatment plan adjustments and aid assessments for discharge.	no

2021	Association between the HLA genotype and the severity of COVID-19 infection among South Asians.	Regional variations are found in the incidence and severity of the COVID-19 infection. Human leukocyte antigen (HLA) polymorphism is one of the genetic factors that might have an impact on the outcome of the disease. This study explored the association between the HLA genotype and the severity of COVID-19 among patients from South Asia. Blood samples from 95 Asians (Bangladeshis, Indians, and Pakistanis) with COVID-19 were collected. The patients were divided according to the severity of their infection: mild (N = 64), severe (N = 31), and fatal (N = 20). DNA was extracted from all samples, and HLA genotyping was performed for both class I (A, B, and C) and class II (DRB1, DQA1, and DQB1) using the PCR-rSSO (polymerase chain reaction-reverse sequence-specific oligonucleotide) molecular method. The frequency of HLA-B*51 was significantly higher among patients in the fatal group than among those in the mild infection group (15% vs. 4.7%, p = 0.027). Additionally, the frequency of HLA-B*35 was significantly higher in the mild infection group than in the fatal group (21.1% vs. 7.5%, p = 0.050 [a borderline p-value]). In terms of HLA class II, DRB1*13 was significantly observed in the fatal group than in the mild infection group (17.5% vs. 11.3%, p = 0.049). However, the p-value for all alleles became insignificant after a statistical correction for the p-values (p c = 0.216, p c = 0.4, and p c = 0.49, respectively). Compared with all published data, this study highlights that the association between the HLA system and the COVID-19 outcome might be ethnic-dependent. Genetic variation between populations must be examined on a wider scale to assess infection prognosis and vaccine effectiveness.	yes
2021	Association of ABO blood groups with presentation and outcomes of confirmed SARS CoV-2 infection: A prospective study in the largest COVID-19 dedicated hospital in Bangladesh.	Globally, studies have shown conflicting results regarding the association of blood groups with SARS CoV-2 infection. To observe the association between ABO blood groups and the presentation and outcomes of confirmed COVID-19 cases. This was a prospective cohort study of patients with mild-to-moderately severe COVID-19 infections who presented in the COVID-19 unit of Dhaka Medical College Hospital and were enrolled between 01 June and 25 August, 2020. Patients were followed up for at least 30 days after disease onset. We grouped participants with A-positive and A-negative blood groups into group I and participants with other blood groups into group II. The cohort included 438 patients; 52 patients were lost to follow-up, five died, and 381 completed the study. The prevalence of blood group A [144 (32.9%)] was significantly higher among COVID-19 patients than in the general population (p < 0.001). The presenting age [mean (SD)] of group I [42.1 (14.5)] was higher than that of group II [38.8 (12.4), p = 0.014]. Sex (p = 0.23) and co-morbidity (hypertension, p = 0.34; diabetes, p = 0.13) did not differ between the patients in groups I and II. No differences were observed regarding important presenting symptoms, including fever (p = 0.72), cough (p = 0.69), and respiratory distress (p = 0.09). There was no significant difference in the median duration of symptoms in the two group (12 days), and conversion to the next level of severity was observed in 26 (20.6%) and 36 patients (13.8%) in group I and II, respectively. However, persistent positivity of RT-PCR at 14 days of initial positivity was more frequent among the patients in group I [24 (19%)] than among those in group II [29 (11.1%)]. The prevalence of blood group A was higher among COVID-19 patients. Although ABO blood groups were not associated with the presentation or recovery period of COVID-19, patients with blood group A had delayed seroconversion.	yes

2021	Evaluation the relationship of left ventricular global longitudinal strain and laboratory parameters in discharged patients with COVID-19: a follow-up study.	The novel coronavirus infection (COVID-19) disease has spread rapidly and posed a great threat to global public health. The laboratory parameters and clinical outcomes of the disease in discharged patients remain unknown. In this study, we aimed to investigate the laboratory and echocardiographic findings of patients with COVID-19 after discharge and the relation between left ventricular global longitudinal strain (LVGLS) and inflammatory parameters in discharged patients. A total of 75 patients recovering from COVID-19 as the study group were prospectively recruited from the COVID-19 outpatient clinic for their follow-up visits at a median 6 months after discharge. Patients were classified into groups according to pneumonia severity and impairment in LVGLS. Laboratory findings of patients both at admission and after discharge were evaluated and the relation with pneumonia severity at admission and LVGLS after discharge were analyzed. Serum ferritin, lactate dehydrogenase (LDH) and prohormone B-type natriuretic peptide (pro-BNP) levels after discharge were significantly higher in the study group than the control group (n = 44). Ferritin was found to be related to pneumonia severity. Serum ferritin and LDH values after discharge were significantly higher in patients with impaired LVGLS than those with preserved. There was a significant correlation between LVGLS, serum ferritin and LDH values after discharge (r = -0.252, p = 0.012; r = -0.268, p = 0.005, respectively). Clinicians should pay close attention to the serum ferritin and LDH levels in discharged patients for predicting the severity of COVID-19 disease and early identification of subclinical left ventricular myocardial dysfunction.	no
2021	CD169/SIGLEC1 is expressed on circulating monocytes in COVID-19 and expression levels are associated with disease severity.	Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Type I interferons are important in the defense of viral infections. Recently, neutralizing IgG auto-antibodies against type I interferons were found in patients with severe COVID-19 infection. Here, we analyzed expression of CD169/SIGLEC1, a well described downstream molecule in interferon signaling, and found increased monocytic CD169/SIGLEC1 expression levels in patients with mild, acute COVID-19, compared to patients with severe disease. We recommend further clinical studies to evaluate the value of CD169/SIGLEC1 expression in patients with COVID-19 with or without auto-antibodies against type I interferons.	no
2021	Preinfection glycaemic control and disease severity among patients with type 2 diabetes and COVID-19: A retrospective, cohort study.	NA	no

2021	Diabetes prevalence and mortality in COVID-19 patients: a systematic review, meta-analysis, and meta-regression.	The coronavirus disease 2019 (COVID-19) patients with diabetes mellitus (DM) are at high risk of fatal outcomes. This meta-analysis quantifies the prevalence of mortality among (1) diabetic and (2) non-diabetic, and (3) the prevalence of DM, in hospitalized COVID-19 patients. Published studies were retrieved from four electronic databases (PubMed, Embase, Scopus, and medRxiv) and appraised critically utilizing the National Heart, Lung, and Blood Institute's tool. Meta-analyses were performed using the random-effects model. The measures of heterogeneity were ascertained by I- squared (I 2) and Chi-squared (Chi 2) tests statistics. Predictors of heterogeneity were quantified using meta-regression models. Of the reviewed 475 publications, 22 studies (chiefly case series (59.09 %)), sourcing data of 45,775 hospitalized COVID-19 patients, were deemed eligible. The weighted prevalence of mortality in hospitlized COVID-19 patients with DM (20.0 %, 95 % CI: 15.0-26.0; I 2 , 96.8 %) was 82 % (1.82-time) higher than that in non-DM patients (11.0 %, 95 % CI: 5.0-16.0; I 2 , 99.3 %). The prevalence of mortality among DM patients was highest in Europe (28.0 %; 95 % CI: 14.0-44.0) followed by the United States (20.0 %, 95 % CI: 11.0-32.0) and Asia (17.0 %, 95 % CI: 8.0-28.0). Sample size and severity of the COVID-19 were associated ($p < 0.05$) with variability in the prevalence of mortality. The weighted prevalence of DM among hospitalized COVID-19 patients was 20 % (95 % confidence interval [CI]: 15-25, I 2 , 99.3 %). Overall, the quality of the studies was fair. Hospitalized COVID-19 patients were appreciably burdened with a high prevalence of DM. DM contributed to the increased risk of mortality among hospitalized COVID-19 patients compared to non-DM patients, particularly among critically ill patients. Registration : PROSPERO (registration no. CRD42020196589). The online version contains supplementary material available at 10.1007/s40200-021-00779-2.	no
2021	Association of Sociodemographic Factors and Blood Group Type With Risk of COVID-19 in a US Population.	NA	yes
2021	Covid-19 and diabetes in primary care - How do hematological parameters present in this cohort?	Objectives : Changes in hematological parameters are becoming evident as important early markers of COVID-19. Type 2 Diabetes Mellitus (T2DM) has been shown to be associated with increased severity of COVID-19. In this study, we aim to explore the various hematological variables in COVID-19 positive patients with T2DM, so as to act early and improve patient outcomes. Methods : Medical e-records of seventy adult patients with T2DM who were COVID-19 positive have been analyzed in this retrospective cohort study. Demographic, clinical and laboratory parameters for these patients were examined. Results : Of the seventy patients with T2DM, 48.88% had poorly controlled diabetes. 70.69% were pyrexial, 56.25% were tachycardic and 38.58% were asymptomatic on presentation. Amongst the hematological parameters, anemia was seen in 10% of males and 15.38% of females. 20% had a high red-blood-cell-distribution-width (RDW). 7.27% had thrombocytosis and 3.64% had thrombocytopenia. 73.3% had a high platelet-distribution-width (PDW) and 44.44% had an increased mean-platelet-volume (MPV). 16.36% were neutropenic and 16.67% had lymphocytopenia. Conclusion : Diabetic COVID-19 positive patients have been shown to have prominent manifestations of the hemopoietic-system with varied hematological profiles. Recognizing the implications	no

		of these variables early in primary-care, can help clinicians aid management decisions and dictate early referral to secondary-care services, to help improve prognosis.	
2021	Downregulation of type III interferons in patients with severe COVID-19.	Coronavirus disease 2019 (COVID-19) is globally rampant, and to curb the growing burden of this disease, in-depth knowledge about its pathophysiology is needed. This was an observational study conducted at a single center to investigate serum cytokine and chemokine levels of COVID-19 patients, based on disease severity. We included 72 consecutive COVID-19 patients admitted to our hospital from March 21 to August 31, 2020. Patients were divided into Mild-Moderate I (mild) and Moderate II-Severe (severe) groups based on the COVID-19 severity classification developed by the Ministry of Health, Labor and Welfare (MHLW) of Japan. We compared the patient characteristics as well as the serum cytokine and chemokine levels on the day of admission between the two groups. Our findings indicated that the severe group had significantly higher levels of serum fibrinogen, d-dimer, lactate dehydrogenase, C-reactive protein, ferritin, Krebs von den Lungen-6, surfactant protein (SP)-D, and SP-A than the mild group. Strikingly, the levels of interleukin (IL)-28A/interferon (IFN)-λ2 were significantly lower in the severe group than in the mild group. We believe that reduced levels of type III interferons (IFN-λs) and alterations in the levels of other cytokines and chemokines may impact the severity of the disease.	no

2021	The Role of Immunogenetics in COVID-19.	Coronavirus disease 2019 (COVID-19) is induced by SARS-CoV-2 and may arise as a variety of clinical manifestations, ranging from an asymptomatic condition to a life-threatening disease associated with cytokine storm, multiorgan and respiratory failure. The molecular mechanism behind such variability is still under investigation. Several pieces of experimental evidence suggest that genetic variants influencing the onset, maintenance and resolution of the immune response may be fundamental in predicting the evolution of the disease. The identification of genetic variants behind immune system reactivity and function in COVID-19 may help in the elaboration of personalized therapeutic strategies. In the frenetic look for universally shared treatment plans, those genetic variants that are common to other diseases/models may also help in addressing future research in terms of drug repurposing. In this paper, we discuss the most recent updates about the role of immunogenetics in determining the susceptibility to and the history of SARS-CoV-2 infection. We propose a narrative review of available data, speculating about lessons that we have learnt from other viral infections and immunosenescence, and discussing what kind of aspects of research should be deepened in order to improve our knowledge of how host genetic variability impacts the outcome for COVID-19 patients.	yes
2021	The association of ABO blood type with the risk and severity of COVID-19 infection.	There is conflicting data in the literature about the association of ABO blood type and susceptibility to COVID-19 infection. Moreover, very few studies have examined the effect of blood type on severity of COVID-19 infection. This was a retrospective, single-center analysis of adult patients with COVID-19 infection who were hospitalized between March 8 th to July 31 st , 2020 at a regional tertiary care hospital. All patients who were hospitalized with a diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and had a documented ABO blood type were enrolled in this analysis. Aims of this study were to examine the prevalence of ABO blood types in patients with COVID-19 infection and to determine the frequency of severe COVID-19 infection among ABO blood types. A total of 227 cases were identified. Our cohort had a mean age of 63.3 years and 60% were males. The most common blood type was O (49%) followed by A (36%), which was similar to the prevalence of ABO blood types in our regional population. Moreover, there was no significant difference in the frequency of severe COVID-19 infection between ABO blood types (O: 50%, A: 53%, B: 56%, AB: 57%; P=0.93), or any additional outcomes including in-hospital mortality rate (P=0.72), need for ICU admission (P=0.66), ICU free days at day 28 (P=0.51), hospital free days at day 28 (P=0.43), or need for acute renal replacement therapy (P=0.09). We did not find an increased susceptibility of any blood type to COVID-19 infection, nor was there an increased risk of severe COVID-19 infection in any ABO blood types.	yes

2021	Differentially expressed immune response genes in COVID-19 patients based on disease severity.	Dysregulated immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are thought to underlie the progression of coronavirus disease 2019 (COVID-19). We sought to further characterize host antiviral and cytokine gene expression in COVID-19 patients based on illness severity. In this case-control study, we retrospectively analyzed 46 recovered COVID-19 patients and 24 healthy subjects (no history of COVID-19) recruited from the Second People's Hospital of Fuyang City. Blood samples were collected from each study participant for RNA extraction and PCR. We assessed changes in antiviral gene expression between healthy controls and patients with mild/moderate (MM) and severe/critical (SC) disease. We found that type I interferon signaling (IFNA2, TLR8, IFNA1, IFNAR1, TLR9, IRF7, ISG15, APOBEC3G, and MX1) and genes encoding proinflammatory cytokines (IL12B, IL15, IL6, IL12A and IL1B) and chemokines (CXCL9, CXCL11 and CXCL10) were upregulated in patients with MM and SC disease. Moreover, we found that IFNA1, apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G (APOBEC3G), and Fas-associated protein with death domain (FADD) were significantly downregulated ($P < 0.05$) in the SC group compared to the MM group. We also observed that microRNA (miR)-155 and miR-130a levels were markedly higher in the MM group compared to the SC group. COVID-19 is associated with the activation of host antiviral genes. Induction of the IFN system appears to be particularly important in controlling SARS-CoV-2 infection, as decreased expression of IFNA1, APOBEC3G and FADD genes in SC patients, relative to MM patients, may be associated with disease progression.	yes
2021	Increased sCD163 and sCD14 Plasmatic Levels and Depletion of Peripheral Blood Pro-Inflammatory Monocytes, Myeloid and Plasmacytoid Dendritic Cells in Patients With Severe COVID-19 Pneumonia.	Emerging evidence argues that monocytes, circulating innate immune cells, are principal players in COVID-19 pneumonia. The study aimed to investigate the role of soluble (s)CD163 and sCD14 plasmatic levels in predicting disease severity and characterize peripheral blood monocytes and dendritic cells (DCs), in patients with COVID-19 pneumonia (COVID-19 subjects). On admission, in COVID-19 subjects sCD163 and sCD14 plasmatic levels, and peripheral blood monocyte and DC subsets were compared to healthy donors (HDs). According to clinical outcome, COVID-19 subjects were divided into ARDS and non-ARDS groups. Compared to HDs, COVID-19 subjects showed higher sCD163 ($p<0.0001$) and sCD14 ($p<0.0001$) plasmatic levels. We observed higher sCD163 plasmatic levels in the ARDS group compared to the non-ARDS one ($p=0.002$). The cut-off for sCD163 plasmatic level greater than 2032 ng/ml was predictive of disease severity (AUC: 0.6786, $p=0.0022$; sensitivity 56.7% [CI: 44.1-68.4] specificity 73.8% [CI: 58.9-84.7]). Positive correlation between plasmatic levels of sCD163, LDH and IL-6 and between plasmatic levels of sCD14, D-dimer and ferritin were found. Compared to HDs, COVID-19 subjects showed lower percentages of non-classical ($p=0.0012$) and intermediate monocytes ($p=0.0447$), slanDCs ($p<0.0001$), myeloid DCs (mDCs, $p<0.0001$), and plasmacytoid DCs (pDCs, $p=0.0014$). Compared to the non-ARDS group, the ARDS group showed lower percentages of non-classical monocytes ($p=0.0006$), mDCs ($p=0.0346$), and pDCs ($p=0.0492$). The increase in sCD163 and sCD14 plasmatic levels, observed on hospital admission in COVID-19 subjects, especially in those who developed ARDS, and the correlations of these monocyte/macrophage activation markers with typical inflammatory markers of COVID-19 pneumonia, underline their potential use to assess the risk of progression of the disease. In an early stage of the disease, the assessment of sCD163	no

		plasmatic levels could have clinical utility in predicting the severity of COVID-19 pneumonia.	
2021	Immunological Characteristics in Type 2 Diabetes Mellitus Among COVID-19 Patients.	www.ClinicalTrials.gov, identifier: NCT04365634. Diabetes mellitus was associated with increased severity and mortality of disease in COVID-19 pneumonia. So far the effect of type 2 diabetes (T2DM) or hyperglycemia on the immune system among COVID-19 disease has remained unclear. We aim to explore the clinical and immunological features of type 2 diabetes mellitus (T2DM) among COVID-19 patients. In this retrospective study, the clinical and immunological characteristics of 306 hospitalized confirmed COVID-19 patients (including 129 diabetic and 177 non-diabetic patients) were analyzed. The serum concentrations of laboratory parameters including cytokines and numbers of immune cells were measured and compared between diabetic and non-diabetic groups. Compared with non-diabetic group, diabetic cases more frequently had lymphopenia and hyperglycemia, with higher levels of urea nitrogen, myoglobin, D-dimer and ferritin. Diabetic cases indicated the obviously elevated mortality and the higher levels of cytokines IL-2R, IL-6, IL-8, IL-10, and TNF-α, as well as the distinctly reduced Th1/Th2 cytokines ratios compared with non-diabetic cases. The longitudinal assays showed that compared to that at week 1, the levels of IL-6 and IL-8 were significantly elevated at week 2 after admission in non-survivors of diabetic cases, whereas there were greatly reductions from week 1 to week 2 in survivors of diabetic cases. Compared with survival diabetic patients, non-survival diabetic cases displayed distinct higher serum concentrations of IL-2R, IL-6, IL-8, IL-10, TNF-α, and lower Th1/Th2 cytokines ratios at week 2. Samples from a subset of participants were evaluated by flow cytometry for the immune cells. The counts of peripheral total T lymphocytes, CD4 + T cells, CD8 + T cells and NK cells were markedly lower in diabetic cases than in non-diabetic cases. The non-survivors showed the markedly declined counts of CD8 + T cells and NK cells than survivors. The elevated cytokines, imbalance of Th1/Th2 cytokines	no

		ratios and reduced of peripheral numbers of CD8 + T cells and NK cells might contribute to the pathogenic mechanisms of high mortality of COVID-19 patients with T2DM.	
2021	Type I, II, and III interferon signatures correspond to COVID-19 disease severity.	We analyzed the plasma levels of interferons and cytokines, and the expression of interferon-stimulated genes in peripheral blood mononuclear cells in COVID-19 patients with different disease severity. Mild patients exhibited transient type I interferon responses, while ICU patients had prolonged type I interferon responses with hyper-inflammation mediated by interferon regulatory factor 1. Type II interferon responses were compromised in ICU patients. Type III interferon responses were induced in the early phase of SARS-CoV-2 infection, even in convalescent patients. These results highlight the importance of type I and III interferon responses during the early phase of infection in controlling COVID-19 progression.	no
2021	Longitudinal single-cell epitope and RNA-sequencing reveals the immunological impact of type 1 interferon autoantibodies in critical COVID-19.	Type I interferon (IFN-I) neutralizing autoantibodies have been found in some critical COVID-19 patients; however, their prevalence and longitudinal dynamics across the disease severity scale, and functional effects on circulating leukocytes remain unknown. Here, in 284 COVID-19 patients, we found IFN-I autoantibodies in 19% of critical, 6% of severe and none of the moderate cases. Longitudinal profiling of over 600,000 peripheral blood mononuclear cells using multiplexed single-cell epitope and transcriptome sequencing from 54 COVID-19 patients, 15 non-COVID-19 patients and 11 non-hospitalized healthy controls, revealed a lack of IFN-I stimulated gene (ISG-I) response in myeloid cells from critical cases, including those producing anti-IFN-I autoantibodies. Moreover, surface protein analysis showed an inverse correlation of the inhibitory receptor LAIR-1 with ISG-I expression response early in the disease course. This aberrant ISG-I response in critical patients with and without IFN-I autoantibodies, supports a unifying model for disease pathogenesis involving ISG-I suppression via convergent mechanisms.	no

2021	Evaluation of glycemic traits in susceptibility to COVID-19 risk: a Mendelian randomization study.	Observational studies suggest poorer glycemic traits and type 2 diabetes associated with coronavirus disease 2019 (COVID-19) risk although these findings could be confounded by socioeconomic position. We conducted a two-sample Mendelian randomization to clarify their role in COVID-19 risk and specific COVID-19 phenotypes (hospitalized and severe cases). We identified genetic instruments for fasting glucose (n = 133,010), 2 h glucose (n = 42,854), glycated hemoglobin (n = 123,665), and type 2 diabetes (74,124 cases and 824,006 controls) from genome wide association studies and applied them to COVID-19 Host Genetics Initiative summary statistics (17,965 COVID-19 cases and 1,370,547 population controls). We used inverse variance weighting to obtain the causal estimates of glycemic traits and genetic predisposition to type 2 diabetes in COVID-19 risk. Sensitivity analyses included MR-Egger and weighted median method. We found genetic predisposition to type 2 diabetes was not associated with any COVID-19 phenotype (OR: 1.00 per unit increase in log odds of having diabetes, 95%CI 0.97 to 1.04 for overall COVID-19; OR: 1.02, 95%CI 0.95 to 1.09 for hospitalized COVID-19; and OR: 1.00, 95%CI 0.93 to 1.08 for severe COVID-19). There were no strong evidence for an association of glycemic traits in COVID-19 phenotypes, apart from a potential inverse association for fasting glucose albeit with wide confidence interval. We provide some genetic evidence that poorer glycemic traits and predisposition to type 2 diabetes unlikely increase the risk of COVID-19. Although our study did not indicate glycemic traits increase severity of COVID-19, additional studies are needed to verify our findings.	no
2021	Identification of macrophage activation-related biomarkers in obese type 2 diabetes that may be indicative of enhanced respiratory risk in COVID-19.	Hyperactivation of the immune system through obesity and diabetes may enhance infection severity complicated by Acute Respiratory Distress Syndrome (ARDS). The objective was to determine the circulatory biomarkers for macrophage activation at baseline and after serum glucose normalization in obese type 2 diabetes (OT2D) subjects. A case-controlled interventional pilot study in OT2D (n = 23) and control subjects (n = 23). OT2D subjects underwent hyperinsulinemic clamp to normalize serum glucose. Plasma macrophage-related proteins were determined using Slow Off-rate Modified Aptamer-scan plasma protein measurement at baseline (control and OT2D subjects) and after 1-h of insulin clamp (OT2D subjects only). Basal M1 macrophage activation was characterized by elevated levels of M1 macrophage-specific surface proteins, CD80 and CD38, and cytokines or chemokines (CXCL1, CXCL5, RANTES) released by activated M1 macrophages. Two potent M1 macrophage activation markers, CXCL9 and CXCL10, were decreased in OT2D. Activated M2 macrophages were characterized by elevated levels of plasma CD163, TFGβ-1, MMP7 and MMP9 in OT2D. Conventional mediators of both M1 and M2 macrophage activation markers (IFN-γ, IL-4, IL-13) were not altered. No changes were observed in plasma levels of M1/M2 macrophage activation markers in OT2D in response to acute normalization of glycemia. In the basal state, macrophage activation markers are elevated, and these reflect the expression of circulatory cytokines, chemokines, growth factors and matrix metalloproteinases in obese individuals with type 2 diabetes, that were not changed by glucose normalisation. These differences could potentially predispose diabetic individuals to increased infection severity complicated by ARDS. Clinical trial reg. no: NCT03102801; registration date April 6, 2017.	no

2021	Observational cohort study of neurological involvement among patients with SARS-CoV-2 infection.	A growing number of reports suggest that infection with SARS-CoV-2 often leads to neurological involvement; however, data on the incidence and severity are limited to mainly case reports and retrospective studies. This prospective, cross-sectional study of 102 SARS-CoV-2 PCR positive patients investigated the frequency, type, severity and risk factors as well as underlying pathophysiological mechanisms of neurological involvement (NIV) in COVID-19 patients. Across the cohort, 59.8% of patients had NIV. Unspecific NIV was suffered by 24.5%, mainly general weakness and cognitive decline or delirium. Mild NIV was found in 9.8%; most commonly, impaired taste or smell. Severe NIV was present in 23.5%; half of these suffered cerebral ischaemia. Incidence of NIV increased with respiratory symptoms of COVID-19. Mortality was higher with increasing NIV severity. Notably, 83.3% with severe NIV had a pre-existing neurological co-morbidity. All cerebrospinal fluid (CSF) samples were negative for SARS-CoV-2 RNA, and SARS-CoV-2 antibody quotient did not suggest intrathecal antibody synthesis. Of the patients with severe NIV, 50% had blood-brain barrier (BBB) disruption and showed a trend of elevated interleukin levels in CSF. Antibodies against neuronal and glial epitopes were detected in 35% of the patients tested. Cerebrovascular events were the most frequent severe NIV and severe NIV was associated with high mortality. Incidence of NIV increased with respiratory symptoms and NIV and pre-existing neurological morbidities were independent risk factors for fatality. Inflammatory involvement due to BBB disruption and cytokine release drives NIV, rather than direct viral invasion. These findings might help physicians define a further patient group requiring particular attention during the pandemic.	no

2021	The effect of age on the clinical and immune characteristics of critically ill patients with COVID-19: A preliminary report.	In December 2019, a new disease named coronavirus disease 2019 (COVID-19) was occurred. Patients who are critically ill with COVID-19 are more likely to die, especially elderly patients. We aimed to describe the effect of age on the clinical and immune characteristics of critically ill patients with COVID-19. We retrospectively included 32 patients with COVID-19 who were confirmed to have COVID-19 by the local health authority and who were admitted to the first affiliated hospital of Zhengzhou University in Zhengzhou, China between January 3 and March 20, 2020. Clinical information and experimental test data were retrospectively collected for the patients. The 32 patients in this study were all in a critical condition and were classified as severe, according to the guidelines of 2019-nCoV infection from the National Health Commission of the People's Republic of China. Data were compared between those <60 years old and ≥60 years old. Of 32 patients, 13 were under 60 years old, and 19 patients were ≥60 years old. The most common symptom among all patients upon admission was fever (93.8%, 30/32). Compared to younger patients, older patients exhibited increased comorbidities. Among patients who were 60 years and older, platelet count, direct bilirubin (DBIL), indirect bilirubin(IBIL), lactate dehydrogenase (LDH), B-type natriuretic peptide (BNP), C-reactive protein (CRP), procalcitonin (PCT), and interleukin-10 (IL-10) were significantly higher than in younger patients who were less than 60 years old. CD4+ T lymphocytes, CD8+ T lymphocytes, and NKT lymphocytes were decreased, CD4+/CD8+ T lymphocytes were significantly increased in all 32 patients, while there were no evident differences between younger and older patients. The CURB-65 (confusion, urea, respiratory, rate, blood pressure plus age ≥65 years), Acute Physiology and Chronic Health Evaluation (APACHE) II and pH value were significantly higher in older patients than in patients who were under 60 years old. However, the PaO2 and PaO2:FiO2 were lower in older patients than the younger. Compared to patients under 60 years old, patients who were 60 years and older tended to develop ARDS (15 [78.9%] vs 5 [38.5%]), septic shock (7 [36.8%] vs 0 [0.0%]) and were more likely to receive mechanical ventilation (13 [68.4%] vs 3[23.1%]). Dynamic trajectories of seven laboratory parameters were tracked on days 1, 3, 5 and 7, and significant differences in lymphocyte count (P = 0.026), D-dimer (P = 0.010), lactate dehydrogenase (P = 0.000) and C-reactive protein (P = 0.000) were observed between the two age groups. A high proportion of critically ill patients were 60 or older. Furthermore, rapid disease progression was noted in elderly patients. Therefore, close monitoring and timely treatment should be performed in elderly COVID-19 patients.	no
2021	COVID-19 and ABO blood groups.	NA	yes

2021	SARS-CoV-2 Causes a Different Cytokine Response Compared to Other Cytokine Storm-Causing Respiratory Viruses in Severely Ill Patients.	Hyper-induction of pro-inflammatory cytokines, also known as a cytokine storm or cytokine release syndrome (CRS), is one of the key aspects of the currently ongoing SARS-CoV-2 pandemic. This process occurs when a large number of innate and adaptive immune cells activate and start producing pro-inflammatory cytokines, establishing an exacerbated feedback loop of inflammation. It is one of the factors contributing to the mortality observed with coronavirus 2019 (COVID-19) for a subgroup of patients. CRS is not unique to the SARS-CoV-2 infection; it was prevalent in most of the major human coronavirus and influenza A subtype outbreaks of the past two decades (H5N1, SARS-CoV, MERS-CoV, and H7N9). With a comprehensive literature search, we collected changing the cytokine levels from patients upon infection with the viral pathogens mentioned above. We analyzed published patient data to highlight the conserved and unique cytokine responses caused by these viruses. Our curation indicates that the cytokine response induced by SARS-CoV-2 is different compared to other CRS-causing respiratory viruses, as SARS-CoV-2 does not always induce specific cytokines like other coronaviruses or influenza do, such as IL-2, IL-10, IL-4, or IL-5. Comparing the collated cytokine responses caused by the analyzed viruses highlights a SARS-CoV-2-specific dysregulation of the type-I interferon (IFN) response and its downstream cytokine signatures. The map of responses gathered in this study could help specialists identify interventions that alleviate CRS in different diseases and evaluate whether they could be used in the COVID-19 cases.	no
2021	Pernio (Chilblains), SARS-CoV-2, and COVID Toes Unified Through Cutaneous and Systemic Mechanisms.	Pernio or chilblains is characterized by erythema and swelling at acral sites (eg, toes and fingers), typically triggered by cold exposure. Clinical and histopathologic features of pernio are well described, but the pathogenesis is not entirely understood; vasospasm and a type I interferon (IFN-I) immune response are likely involved. During the coronavirus disease 2019 (COVID-19) pandemic, dermatologists have observed an increase in pernio-like acral eruptions. Direct causality of pernio due to COVID-19 has not been established in many cases because of inconsistent testing methods (often negative results) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, a form of COVID-19–associated pernio (also called COVID toes) is probable because of increased occurrence, frequently in young patients with no cold exposure or a history of pernio, and reports of skin biopsies with positive SARS-CoV-2 immunohistochemistry. PubMed was searched between January 1, 2020, and December 31, 2020 for publications using the following keywords: pernio, chilblain, and acral COVID-19. On the basis of our review of the published literature, we speculate that several unifying cutaneous and systemic mechanisms may explain COVID-19–associated pernio: (1) SARS-CoV-2 cell infection occurs through the cellular receptor angiotensin-converting enzyme 2 mediated by transmembrane protease serine 2, subsequently affecting the renin-angiotensin-aldosterone system with an increase in the vasoconstricting, pro-inflammatory, and prothrombotic angiotensin II pathway. (2) Severe acute respiratory syndrome coronavirus 2 cell infection triggers an immune response with robust IFN-I release in patients predisposed to COVID-19–associated pernio. (3) Age and sex discrepancies correlated with COVID-19 severity and manifestations, including pernio as a sign of mild disease, are likely explained by age-related immune and vascular differences influenced by sex hormones and genetics, which affect susceptibility to viral cellular infection, the renin-angiotensin-aldosterone system balance, and the IFN-I response.	no

2021	Qualitative and quantitative DECT pulmonary angiography in COVID-19 pneumonia and pulmonary embolism.	To assess differences in qualitative and quantitative parameters of pulmonary perfusion from dual-energy computed tomography (CT) pulmonary angiography (DECT-PA) in patients with COVID-19 pneumonia with and without pulmonary embolism (PE). This retrospective institutional review board-approved study included 74 patients (mean age 61±18 years, male:female 34:40) with COVID-19 pneumonia in two countries (one with 68 patients, and the other with six patients) who underwent DECT-PA on either dual-source (DS) or single-source (SS) multidetector CT machines. Images from DS-DECT-PA were processed to obtain virtual mono-energetic 40 keV (Mono40), material decomposition iodine (MDI) images and quantitative perfusion statistics (QPS). Two thoracic radiologists determined CT severity scores based on type and extent of pulmonary opacities, assessed presence of PE, and pulmonary parenchymal perfusion on MDI images. The QPS were calculated from the CT Lung Isolation prototype (Siemens). The correlated clinical outcomes included duration of hospital stay, intubation, SpO 2 and death. The significance of association was determined by receiver operating characteristics and analysis of variance. One-fifth (20.2%, 15/74 patients) had pulmonary arterial filling defects; most filling defects were occlusive (28/44) located in the segmental and sub-segmental arteries. The parenchymal opacities were more extensive and denser (CT severity score 24±4) in patients with arterial filling defects than without filling defects (20±8; p=0.028). Ground-glass opacities demonstrated increased iodine distribution; mixed and consolidative opacities had reduced iodine on DS-DECT-PA but increased or heterogeneous iodine content on SS-DECT-PA. QPS were significantly lower in patients with low SpO 2 (p=0.003), intubation (p=0.006), and pulmonary arterial filling defects (p=0.007). DECT-PA QPS correlated with clinical outcomes in COVID-19 patients.	no
2021	The effect of ABO blood group and antibody class on the risk of COVID-19 infection and severity of clinical outcomes.	The COVID-19 pandemic has affected more than 100 million cases and caused immense burdens on governments and healthcare systems worldwide. Since its emergence in December 2019, research has been focused on treating the infected, identifying those at risk and preventing spread. There is currently no known biological biomarker that predicts the risk of infection. Several studies emerged suggesting an association between ABO blood group and the risk of COVID-19 infection. In this study, we used retrospective observational data in Bahrain to investigate the association between ABO blood group and risk of infection, as well as susceptibility to severe ICU-requiring infection. We found a higher risk associated with blood group B, and a lower risk with blood group AB. No association was observed between blood group and the risk of a severe ICU-requiring infection. We extended the analysis to study the association by antibodies; anti-a (blood groups B and O) and anti-b (blood groups A and O). No association between antibodies and both risk of infection or susceptibility to severe infection was found. The current study, along with the variation in blood group association results, indicates that blood group may not be an ideal biomarker to predict risk of COVID-19 infection.	yes
2021	Newly diagnosed diabetes in patients with mild to moderate COVID-19.	We aimed to study newly diagnosed diabetes in patients with mild to moderate COVID-19. This was a retrospective cohort study of COVID-19 patients who were admitted to a tertiary care hospital in India from May to October 2020. Of 102 patients, 21 (20.6%) had newly diagnosed diabetes on admission. Of which, four (19.0%) had marked hyperglycemia with no ketosis or ketoacidosis. In this study of patients with mild to moderate COVID-19, newly diagnosed diabetes and	no

		marked hyperglycemia in those with newly diagnosed diabetes were common.	
2021	Modelling suggests ABO histo-incompatibility may substantially reduce SARS-CoV-2 transmission.	Several independent datasets suggest blood type A is over-represented and type O under-represented among COVID-19 patients. However, blood group antigens appear not to be conventional susceptibility factors in that they do not affect disease severity, and the relative risk to non-O individuals is attenuated when population prevalence is high. Here, I model a scenario in which ABO transfusion incompatibility reduces the chance of a patient transmitting the virus to an incompatible recipient - thus in Western populations type A and AB individuals are "super-recipients" while type O individuals are "super-spreaders". This results in an offset in the timing of the epidemic among individuals of different blood types, and an increased relative risk to type A/AB patients that is most pronounced during early stages of the epidemic. However, once the majority of any given population is infected, the relative risk to each blood type approaches unity. Published data on COVID-19 prevalence from regions in the early stages of the SARS-CoV-2 epidemic suggests that if this model holds true, ABO incompatibility reduces virus transmissibility by at least 60 %. Exploring the implications of this model for vaccination strategies shows that paradoxically, targeted vaccination of either high-susceptibility type A/AB or "super-spreader" type O individuals is less effective than random vaccination at blocking community spread of the virus. Instead, the key is to maintain blood type diversity among the remaining susceptible individuals. Given the good agreement between this model and observational data on disease prevalence, the underlying biochemistry urgently requires experimental investigation.	yes
2021	SARS-CoV-2-directed antibodies persist for more than six months in a cohort with mild to moderate COVID-19.	To follow serological immune responses of front-line healthcare workers after PCR-confirmed COVID-19 for a mean of 30 weeks, describe the time-course of SARS-CoV-2 spike protein-specific IgG, IgA and IgM levels and to identify associations of the immune response with symptoms, demographic parameters and severity of disease. Anti-SARS-CoV-2 S protein-specific IgG, IgA and IgM antibodies were measured at three time points during the 30-week follow-up. COVID-19-specific symptoms were assessed with standardized questionnaires. 95% of the participants mounted an IgG response with only modest decline after week 12. IgG-type antibodies were still detectable in almost 90% of the subjects at 30 weeks. IgA and IgM responses were less robust and antibody titers decreased more rapidly. At 30 weeks, only 25% still had detectable IgA-type and none had IgM-type antibodies. Higher age and higher disease severity were independently associated with higher IgG antibody levels, albeit with wide variations. Serological immune responses after COVID-19 show considerable inter-individual variability, but show an association with increasing age and higher severity of disease. IgG-type anti-SARS-CoV-2 antibodies remain positive in 90% of the individuals 30 weeks after onset of symptoms.	yes

2021	Association between ABO blood types and coronavirus disease 2019 (COVID-19), genetic associations, and underlying molecular mechanisms: a literature review of 23 studies.	An association of various blood types and the 2019 novel coronavirus disease (COVID-19) has been found in a number of publications. The aim of this literature review is to summarize key findings related to ABO blood types and COVID-19 infection rate, symptom presentation, and outcome. Summarized findings include associations between ABO blood type and higher infection susceptibility, intubation duration, and severe outcomes, including death. The literature suggests that blood type O may serve as a protective factor, as individuals with blood type O are found COVID-19 positive at far lower rates. This could suggest that blood type O individuals are less susceptible to infection, or that they are asymptomatic at higher rates and therefore do not seek out testing. We also discuss genetic associations and potential molecular mechanisms that drive the relationship between blood type and COVID-19. Studies have found a strong association between a locus on a specific gene cluster on chromosome three (chr3p21.31) and outcome severity, such as respiratory failure. Cellular models have suggested an explanation for blood type modulation of infection, evidencing that spike protein/Angiotensin-converting enzyme 2 (ACE2)-dependent adhesion to ACE2-expressing cell lines was specifically inhibited by monoclonal or natural human anti-A antibodies, so individuals with non-A blood types, specifically O, or B blood types, which produce anti-A antibodies, may be less susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection due to the inhibitory effects of anti-A antibodies.	yes
2021	The impact of ABO blood groups on clinical outcomes and susceptibility to COVID-19: A retrospective study in an unselected population.	ABO blood groups have been linked to susceptibility to infection with certain microorganisms, including coronaviruses. We examined the relationship between blood group and clinical outcomes in individuals infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and compared their blood group distribution with the general population. At the inception of the pandemic, all individuals testing positive for SARS-CoV-2 in Kuwait were admitted to one designated coronavirus disease 2019 (COVID-19) hospital and enrolled in a prospective registry. Patients admitted from February 24 to May 27, 2020, were stratified according to blood group. As a control, blood groups of 3,730,027 anonymized individuals representing almost Kuwait's entire population were obtained from a national database. Of 3305 SARS-CoV-2-positive patients, 37.1%, 25.5%, 28.9%, and 8.5% were groups O, A, B, and AB, respectively. Univariate analysis revealed no significant differences in severe clinical outcomes or death among the blood groups. However, multivariable analysis demonstrated that group A individuals had higher odds of developing pneumonia compared with non-group A (adjusted odds ratio 1.32, 95% confidence interval 1.02-1.72, $p < .036$). Compared with the general population, the COVID-19 cohort had a lower frequency of group O, equivalent frequency of A, and higher frequency of B and AB. No significant difference in the RhD group was found. This study supports potential involvement of the ABO blood group system in predisposing to infection with SARS-CoV-2 in an unselected population. Examination of the mechanistic link between blood group and COVID-19 and its implications on controlling the current pandemic is warranted.	yes

2021	Inflammation and Antiviral Immune Response Associated With Severe Progression of COVID-19.	Coronavirus disease-2019 (COVID-19) is a novel respiratory disease induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It remains poorly understood how the host immune system responds to the infection during disease progression. We applied microarray analysis of the whole genome transcriptome to peripheral blood mononuclear cells (PBMCs) taken from severe and mild COVID-19 patients as well as healthy controls. Functional enrichment analysis of genes associated with COVID-19 severity indicated that disease progression is featured by overactivation of myeloid cells and deficient T cell function. The upregulation of TLR6 and MMP9, which promote the neutrophils-mediated inflammatory response, and the downregulation of SKAP1 and LAG3, which regulate T cells function, were associated with disease severity. Importantly, the regulation of these four genes was absent in patients with influenza A (H1N1). And compared with stimulation with hemagglutinin (HA) of H1N1 virus, the regulation pattern of these genes was unique in PBMCs response to Spike protein of SARS-CoV-2 ex vivo . Our data also suggested that severe SARS-CoV-2 infection largely silenced the response of type I interferons (IFNs) and altered the proportion of immune cells, providing a potential mechanism for the hypercytokinemia. This study indicates that SARS-CoV-2 infection impairs inflammatory and immune signatures in patients, especially those at severe stage. The potential mechanisms underpinning severe COVID-19 progression include overactive myeloid cells, impaired function of T cells, and inadequate induction of type I IFNs signaling.	no
2021	Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection.	The immune response to SARS-CoV-2 is critical in controlling disease, but there is concern that waning immunity may predispose to reinfection. We analyzed the magnitude and phenotype of the SARS-CoV-2-specific T cell response in 100 donors at 6 months following infection. T cell responses were present by ELISPOT and/or intracellular cytokine staining analysis in all donors and characterized by predominant CD4 + T cell responses with strong interleukin (IL)-2 cytokine expression. Median T cell responses were 50% higher in donors who had experienced a symptomatic infection, indicating that the severity of primary infection establishes a 'set point' for cellular immunity. T cell responses to spike and nucleoprotein/membrane proteins were correlated with peak antibody levels. Furthermore, higher levels of nucleoprotein-specific T cells were associated with preservation of nucleoprotein-specific antibody level although no such correlation was observed in relation to spike-specific responses. In conclusion, our data are reassuring that functional SARS-CoV-2-specific T cell responses are retained at 6 months following infection.	no

2021	Vitamin D and Lung Outcomes in Elderly COVID-19 Patients.	Background and aim: Vitamin D deficiency is frequently reported in patients with SARS-CoV-2 infection. The aim of this study was to correlate the 25OH-Vitamin D serum concentrations with clinical parameters of lung involvement, in elderly patients hospitalized for SARS-CoV-2 infection. Methods: Sixty-five consecutive COVID-19 patients (mean age 76 ± 13 years) and sixty-five sex- and age-matched control subjects (CNT) were analyzed. The following clinical parameters, including comorbidities, were collected at admission: type of pulmonary involvement, respiratory parameters (PaO 2 , SO 2 , PaCO 2 , PaO 2 /FiO 2), laboratory parameters (including 25OH-vitamin D, D-dimer, C-reactive protein). Results: Significantly lower vitamin D serum levels were found in COVID-19 patients than in CNT (median 7.9 vs 16.3 ng/mL, p = 0.001). Interestingly, a statistically significant positive correlation was observed between vitamin D serum levels and PaO 2 (p = 0.03), SO 2 (p = 0.05), PaO 2 /FiO 2 (p = 0.02), while a statistically significant negative correlation was found between vitamin D serum levels and D-dimer (p = 0.04), C-reactive protein (p = 0.04) and percentage of O 2 in a venturi mask (p = 0.04). A negative correlation was also observed between vitamin D serum levels and severity of radiologic pulmonary involvement, evaluated by computed tomography: in particular, vitamin D was found significantly lower in COVID-19 patients with either multiple lung consolidations (p = 0.0001) or diffuse/severe interstitial lung involvement than in those with mild involvement (p = 0.05). Finally, significantly lower vitamin D serum levels were found in the elderly COVID-19 patients who died during hospitalization, compared to those who survived (median 3.0 vs 8.4 ng/mL, p = 0.046). Conclusions: This study confirms that 25OH-vitamin D serum deficiency is associated with more severe lung involvement, longer disease duration and risk of death, in elderly COVID-19 patients. The detection of low vitamin D levels also in younger COVID-19 patients with less comorbidities further suggests vitamin D deficiency as crucial risk factor at any age.	no
2021	Association of serum HDL-cholesterol and apolipoprotein A1 levels with risk of severe SARS-CoV-2 infection.	Individuals with features of metabolic syndrome are particularly susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus associated with the severe respiratory disease, coronavirus disease 2019 (COVID-19). Despite considerable attention dedicated to COVID-19, the link between metabolic syndrome and SARS-CoV-2 infection remains unclear. Using data from the UK Biobank, we investigated the relationship between severity of COVID-19 and metabolic syndrome-related serum biomarkers measured prior to SARS-CoV-2 infection. Logistic regression analyses were used to test biomarker levels and biomarker-associated genetic variants with SARS-CoV-2-related outcomes. Among SARS-CoV-2-positive cases and negative controls, a 10 mg/dl increase in serum HDL-cholesterol or apolipoprotein A1 levels was associated with ~10% reduced risk of SARS-CoV-2 infection, after adjustment for age, sex, obesity, hypertension, type 2 diabetes, and coronary artery disease. Evaluation of known genetic variants for HDL-cholesterol revealed that individuals homozygous for apolipoprotein E4 alleles had ~2- to 3-fold higher risk of SARS-CoV-2 infection or mortality from COVID-19 compared with apolipoprotein E3 homozygotes, even after adjustment for HDL-cholesterol levels. However, cumulative effects of all evaluated HDL-cholesterol-raising alleles and Mendelian randomization analyses did not reveal association of genetically higher HDL-cholesterol levels with decreased risk of SARS-CoV-2 infection. These results implicate serum HDL-cholesterol and apolipoprotein A1 levels measured prior to SAR-	no

		CoV-2 exposure as clinical risk factors for severe COVID-19 infection but do not provide evidence that genetically elevated HDL-cholesterol levels are associated with SAR-CoV-2 infection.	
2021	Biomarkers of Cardiac Stress and Cytokine Release Syndrome in COVID-19: A Review.	The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in the coronavirus 2019 (COVID-19) global pandemic. While primarily a respiratory virus, SARS-CoV-2 can cause myocardial injury. The pattern of injury, referred to as acute COVID-19 cardiovascular syndrome (ACovCS), is defined by cardiac troponin leak in the absence of obstructive coronary artery disease. Although the etiology of the injury is unknown, many speculate that a cytokine release syndrome (CRS) may be an important factor. We aim to review recent data concerning markers of cardiac injury in ACovCS and its relation to the CRS. Cardiac injury was common in patients hospitalized for COVID-19, with both cardiac troponin and B-type natriuretic peptide (BNP) being elevated in this population. Biomarkers were correlated with illness severity and increased mortality. Cytokines such as IL-6 were more often elevated in patients with ACovCS. Myocarditis evident on cardiac MR following COVID-19 may be associated with cardiac troponin levels. The impact of dexamethasone and remdesivir, two therapies shown to have clinical benefit in COVID-19, on myocardial injury is unknown. Biomarkers of cardiac stress and injury in COVID-19 may be used to stratify risk in the future. Currently, there is no evidence that inhibition of cytokine release will reduce myocardial injury in patients with COVID-19.	no

2021	Clot waveform of APTT has abnormal patterns in subjects with COVID-19.	In Coronavirus disease 2019 (COVID-19) subjects, recent evidence suggests the presence of unique coagulation abnormalities. In this study, we performed clot waveform analyses to investigate whether specific modulations are observed in COVID-19 subjects. We analyzed the second derivative of the absorbance in routine APTT tests performed using an ACL-TOP system. We observed high frequencies of abnormal patterns in APTT second-derivative curves that could be classified into an early shoulder type, a late shoulder type, or a biphasic type, high maximum first-derivative and second-derivative peak levels, and a low minimum second-derivative peak level in COVID-19 subjects. These modulations were not observed in subjects with disseminated intravascular coagulation. These abnormal patterns are also observed in patients with lupus anticoagulant, hemophilia, or factor IX deficiency. The plasma fibrinogen levels might also be involved in the abnormal APTT waveforms, especially the high maximum first-derivative and second-derivative peak levels. The abnormal patterns in the APTT second-derivative curves appear with highest frequency at around 2 weeks after the onset of COVID-19 and were not associated with the severity of COVID-19. These results suggest the possible presence of a specific abnormal coagulopathy in COVID-19.	no
2021	SARS-CoV-2 mutations in MHC-I-restricted epitopes evade CD8+ T cell responses.	CD8 + T cell immunity to SARS-CoV-2 has been implicated in COVID-19 severity and virus control. Here, we identified nonsynonymous mutations in MHC-I-restricted CD8 + T cell epitopes after deep sequencing of 747 SARS-CoV-2 virus isolates. Mutant peptides exhibited diminished or abrogated MHC-I binding in a cell-free in vitro assay. Reduced MHC-I binding of mutant peptides was associated with decreased proliferation, IFN-γ production and cytotoxic activity of CD8 + T cells isolated from HLA-matched COVID-19 patients. Single cell RNA sequencing of ex vivo expanded, tetramer-sorted CD8 + T cells from COVID-19 patients further revealed qualitative differences in the transcriptional response to mutant peptides. Our findings highlight the capacity of SARS-CoV-2 to subvert CD8 + T cell surveillance through point mutations in MHC-I-restricted viral epitopes.	no
2021	The clinical course and prognostic factors of severe COVID-19 in Wuhan, China: A retrospective case-control study.	With the surge of newly diagnosed and severe cases of coronavirus disease 2019 (COVID-19), the death toll is mounting, this study is aimed to explore the prognostic factors of severe COVID-19. This retrospective study included 122 inpatients diagnosed with COVID-19 from January 13 to February 25, 2020. Univariate and multivariate analysis were used to identity the risk factors, receiver operating characteristics curve (ROC) analysis was used for risk stratification. The baseline neutrophil-to-lymphocyte ratio (NLR) (OR=1.171, 95%CI=1.049-1.306, P=.005) and Lactate dehydrogenase (LDH) (OR=1.007, 95%CI=1.002-1.011, P=.004) were identified as the independent risk factors for severe COVID-19 conditions, and the NLR-LDH grading system was developed to perform risk stratification. The baseline C-reactive protein (CRP) (OR=1.019, 95%CI=1.004-1.306, P=.016) and B-type natriuretic peptide (BNP) (OR=1.018, 95%CI=1.004-1.035, P=.007) were identified as the independent predictors for disease progression of severe patients. Accordingly, The NLR-LDH grading system was a useful prognostic tool for the early detection of severe COVID-19. And in the severe patients, CRP and BNP seemed to be helpful for predicting the disease progression or death.	yes

2021	Anti-A and SARS-CoV-2: an intriguing association.	Blood groups and anti-A isohemagglutinin may be involved in susceptibility to SARS-CoV-2 infection. We retrospectively studied 268 COVID-19 convalescent plasma donors and 162 COVID-19 inpatients (total 430 subjects, confirmed by RT-PCR) and 2,212 healthy volunteer first-time blood donors as a control group. These were further divided into two groups: those with anti-A (blood types O and B) and those without it (types A and AB). Titres of nucleoproteins, and neutralizing SARS-CoV-2 antibody were measured in the convalescent plasma donors and inpatients. Multivariate logistic regression and non-parametric tests were applied. Persons having types O or B showed less infection prevalence than those of types A or AB (OR = 0·62, 95% CI 0·50-0·78; P < 0·001), but there was no difference when COVID-19 inpatients were analysed. Immunoglobulins M, G and A were lower in COVID-19 subjects of types O or B group than those of A or AB (0·16 vs. 0·19; P = 0·03, 2·11 vs. 2·55; P = 0·02, 0·23 vs. 0·32; P = 0·03, respectively). In this retrospective cohort, COVID-19 individuals were less likely to belong to blood types O and B, and also had lower SARS-CoV-2 antibody titres than A and AB individuals. COVID-19 severity did not associate with the blood groups.	yes
2021	Association of Blood Groups with the Severity and Outcome of COVID-19 Infection in Children.	The objective of this study was to find out the association of ABO blood groups with the severity and outcome of corona virus disease 2019 (COVID-19) in children. It included all laboratory-confirmed cases of COVID-19 and post-COVID multisystem inflammatory syndrome in children (MIS-C)/ Kawasaki disease (KD) like illness, admitted from March to September, 2020 to The Children's Hospital, Lahore. Out of 66 children, 45 (68.2%) were COVID-19 and 21 (31.8%) MIS-C/KD temporally associated with SARS-C0V-2. The mean age was 7.9 ± 4.2 years. Majority of children had mild to moderate illness 38 (57.6%), while 23 (34.8%) had severe or critical disease. Among all patients, 24 (36.4%) had some underlying comorbidity. Blood group A was significantly associated with severe and critical disease (p=0.030). COVID-19 in children had generally a good outcome, but children with blood group A were more susceptible to severe/critical disease. Key Words: Coronavirus disease 2019, ABO blood groups, Children, Severity, Outcome.	yes
2021	Lung expression of genes putatively involved in SARS-CoV-2 infection is modulated in cis by germline variants.	Germline variants in genes involved in SARS-CoV-2 cell entry and in host innate immune responses to viruses may influence the susceptibility to infection. This study used whole-genome analyses of lung tissue to identify polymorphisms acting as expression quantitative trait loci (eQTLs) for 60 genes of relevance to SARS-CoV-2 infection susceptibility. The expression of genes with confirmed or possible roles in viral entry-replication and in host antiviral responses was studied in the non-diseased lung tissue of 408 lung adenocarcinoma patients. No gene was differently expressed by sex, but APOBEC3H levels were higher and PARP12 levels lower in older individuals. A total of 125 cis-eQTLs (false discovery rate < 0.05) was found to modulate mRNA expression of 15 genes (ABO, ANPEP, AP2A2, APOBEC3D, APOBEC3G, BSG, CLEC4G, DDX58, DPP4, FURIN, FYCO1, RAB14, SERINC3, TRIM5, ZCRB1). eQTLs regulating ABO and FYCO1 were found in COVID-19 susceptibility loci. No trans-eQTLs were identified. Genetic control of the expression of these 15 genes, which encode putative virus receptors, proteins required for vesicle trafficking, enzymes that interfere with viral replication, and other restriction factors, may underlie interindividual differences in risk or severity of infection with SARS-CoV-2 or other viruses.	no

2021	Abnormal liver tests in patients with SARS-CoV-2 or influenza - prognostic similarities and temporal disparities.	Abnormal liver tests are common in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but a possible direct role of the virus in liver injury and its association with short-term outcomes are controversial. Therefore, we aimed to compare the pattern of abnormal liver tests in patients with SARS-CoV-2 with those of patients infected with influenza, a non-hepatotropic respiratory virus, and their association with worse outcomes during hospitalisation. We performed a retrospective cohort study of 1,737 hospitalised patients (865 with influenza and 872 with SARS-CoV-2) in a tertiary medical centre. We defined abnormal liver tests as alanine transaminase or aspartate transaminase ≥40 IU/ml at any time-point during hospitalisation. Abnormal liver tests were mild to moderate in most patients regardless of infection type, but the majority of patients with influenza had a transaminase peak earlier during hospitalisation compared with patients with SARS-CoV-2. Abnormal liver tests correlated with markers of severe disease in either influenza or SARS-CoV-2 infections, and were associated with death, occurring mainly in patients with severe liver test abnormalities (>200 IU/L) (38.7% and 60% of patients with influenza or SARS-CoV-2, respectively). In multivariate analysis, controlling for age, sex, lymphopaenia, and C-reactive protein, liver test abnormalities remained significantly associated with death for influenza (odds ratio 4.344; 95% CI 2.218-8.508) and SARS-CoV-2 (odds ratio 3.898; 95% CI 2.203-6.896). These results were confirmed upon propensity score matching. Abnormal liver tests during hospitalisation with SARS-CoV-2 or influenza infections are common, may differ in their time course, and reflect disease severity. They are associated with worse outcomes, mainly in patients with severe liver test abnormalities, regardless of infection type. Coronavirus disease 2019 (COVID-19) is a serious global health pandemic, the causative agent of which is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Abnormal liver tests are common among SARS-CoV-2 infected patients and are often associated with worse outcomes. Herein, we compare the pattern of abnormal liver tests and their association with disease severity between 2 major non-hepatotropic respiratory viruses: SARS-CoV-2 and influenza. We show that abnormal liver tests are common in both infections, may slightly differ in their kinetics, and are associated with worse outcomes, especially in patients with severe liver test abnormalities. These results strongly suggest that abnormal liver tests in SARS-CoV-2 patients reflect disease severity, rather than a virus-mediated direct liver injury, and should be closely followed in admitted patients.	no
2021	Elevation in viral entry genes and innate immunity compromise underlying increased infectivity and severity of COVID-19 in cancer patients.	Multiple studies have reported a doubling in risk of Coronavirus Disease-2019 (COVID-19) among cancer patients. Here, we examine the potential biological rationale behind this recurrent epidemiological observation. By leveraging large-scale genome-wide transcriptional data of normal and malignant tissues from adults and children, we found evidence of increased expression of SARS-CoV-2 viral entry genes in the cancer state, particularly in respiratory, gastrointestinal, and genitourinary tract tissues, with decreased expression in pediatric vs. adult samples. Additionally, by interrogating the temporal effects of radiotherapy on human peripheral blood mononuclear and mucosal cells, we observed important treatment-related alterations in host innate immunity, specifically type I interferon responses. Overall, cancers enhance expression of critical viral entry genes, and innate viral defenses can be dysregulated transiently during radiation treatments.	no

		These factors may contribute to the observed increased susceptibility to SARS-CoV-2 entry and severity of COVID-19 in cancer patients.	
2021	Flow cytometric evaluation of the neutrophil compartment in COVID-19 at hospital presentation: A normal response to an abnormal situation.	Coronavirus disease 2019 (COVID-19) is a rapidly emerging pandemic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Critical COVID-19 is thought to be associated with a hyper-inflammatory process that can develop into acute respiratory distress syndrome, a critical disease normally mediated by dysfunctional neutrophils. This study tested the hypothesis whether the neutrophil compartment displays characteristics of hyperinflammation in COVID-19 patients. Therefore, a prospective study was performed on all patients with suspected COVID-19 presenting at the emergency room of a large academic hospital. Blood drawn within 2 d after hospital presentation was analyzed by point-of-care automated flow cytometry and compared with blood samples collected at later time points. COVID-19 patients did not exhibit neutrophilia or eosinopenia. Unexpectedly neutrophil activation markers (CD11b, CD16, CD10, and CD62L) did not differ between COVID-19-positive patients and COVID-19-negative patients diagnosed with other bacterial/viral infections, or between COVID-19 severity groups. In all patients, a decrease was found in the neutrophil maturation markers indicating an inflammation-induced left shift of the neutrophil compartment. In COVID-19 this was associated with disease severity.	no
2021	Prediction of The New Coronavirus Spread and Infected People Numbers Based on Embedded Wearable Devices and Seir Models.	Covers are a well-known group of organisms infected with the disease caused by two people. A new type of COVID-19 is soon discovered in Wuhan, China. Even so, infections cause a pandemic, as indicated by the World Health Organization and are widespread throughout the world, as it can be slow. Also, these days, every country in the world is working hard to control COVID-19. There are many components to distinguish Covid, including pictures of clinical studies of chest CT and blood test results. Show patients confirmed to have a fever, stagnation, and dry COVID-19. In particular, several strategies can be used to distinguish the underlying squeal of infection, such as kits for clinical locations. Nevertheless, such gadgets have set aside some effort to introduce and use them, incurring huge costs. Another structure, COVID-19, for engineering and identification using mobile phone sensors along these lines of thought. This proposition can be easily placed because most radiologists only have various daily use needs for mobile phones. At the same standard, individuals will be able to use their mobile phones to infect the system for identification purposes. The phone is not reliable if the camera, receiver, temperature sensors, inertial sensors, gas-tight sensor, light-shielded sensor, existing computing rich processor, viscosity sensor and remote chipset/sensors, memory space, and huge sensors have a number. Planning Detection Combination Algorithm (DCA) structure carefully as expected of function, as a result	no

		of the infection, reads the mobile phone sensors' signs to estimate the severity of pneumonia.	
2021	Multi-omics highlights ABO plasma protein as a causal risk factor for COVID-19.	SARS-CoV-2 is responsible for the coronavirus disease 2019 (COVID-19) and the current health crisis. Despite intensive research efforts, the genes and pathways that contribute to COVID-19 remain poorly understood. We, therefore, used an integrative genomics (IG) approach to identify candidate genes responsible for COVID-19 and its severity. We used Bayesian colocalization (COLOC) and summary-based Mendelian randomization to combine gene expression quantitative trait loci (eQTLs) from the Lung eQTL (n = 1,038) and eQTLGen (n = 31,784) studies with published COVID-19 genome-wide association study (GWAS) data from the COVID-19 Host Genetics Initiative. Additionally, we used COLOC to integrate plasma protein quantitative trait loci (pQTL) from the INTERVAL study (n = 3,301) with COVID-19 loci. Finally, we determined any causal associations between plasma proteins and COVID-19 using multi-variable two-sample Mendelian randomization (MR). The expression of 18 genes in lung and/or blood co-localized with COVID-19 loci. Of these, 12 genes were in suggestive loci (P GWAS $< 5 \times 10$ -05). LZTFL1, SLC6A20, ABO, IL10RB and IFNAR2 and OAS1 had been previously associated with a heightened risk of COVID-19 (P GWAS $< 5 \times 10$ -08). We identified a causal association between OAS1 and COVID-19 GWAS. Plasma ABO protein, which is associated with blood type in humans, demonstrated a significant causal relationship with COVID-19 in the MR analysis; increased plasma levels were associated with an increased risk of COVID-19 and, in particular, severe COVID-19. In summary, our study identified genes associated with COVID-19 that may be prioritized for future investigations. Importantly, this is the first study to demonstrate a causal association between plasma ABO protein and COVID-19.	yes

2021	Characteristics and Outcome of SARS-CoV-2 Infection in Cancer Patients.	Concerns have emerged about the higher risk of fatal coronavirus disease 2019 (COVID-19) in cancer patients. In this article, we review the experience of a comprehensive cancer center. A prospective registry was set up at Institut Curie at the beginning of the COVID-19 pandemic. All cancer patients with suspected or proven COVID-19 were entered and actively followed for 28 days. Among 9842 patients treated at Institut Curie between March 13 and May 1, 2020, 141 (1.4%) were diagnosed with COVID-19, based on reverse transcription polymerase chain reaction testing and/or computerized tomography scan. In line with our case mix, breast cancer (40.4%) was the most common tumor type, followed by hematological and lung malignancies. Patients with active cancer therapy or/and advanced cancer accounted for 87.9% and 68.9% of patients, respectively. At diagnosis, 78.7% of patients had COVID-19-related symptoms, with an extent of lung parenchyma involvement inferior to 50% in 95.8% of patients. Blood count variations and C-reactive protein elevation were the most common laboratory abnormalities. Antibiotics and antiviral agents were administered in 48.2% and 6.4% of patients, respectively. At the time of analysis, 26 patients (18.4%) have died from COVID-19, and 100 (70.9%) were cured. Independent prognostic factors at the time of COVID-19 diagnosis associated with death or intensive care unit admission were extent of COVID-19 pneumonia and decreased O 2 saturation. COVID-19 incidence and presentation in cancer patients appear to be very similar to those in the general population. The outcome of COVID-19 is primarily driven by the initial severity of infection rather than patient or cancer characteristics.	yes
2021	Impact of undiagnosed type 2 diabetes and pre-diabetes on severity and mortality for SARS-CoV-2 infection.	Diabetes and hyperglycemia are risk factors for critical COVID-19 outcomes; however, the impact of pre-diabetes and previously unidentified cases of diabetes remains undefined. Here, we profiled hospitalized patients with undiagnosed type 2 diabetes and pre-diabetes to evaluate its impact on adverse COVID-19 outcomes. We also explored the role of de novo and intrahospital hyperglycemia in mediating critical COVID-19 outcomes. Prospective cohort of 317 hospitalized COVID-19 cases from a Mexico City reference center. Type 2 diabetes was defined as previous diagnosis or treatment with diabetes medication, undiagnosed diabetes and pre-diabetes using glycosylated hemoglobin (HbA1c) American Diabetes Association (ADA) criteria and de novo or intrahospital hyperglycemia as fasting plasma glucose (FPG) ≥140 mg/dL. Logistic and Cox proportional regression models were used to model risk for COVID-19 outcomes. Overall, 159 cases (50.2%) had type 2 diabetes and 125 had pre-diabetes (39.4%), while 31.4% of patients with type 2 diabetes were previously undiagnosed. Among 20.0% of pre-diabetes cases and 6.1% of normal-range HbA1c had de novo hyperglycemia. FPG was the better predictor for critical COVID-19 compared with HbA1c. Undiagnosed type 2 diabetes (OR: 5.76, 95% CI 1.46 to 27.11) and pre-diabetes (OR: 4.15, 95% CI 1.29 to 16.75) conferred increased risk of severe COVID-19. De novo/intrahospital hyperglycemia predicted critical COVID-19 outcomes independent of diabetes status. Undiagnosed type 2 diabetes, pre-diabetes and de novo hyperglycemia are risk factors for critical COVID-19. HbA1c must be measured early to adequately assess individual risk considering the large rates of undiagnosed type 2 diabetes in Mexico.	no

2021	von Willebrand Factor Multimer Formation Contributes to Immunothrombosis in Coronavirus Disease 2019.	Prevention and therapy of immunothrombosis remain crucial challenges in the management of coronavirus disease 2019, since the underlying mechanisms are incompletely understood. We hypothesized that endothelial damage may lead to substantially increased concentrations of von Willebrand factor with subsequent relative deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). Prospective controlled cross-over trial. Blood samples of patients with confirmed coronavirus disease 2019 and healthy controls were obtained in three German hospitals and analyzed in a German hemostaseologic laboratory. Seventy-five patients with confirmed coronavirus disease 2019 of mild to critical severity and 30 healthy controls. von Willebrand factor antigen, ADAMTS13, and von Willebrand factor multimer formation were analyzed. von Willebrand factor antigen was 4.1 times higher in COVID-19 patients compared with healthy controls ($p < 0.0001$), whereas ADAMTS13 activities were not significantly different ($p = 0.18$). The ADAMTS13/von Willebrand factor antigen ratio was significantly lower in COVID-19 than in the control group (24.4 ± 20.5 vs 82.0 ± 30.7; $p < 0.0001$). Fourteen patients (18.7%) undercut a critical ratio of 10 as described in thrombotic thrombocytopenic purpura. Gel analysis of multimers resembled a thrombotic thrombocytopenic purpura pattern with loss of the largest multimers in 75% and a smeary triplet pattern in 39% of the patients. The ADAMTS13/von Willebrand factor antigen ratio decreased continuously from mild to critical disease (analysis of variance $p = 0.026$). Furthermore, it differed significantly between surviving patients and those who died from COVID-19 ($p = 0.001$) yielding an area under the curve of 0.232 in receiver operating characteristic curve curve analysis. COVID-19 is associated with a substantial increase in von Willebrand factor levels, which can exceed the ADAMTS13 processing capacity resulting in the formation of large von Willebrand factor multimers indistinguishable from thrombotic thrombocytopenic purpura. The ADAMTS13/von Willebrand factor antigen ratio is an independent predictor of severity of disease and mortality. These findings provide a rationale to consider plasma exchange as a therapeutic option in COVID-19 and to include von Willebrand factor and ADAMTS13 in the diagnostic workup.	yes

2021	Recurrent COVID-19 including evidence of reinfection and enhanced severity in thirty Brazilian healthcare workers.	There is growing concern about individuals reported to suffer repeat COVID-19 disease episodes, these in a small number of cases characterised as de novo infections with distinct sequences, indicative of insufficient protective immunity even in the short term. Observational case series and case-control studies reporting 33 cases of recurrent, symptomatic, qRT-PCR positive COVID-19. Recurrent disease was defined as symptomatic recurrence after symptom-free clinical recovery, with release from isolation >14 days from the beginning of symptoms confirmed by qRT-PCR. The case control study-design compared this group of patients with a control group of 62 patients randomly selected from the same COVID-19 database. Of 33 recurrent COVID-19 patients, 26 were female and 30 were HCW. Mean time to recurrence was 50.5 days which was associated with being a HCW (OR 36.4 ($p < 0.0001$)), and blood type A (OR 4.8 ($p = 0.002$)). SARS-CoV-2 antibodies were signifcantly lower in recurrent patients after initial COVID-19 (2.4 ± 0.610; $p<0.0001$) and after recurrence (6.4 ± 11.34; $p = 0.007$). Virus genome sequencing identified reinfection by a different isolate in one patient. This is the first detailed case series showing COVID-19 recurrence with qRT-PCR positivity. For one individual detection of phylogenetically distinct genomic sequences in the first and second episodes confirmed bona fide renfection, but in most cases the data do not formally distinguish between reinfection and re-emergence of a chronic infection reservoir. These episodes were significantly associated with reduced Ab response during initial disease and argue the need for ongoing vigilance without an assumption of protection after a first episode.	yes
2021	Clinical characteristics of COVID-19 complicated with pleural effusion.	Epidemiological and clinical features of patients with corona virus disease 2019 (COVID-19) were well delineated. However, no researches described the patients complicated with pleural effusion (PE). In the present study, we aimed to clinically characterize the COVID-19 patients complicated with PE and to create a predictive model on the basis of PE and other clinical features to identify COVID-19 patients who may progress to critical condition. This retrospective study examined 476 COVID-19 inpatients, involving 153 patients with PE and 323 without PE. The data on patients' past history, clinical features, physical checkup findings, laboratory results and chest computed tomography (CT) findings were collected and analyzed. LASSO regression analysis was employed to identify risk factors associated with the severity of COVID-19. Laboratory findings showed that patients with PE had higher levels of white blood cells, neutrophils, lactic dehydrogenase, C-reactive protein and D-dimer, and lower levels of lymphocytes, platelets, hemoglobin, partial pressure of oxygen and oxygen saturation. Meanwhile, patients with PE had higher incidence of severe or critical illness and mortality rate, and longer hospital stay time compared to their counterparts without pleural effusion. Moreover, LASSO regression analysis exhibited that pleural effusion, lactic dehydrogenase (LDH), D-dimer and total bilirubin (TBIL) might be risk factors for critical COVID-19. Pleural effusion could serve as an indicator for severe inflammation and poor clinical outcomes, and might be a complementary risk factor for critical type of COVID-19.	no

2021	Hyper-Inflammatory Response Involves in Cardiac Injury Among Patients With Coronavirus Disease 2019.	Inflammation can facilitate development of coronavirus disease 2019 (COVID-19) and cardiac injury is associated with worse clinical outcomes. However, data are relatively scarce on the association between hyper-inflammatory response and cardiac injury among COVID-19 patients. The study was designed based on severe and critically ill patients with COVID-19. Information on clinical characteristics and laboratory examinations was collected from the electronic medical records and analyzed. There were 32.4% (n = 107) of patients with cardiac injury. The median age was 67 years, and 48.8% (n = 161) of patients were men. Hypertension was the most common in 161 (48.8%) patients, followed by diabetes (16.7%, n = 55) and coronary heart disease (13.3%, n = 44). Compared to cases without cardiac injury, those with cardiac injury were older, had higher proportions of coronary heart disease, and leukocyte counts, significantly elevated concentrations of N-terminal pro-B-Type natriuretic peptide, high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor (TNF)-α, interleukin-2 receptor (IL-2R), IL-6, and IL-8, but lower lymphocyte counts. A significant positive correlation was observed between high-sensitivity troponin I and inflammatory cytokines. Logistic regression analysis showed that hs-CRP, TNF-α and IL-6 were independent risk factors for cardiac injury. Cardiac injury was associated with elevated levels of inflammatory cytokines among severe and critically ill patients with COVID-19, suggesting that hyper-inflammatory response may involve in cardiac injury.	no
2021	The Inflammatory Factors Associated with Disease Severity to Predict COVID-19 Progression.	Coronavirus disease 2019 (COVID-19) is associated with immune dysregulation and cytokine storm. Exploring the immune-inflammatory characteristics of COVID-19 patients is essential to reveal pathogenesis and predict progression. In this study, COVID-19 patients showed decreased CD3 + , CD4 + , and CD8 + T cells but increased neutrophils in circulation, exhibiting upregulated neutrophil-to-lymphocyte and neutrophil-to-CD8 + T cell ratio. IL-6, TNF-α, IL-1β, IL-18, IL-12/IL-23p40, IL-10, Tim-3, IL-8, neutrophil extracellular trap-related proteinase 3, and S100A8/A9 were elevated, whereas IFN-γ and C-type lectin domain family 9 member A (clec9A) were decreased in COVID-19 patients compared with healthy controls. When compared with influenza patients, the expressions of TNF-α, IL-18, IL-12/IL-23p40, IL-8, S100A8/A9 and Tim-3 were significantly increased in critical COVID-19 patients, and carcinoembryonic Ag, IL-8, and S100A8/A9 could serve as clinically available hematologic indexes for identifying COVID-19 from influenza. Moreover, IL-6, IL-8, IL-1β, TNF-α, proteinase 3, and S100A8/A9 were increased in bronchoalveolar lavage fluid of severe/critical patients compared with moderate patients, despite decreased CD4 + T cells, CD8 + T cells, B cells, and NK cells. Interestingly, bronchoalveolar IL-6, carcinoembryonic Ag, IL-8, S100A8/A9, and proteinase 3 were found to be predictive of COVID-19 severity and may serve as potential biomarkers for predicting COVID-19 progression and potential targets in therapeutic intervention of COVID-19.	no

2021	ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 Working Group.	Growing evidence suggests that ABO blood group may play a role in the immunopathogenesis of SARS-CoV-2 infection, with group O individuals less likely to test positive and group A conferring a higher susceptibility to infection and propensity to severe disease. The level of evidence supporting an association between ABO type and SARS-CoV-2/COVID-19 ranges from small observational studies, to genome-wide-association-analyses and country-level meta-regression analyses. ABO blood group antigens are oligosaccharides expressed on red cells and other tissues (notably endothelium). There are several hypotheses to explain the differences in SARS-CoV-2 infection by ABO type. For example, anti-A and/or anti-B antibodies (e.g. present in group O individuals) could bind to corresponding antigens on the viral envelope and contribute to viral neutralization, thereby preventing target cell infection. The SARS-CoV-2 virus and SARS-CoV spike (S) proteins may be bound by anti-A isoagglutinins (e.g. present in group O and group B individuals), which may block interactions between virus and angiotensin-converting-enzyme-2-receptor, thereby preventing entry into lung epithelial cells. ABO type-associated variations in angiotensin-converting enzyme-1 activity and levels of von Willebrand factor (VWF) and factor VIII could also influence adverse outcomes, notably in group A individuals who express high VWF levels. In conclusion, group O may be associated with a lower risk of SARS-CoV-2 infection and group A may be associated with a higher risk of SARS-CoV-2 infection along with severe disease. However, prospective and mechanistic studies are needed to verify several of the proposed associations. Based on the strength of available studies, there are insufficient data for guiding policy in this regard.	yes
2021	[Transfusion of convalescent plasma from patients with COVID - 19].	There is currently no vaccine available and no specific medication against Coronavirus 2019 disease (COVID-19). The treatment is mainly based on support measures. In this context, several potentially useful therapies have been approved for use in clinical trials, such as convalescent plasma transfusion (CPT). PubMed was searched for studies on convalescent plasma and COVID-19, SARS or MERS. Studies on clinical efficacy in diseases caused by other coronaviruses (SARS-CoV and MERS-CoV) showed clinical improvement, increase of neutralizing antibodies, decreased mortality and absence of adverse events during and after treatment. We found 13 studies on this type of treatment used in patients with severe and critical COVID-19. Despite limitations regarding methodology, number of patients and the protocols for the analysis of donors' convalescent plasma, patients who received CPT showed clinical improvement, improvement of ventilatory patterns, resolution of lung injuries, decreased mortality, improvement of laboratory parameters, increase of neutralizing antibodies, decreased viral load and low frequency of adverse events.	no

2021	Single-cell transcriptomes of peripheral blood cells indicate and elucidate severity of COVID-19.	The blood and immune system of coronavirus disease 2019 (COVID-19) infected patients are dysfunctional, and numerous studies have been conducted to resolve their characteristics and pathogenic mechanisms. Nevertheless, the variations of immune responses along with disease severity have not been comprehensively documented. Here, we profiled the single-cell transcriptomes of 96,313 peripheral blood mononuclear cells (PBMCs) derived from 12 COVID-19 patients (including four moderate, four severe and four critical cases) and three healthy donors. We showed that proliferative CD8 effector T cells with declined immune functions and cytotoxicity accumulated in the critical stage. By contrast, the quantity of natural killer (NK) cells was significantly reduced, while they exhibited enhanced immune activities. Notably, a gradually attenuated responseto COVID-19 along with disease severity was observed in monocytes, in terms of cellular composition, transcriptional discrepancy and transcription factor regulatory network. Furthermore, we identified immune cell-type dependent cytokine signatures distinguishing the severity of COVID-19 patients. In addition, cell interactions between CD8 effector T/NK cells and monocytes mediated by inflammatory cytokines were enhanced in moderate and severe stages, but weakened in critical cases. Collectively, our work uncovers the cellular and molecular players underlying the disordered and heterogeneous immune responses associated with COVID-19 severity, which could provide valuable insights for the treatment of critical COVID-19 patients.	no
2021	Association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19.	NA	yes

2021	Evaluating the effects of cardiometabolic exposures on circulating proteins which may contribute to severe SARS-CoV-2.	Developing insight into the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is of critical importance to overcome the global pandemic caused by coronavirus disease 2019 (covid-19). In this study, we have applied Mendelian randomization (MR) to systematically evaluate the effect of 10 cardiometabolic risk factors and genetic liability to lifetime smoking on 97 circulating host proteins postulated to either interact or contribute to the maladaptive host response of SARS-CoV-2. We applied the inverse variance weighted (IVW) approach and several robust MR methods in a two-sample setting to systemically estimate the genetically predicted effect of each risk factor in turn on levels of each circulating protein. Multivariable MR was conducted to simultaneously evaluate the effects of multiple risk factors on the same protein. We also applied MR using cis-regulatory variants at the genomic location responsible for encoding these proteins to estimate whether their circulating levels may influence severe SARS-CoV-2. In total, we identified evidence supporting 105 effects between risk factors and circulating proteins which were robust to multiple testing corrections and sensitivity analyzes. For example, body mass index provided evidence of an effect on 23 circulating proteins with a variety of functions, such as inflammatory markers c-reactive protein (IVW Beta=0.34 per standard deviation change, 95% CI=0.26 to 0.41, P = 2.19 × 10 -16) and interleukin-1 receptor antagonist (IVW Beta=0.23, 95% CI=0.17 to 0.30, P = 9.04 × 10 -12). Further analyzes using multivariable MR provided evidence that the effect of BMI on lowering immunoglobulin G, an antibody class involved in protection from infection, is substantially mediated by raised triglycerides levels (IVW Beta=-0.18, 95% CI=-0.25 to -0.12, P = 2.32 × 10 -08 , proportion mediated=44.1%). The strongest evidence that any of the circulating proteins highlighted by our initial analysis influence severe SARS-CoV-2 was identified for soluble glycoprotein 130 (odds ratio=1.81, 95% CI=1.25 to 2.62, P = 0.002), a signal transductor for interleukin-6 type cytokines which are involved in inflammatory response. However, based on current case samples for severe SARS-CoV-2 we were unable to replicate findings in independent samples. Our findings highlight several key proteins which are influenced by established exposures for disease. Future research to determine whether these circulating proteins mediate environmental effects onto risk of SARS-CoV-2 infection or covid-19 progression are warranted to help elucidate therapeutic strategies for severe covid-19 disease. The Medical Research Council, the Wellcome Trust, the British Heart Foundation and UK Research and Innovation.	no
2021	Genomic monitoring of SARS-CoV-2 uncovers an Nsp1 deletion variant that modulates type I interferon response.	The SARS-CoV-2 virus, the causative agent of COVID-19, is undergoing constant mutation. Here, we utilized an integrative approach combining epidemiology, virus genome sequencing, clinical phenotyping, and experimental validation to locate mutations of clinical importance. We identified 35 recurrent variants, some of which are associated with clinical phenotypes related to severity. One variant, containing a deletion in the Nsp1-coding region (Δ500-532), was found in more than 20% of our sequenced samples and associates with higher RT-PCR cycle thresholds and lower serum IFN-β levels of infected patients. Deletion variants in this locus were found in 37 countries worldwide, and viruses isolated from clinical samples or engineered by reverse genetics with related deletions in Nsp1 also induce lower IFN-β responses in infected Calu-3 cells. Taken together, our virologic surveillance characterizes recurrent genetic diversity and identified	no

		mutations in Nsp1 of biological and clinical importance, which collectively may aid molecular diagnostics and drug design.	
2021	Association of the ABO blood group with SARS-CoV-2 infection in a community with low infection rate.	Reports on the association of the ABO phenotypes with infection by the SARS-CoV-2 virus have mostly come from countries with high infection rates. This study examined the possible association between SARS-CoV-2 infection and the ABO phenotype in Black Africa. This report is from a single centre where both asymptomatic and symptomatic patients were quarantined. At the time of this report, Oyo State, Nigeria had carried out 15 733 tests of which 3119 were positive for the virus with 1952 recoveries and 37 deaths. The ABO distribution of patients was compared with that of a blood donor population. Of the 302 participants, 297 (98%) had their blood group determined, asymptomatic and symptomatic individuals were 123 (40·7%) and 179 (59·3%) respectively. Blood group O was significantly less represented among the patients ($P < 0·01$) while blood groups B and AB were significantly more represented ($P < 0·01$, $P = 0·03$ respectively). Patients with anti-B (groups A and O) were significantly less represented than those without anti-B (B and/or AB): B and AB ($P < 0·001$), B ($P = 0·002$), AB ($P = 0·01$). There was no difference in the blood group distribution of symptomatic and asymptomatic patients ($\chi 2$ (3, $N = 302$) = 2·29; $P = 0·51$), but symptomatic patients with anti-A (groups B and O) were more represented than asymptomatic patients with anti-A ($\chi 2$ 4·89; $P = 0·03$). The higher prevalence of blood group O and more potent beta haemolysins (anti-B antibodies) are likely reasons for the lower infectivity by the SARS-CoV-2 virus and severity of COVID-19 disease in the community.	yes

2021	Identification of parameters in routine blood and coagulation tests related to the severity of COVID-19.	Objective: This study aimed to identify the predictive value of simple markers in routine blood and coagulation tests for the severity of coronavirus disease 2019 (COVID-19). Methods: A total of 311 consecutive COVID-19 patients, including 281 patients with mild/moderate COVID-19 and 30 patients with severe/life-threatening COVID-19, were retrospectively enrolled. Logistic modeling and ROC curve analyses were used to assess the indexes for identifying disease severity. Results: Lymphocyte and eosinophil counts of COVID-19 patients in the severe/life-threatening group were significantly lower than those of patients in the mild/moderate group ($P < 0.001$). Coagulation parameters, high-sensitivity C-reactive protein (hsCRP) levels and procalcitonin levels were higher in the severe/life-threatening group compared with the mild/moderate group (all $P < 0.05$). Univariate and multivariate logistic models revealed that hsCRP and fibrinogen degradation products (FDPs) were predictors of severe COVID-19 (OR = 1.072, P = 0.036; and OR = 1.831, P = 0.036, respectively). The AUROCs of hsCRP and FDP for predicting severe/life-threatening COVID-19 were 0.850 and 0.766, respectively. The optimal cutoffs of hsCRP and FDP for the severe/life-threatening type of COVID-19 were 22.41 mg/L and 0.95 μg/ml, respectively. Conclusion: Serum CRP and FDP levels are positively related to the severity of COVID-19. This finding indicates that CRP and FDP levels may potentially be used as early predictors for severe illness and help physicians triage numerous patients in a short time.	yes
2021	Can blood type alter covid-19 risk?	Blood type may affect whether you catch the coronavirus or the severity of your symptoms.	
2021	ACE2/Ang-(1-7)/Mas1 axis and the vascular system: vasoprotection to COVID-19-associated vascular disease.	The two axes of the renin-angiotensin system include the classical ACE/Ang II/AT1 axis and the counter-regulatory ACE2/Ang-(1-7)/Mas1 axis. ACE2 is a multifunctional monocarboxypeptidase responsible for generating Ang-(1-7) from Ang II. ACE2 is important in the vascular system where it is found in arterial and venous endothelial cells and arterial smooth muscle cells in many vascular beds. Among the best characterized functions of ACE2 is its role in regulating vascular tone. ACE2 through its effector peptide Ang-(1-7) and receptor Mas1 induces vasodilation and attenuates Ang II-induced vasoconstriction. In endothelial cells activation of the ACE2/Ang-(1-7)/Mas1 axis increases production of the vasodilator's nitric oxide and prostacyclin's and in vascular smooth muscle cells it inhibits pro-contractile and pro-inflammatory signaling. Endothelial ACE2 is cleaved by proteases, shed into the circulation and measured as soluble ACE2. Plasma ACE2 activity is increased in cardiovascular disease and may have prognostic significance in disease severity. In addition to its enzymatic function, ACE2 is the receptor for severe acute respiratory syndrome (SARS)-coronavirus (CoV) and SARS-Cov-2, which cause SARS and coronavirus disease-19 (COVID-19) respectively. ACE-2 is thus a double-edged sword: it promotes cardiovascular health while also facilitating the devastations caused by coronaviruses. COVID-19 is associated with cardiovascular disease as a risk factor and as a complication. Mechanisms linking COVID-19 and cardiovascular disease are unclear, but vascular ACE2 may be important. This review focuses on the vascular biology and (patho)physiology of ACE2 in cardiovascular health and disease and briefly discusses the role of vascular ACE2 as a potential mediator of vascular injury in COVID-19.	

2021	Circulating Levels of Calcitonin Gene-Related Peptide Are Lower in COVID-19 Patients.	To better understand the biology of COVID-19, we have explored the behavior of calcitonin gene-related peptide (CGRP), an angiogenic, vasodilating, and immune modulating peptide, in severe acute respiratory syndrome coronavirus 2 positive patients. Levels of CGRP in the serum of 57 COVID-19 patients (24 asymptomatic, 23 hospitalized in the general ward, and 10 admitted to the intensive care unit) and healthy donors (n = 24) were measured by enzyme-linked immunosorbent assay (ELISA). In addition, to better understand the physiological consequences of the observed variations, we investigated by immunofluorescence the distribution of receptor activity modifying protein 1 (RAMP1), one of the components of the CGRP receptor, in autopsy lung specimens. CGRP levels were greatly decreased in COVID-19 patients ($P < 0.001$) when compared to controls, and there were no significant differences due to disease severity, sex, age, or comorbidities. We found that COVID-19 patients treated with proton pump inhibitors had lower levels of CGRP than other patients not taking this treatment ($P = 0.001$). RAMP1 immunoreactivity was found in smooth muscle cells of large blood vessels and the bronchial tree and in the airways´ epithelium. In COVID-19 samples, RAMP1 was also found in proliferating type II pneumocytes, a common finding in these patients. The lower levels of CGRP should negatively impact the respiratory physiology of COVID-19 patients due to vasoconstriction, improper angiogenesis, less epithelial repair, and faulty immune response. Therefore, restoring CGRP levels in these patients may represent a novel therapeutic approach for COVID-19.	
2021	Blood biochemical parameters for assessment of COVID-19 in diabetic and non-diabetic subjects: a cross-sectional study.	This study aims to identify blood biomarkers for rapidly predicting progression and severity assessment of COVID-19 in type 2 diabetic (DM) and non-DM (NDM) patients. Among 211 hospitalized patients suspected of COVID-19, 98 were confirmed COVID-19 by rRT-PCR. The COVID-19 positive group contained 58 DM and 40 NDM patients with total death 9 of which 7 were males and 6 were DM, indicating males and DM individuals as more susceptible to COVID-19. Blood biomarkers notably serum ferritin, CRP, D-dimer, ALT, troponin I, and Hb1Ac were significantly ($p < 0.05$) higher in COVID-19 patients. Ferritin and HbA1c levels were significantly ($p < 0.05$) higher in DM than NDM COVID-19 patients. The present study suggests that ferritin and HbA1c levels for DM patients, and ferritin, D-dimer, ALT for NDM patients could be routinely used as biomarkers for progression and severity assessment of COVID-19. CRP and Troponin-I could be the predictor only for poor prognosis of COVID-19.	

2021	Clinical analysis and pluripotent stem cells-based model reveal possible impacts of ACE2 and lung progenitor cells on infants vulnerable to COVID-19.	Introduction: An increasing number of children with severe coronavirus disease 2019 (COVID-19) is being reported, yet the spectrum of disease severity and expression patterns of angiotensin-converting enzyme 2 (ACE2) in children at different developmental stages are largely unknow. Methods: We analysed clinical features in a cohort of 173 children with COVID-19 (0-15 yrs.-old) between January 22, 2020 and March 15, 2020. We systematically examined the expression and distribution of ACE2 in different developmental stages of children by using a combination of children's lung biopsies, pluripotent stem cell-derived lung cells, RNA-sequencing profiles, and ex vivo SARS-CoV-2 pseudoviral infections. Results: It revealed that infants (< 1yrs.-old), with a weaker potency of immune response, are more vulnerable to develop pneumonia whereas older children (> 1 yrs.-old) are more resistant to lung injury. The expression levels of ACE2 however do not vary by age in children's lung. ACE2 is notably expressed not only in Alveolar Type II (AT II) cells, but also in SOX9 positive lung progenitor cells detected in both pluripotent stem cell derivatives and infants' lungs. The ACE2 + SOX9 + cells are readily infected by SARS-CoV-2 pseudovirus and the numbers of the double positive cells are significantly decreased in older children. Conclusions: Infants (< 1 yrs.-old) with SARS-CoV-2 infection are more vulnerable to lung injuries. ACE2 expression in multiple types of lung cells including SOX9 positive progenitor cells, in cooperation with an unestablished immune system, could be risk factors contributing to vulnerability of infants with COVID-19. There is a need to continue monitoring lung development in young children who have recovered from SARS-CoV-2 infection.	
2021	ABO blood group and SARS-CoV-2 antibody response in a convalescent donor population.	ABO blood group may affect risk of SARS-CoV-2 infection and/or severity of COVID-19. We sought to determine whether IgG, IgA and neutralizing antibody (nAb) to SARS-CoV-2 vary by ABO blood group. Among eligible convalescent plasma donors, ABO blood group was determined via agglutination of reagent A1 and B cells, IgA and IgG were quantified using the Euroimmun anti-SARS-CoV-2 ELISA, and nAb titres were quantified using a microneutralization assay. Differences in titre distribution were examined by ABO blood group using non-parametric Kruskal-Wallis tests. Adjusted prevalence ratios (aPR) of high nAb titre (≥1:160) were estimated by blood group using multivariable modified Poisson regression models that adjusted for age, sex, hospitalization status and time since SARS-CoV-2 diagnosis. Of the 202 potential donors, 65 (32%) were blood group A, 39 (19%) were group B, 13 (6%) were group AB, and 85 (42%) were group O. Distribution of nAb titres significantly differed by ABO blood group, whereas there were no significant differences in anti-spike IgA or anti-spike IgG titres by ABO blood group. There were significantly more individuals with high nAb titre (≥1:160) among those with blood group B, compared with group O (aPR = 1·9 [95%CI = 1·1-3·3], P = 0·029). Fewer individuals had a high nAb titre among those with blood group A, compared with group B (aPR = 0·6 [95%CI = 0·4-1·0], P = 0·053). Eligible CCP donors with blood group B may have relatively higher neutralizing antibody titres. Additional studies evaluating ABO blood groups and antibody titres that incorporate COVID-19 severity are needed.	

2021	Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study.	Haematopoietic stem-cell transplantation (HSCT) recipients are considered at high risk of poor outcomes after COVID-19 on the basis of their immunosuppressed status, but data from large studies in HSCT recipients are lacking. This study describes the characteristics and outcomes of HSCT recipients after developing COVID-19. In response to the pandemic, the Center for International Blood and Marrow Transplant Research (CIBMTR) implemented a special form for COVID-19-related data capture on March 27, 2020. All patients-irrespective of age, diagnosis, donor type, graft source, or conditioning regimens-were included in the analysis with data cutoff of Aug 12, 2020. The main outcome was overall survival 30 days after a COVID-19 diagnosis. Overall survival probabilities were calculated using Kaplan-Meier estimator. Factors associated with mortality after COVID-19 diagnosis were examined using Cox proportional hazard models. 318 HSCT recipients diagnosed with COVID-19 were reported to the CIBMTR. The median time from HSCT to COVID-19 diagnosis was 17 months (IQR 8-46) for allogeneic HSCT recipients and 23 months (8-51) for autologous HSCT recipients. The median follow-up of survivors was 21 days (IQR 8-41) for allogeneic HSCT recipients and 25 days (12-35) for autologous HSCT recipients. 34 (18%) of 184 allogeneic HSCT recipients were receiving immunosuppression within 6 months of COVID-19 diagnosis. Disease severity was mild in 155 (49%) of 318 patients, while severe disease requiring mechanical ventilation occurred in 45 (14%) of 318 patients-ie, 28 (15%) of 184 allogeneic HSCT recipients and 17 (13%) of 134 autologous HSCT recipients. At 30 days after the diagnosis of COVID-19, overall survival was 68% (95% CI 58-77) for recipients of allogeneic HSCT and 67% (55-78) for recipients of autologous HSCT. Age 50 years or older (hazard ratio 2·53, 95% CI 1·16-5·52; p=0·020); male sex (3·53; 1·44-8·67; p=0·006), and development of COVID-19 within 12 months of transplantation (2·67, 1·33-5·36; p=0·005) were associated with a higher risk of mortality among allogeneic HSCT recipients, and a disease indication of lymphoma was associated with a higher risk of mortality compared with plasma cell disorder or myeloma (2·41, [1·08-5·38]; p=0·033) in autologous HSCT recipients. Recipients of autologous and allogeneic HSCT who develop COVID-19 have poor overall survival. These data emphasise the need for stringent surveillance and aggressive treatment measures in HSCT recipients who develop COVID-19. American Society of Hematology; Leukemia and Lymphoma Society; National Cancer Institute; National Heart, Lung and Blood Institute; National Institute of Allergy and Infectious Diseases; National Institutes of Health; National Cancer Institute; Health Resources and Services Administration; Office of Naval Research.	
2021	Combined hormonal contraception and COVID-19.	Aim: This article reviews the possibility of using combined hormonal contraception during the COVID-19 pandemic. Methods: narrative review Results: The factors that protect women from the severity of the disease are analysed, as well as the risk factors for the use of this type of contraception, especially related to the increased risk of a thrombotic event in patients affected by the disease. Finally, the information available on the guidelines for action in patients with COVID-19 using combined hormonal contraception is collected. Conclusions: We can continue to prescribe and use hormonal methods with EE.	

2021	Interplay of Antibody and Cytokine Production Reveals CXCL13 as a Potential Novel Biomarker of Lethal SARS-CoV-2 Infection.	The SARS-CoV-2 pandemic is impacting the global population. This study was designed to assess the interplay of antibodies with the cytokine response in SARS-CoV-2 patients. We demonstrate that significant levels of anti-SARS-CoV-2 antibody to receptor binding domain (RBD), nucleocapsid, and spike S1 subunit of SARS-CoV-2 develop over the first 10 to 20 days of infection. The majority of patients produced antibodies against all three antigens (219/255 SARS-CoV-2 + patient specimens, 86%), suggesting a broad response to viral proteins. Antibody levels to SARS-CoV-2 antigens were different based on patient mortality, sex, blood type, and age. Analyses of these findings may help explain variation in immunity between these populations. To better understand the systemic immune response, we analyzed the levels of 20 cytokines by SARS-CoV-2 patients throughout infection. Cytokine analysis of SARS-CoV-2 + patients exhibited increases in proinflammatory markers (interleukin 6 [IL-6], IL-8, IL-18, and gamma interferon [IFN-γ]) and chemotactic markers (IP-10 and eotaxin) relative to healthy individuals. Patients who succumbed to infection produced decreased IL-2, IL-4, IL-12, RANTES, tumor necrosis factor alpha (TNF-α), GRO-α, and MIP-1α relative to patients who survived infection. We also observed that the chemokine CXCL13 was particularly elevated in patients who succumbed to infection. CXCL13 is involved in B cell activation, germinal center development, and antibody maturation, and we observed that CXCL13 levels in blood trended with anti-SARS-CoV-2 antibody levels. Furthermore, patients who succumbed to infection produced high CXCL13 and had a higher ratio of nucleocapsid to RBD antibodies. This study provides insights into SARS-CoV-2 immunity implicating the magnitude and specificity of response in relation to patient outcomes. IMPORTANCE The SARS-CoV-2 pandemic is continuing to impact the global population, and knowledge of the immune response to COVID-19 is still developing. This study assesses the interplay of different parts of the immune system during COVID-19 disease. We demonstrate that COVID-19 patients produce antibodies to three proteins of the COVID-19 virus (SARS-CoV-2) and identify many other immunological proteins that are involved during infection. The data suggest that one of these proteins (CXCL13) may be a novel biomarker for severe COVID-19 that can be readily measured in blood. This information combined with our broad-scale analysis of immune activity during COVID-19 provides new information on the immunological response throughout the course of disease and identifies a novel potential marker for assessing disease severity.	

2021	Risk factors for illness severity in patients with COVID-19 pneumonia: a prospective cohort study.	Background: Although COVID-19 pneumonia is spreading internationally, knowledge regarding the factors associated with the illness severity of patients remains limited. We aimed to identify the factors associated with the disease severity of patients with COVID-19 pneumonia induced by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Methods: We prospectively enrolled a single-center case series of adult patients with COVID-19 admitted to the Infectious Disease Hospital of Jining, Jining City, Shandong Province, China, from January 24 to March 1, 2020. Demographics, clinical characteristics, and laboratory findings were compared to investigate the risk factors related with the disease severity of COVID-19 pneumonia patients. Results: We included a total of 78 patients with COVID-19 pneumonia, of whom 6 had the severe type. As compared to a moderately ill cohort, our analysis showed that shortness of breath, fatigue, longer days from illness onset to diagnosis confirmed, neutrophil percentages > 70%, neutrophil counts > 6.3 × 10 9 /L, lymphocyte percentages < 20%, lymphocyte counts < 1.0 × 10 9 /L, platelet < 100 × 10 9 /L, C-reactive protein (CRP) > 10 mg/L, neutrophil to platelet ratio (NPR) > 2.3, neutrophil to lymphocyte ratio (NLR) > 3.9, aspartate aminotransferase (AST) > 40 U/L, albumin < 40 g/L, lactate dehydrogenase (LDH) > 245 U/L, and glucose > 6.1 mmol/L were predictors of disease severity in COVID-19 pneumonia. In the sex-, age-, and comorbid illness-matched case-control study, neutrophil percentages > 70%, neutrophil counts > 6.3 × 10 9 /L, lymphocyte percentages < 20%, NPR > 2.3, NLR > 3.9, albumin < 40 g/L, and LDH > 245 U/L remained associated with the early detection and identification of severe patients. Conclusion: We demonstrated that neutrophil percentages > 70%, neutrophil counts > 6.3 × 10 9 /L, lymphocyte percentages < 20%, NPR > 2.3, NLR > 3.9, albumin < 40 g/L, and LDH > 245 U/L might predict the severity of illness in patients with COVID-19 pneumonia.	
2021	Employing a systematic approach to biobanking and analyzing clinical and genetic data for advancing COVID-19 research.	Within the GEN-COVID Multicenter Study, biospecimens from more than 1000 SARS-CoV-2 positive individuals have thus far been collected in the GEN-COVID Biobank (GCB). Sample types include whole blood, plasma, serum, leukocytes, and DNA. The GCB links samples to detailed clinical data available in the GEN-COVID Patient Registry (GCPR). It includes hospitalized patients (74.25%), broken down into intubated, treated by CPAP-biPAP, treated with O 2 supplementation, and without respiratory support (9.5%, 18.4%, 31.55% and 14.8, respectively); and non-hospitalized subjects (25.75%), either pauci- or asymptomatic. More than 150 clinical patient-level data fields have been collected and binarized for further statistics according to the organs/systems primarily affected by COVID-19: heart, liver, pancreas, kidney, chemosensors, innate or adaptive immunity, and clotting system. Hierarchical clustering analysis identified five main clinical categories: (1) severe multisystemic failure with either thromboembolic or pancreatic variant; (2) cytokine storm type, either severe with liver involvement or moderate; (3) moderate heart type, either with or without liver damage; (4) moderate multisystemic involvement, either with or without liver damage; (5) mild, either with or without hyposmia. GCB and GCPR are further linked to the GCGDR, which includes data from whole-exome sequencing and high-density SNP genotyping. The data are available for sharing through the Network for Italian Genomes, found within the COVID-19 dedicated section. The study objective is to systematize this comprehensive data collection and begin identifying multi-organ involvement in COVID-19, defining genetic parameters for	

		infection susceptibility within the population, and mapping genetically COVID-19 severity and clinical complexity among patients.	
2021	Ethnicity and outcomes in patients hospitalised with COVID-19 infection in East London: an observational cohort study.	To describe outcomes within different ethnic groups of a cohort of hospitalised patients with confirmed COVID-19 infection. To quantify and describe the impact of a number of prognostic factors, including frailty and inflammatory markers. Five acute National Health Service Hospitals in east London. Prospectively defined observational study using registry data. 1737 patients aged 16 years or over admitted to hospital with confirmed COVID-19 infection between 1 January and 13 May 2020. The primary outcome was 30-day mortality from time of first hospital admission with COVID-19 diagnosis during or prior to admission. Secondary outcomes were 90-day mortality, intensive care unit (ICU) admission, ICU and hospital length of stay and type and duration of organ support. Multivariable survival analyses were adjusted for potential confounders. 1737 were included in our analysis of whom 511 had died by day 30 (29%). 538 (31%) were from Asian, 340 (20%) black and 707 (40%) white backgrounds. Compared with white patients, those from minority ethnic backgrounds were younger, with differing comorbidity profiles and less frailty. Asian and black patients were more likely to be admitted to ICU and to receive invasive ventilation (OR 1.54, (95% CI 1.06 to 2.23); p=0.023 and OR 1.80 (95% CI 1.20 to 2.71); p=0.005, respectively). After adjustment for age and sex, patients from Asian (HR 1.49 (95% CI 1.19 to 1.86); p<0.001) and black (HR 1.30 (95% CI 1.02 to 1.65); p=0.036) backgrounds were more likely to die. These findings persisted across a range of risk factor-adjusted analyses accounting for major comorbidities, obesity, smoking, frailty and ABO blood group. Patients from Asian and black backgrounds had higher mortality from COVID-19 infection despite controlling for all previously identified confounders and frailty. Higher rates of invasive ventilation indicate greater acute disease severity. Our analyses suggest that patients of Asian and black backgrounds suffered disproportionate rates of premature death from COVID-19.	

2021	Chromosome 3 cluster rs11385942 variant links complement activation with severe COVID-19.	Genetic variation at a multigene cluster at chromosome 3p21.31 and the ABO blood group have been associated with the risk of developing severe COVID-19, but the mechanism remains unclear. Complement activation has been associated with COVID-19 severity. The aim of this study was to examine whether chromosome 3p21.31 and the ABO variants are linked to the activation of the complement cascade in COVID-19 patients. We considered 72 unrelated European hospitalized patients with genetic data and evaluation of circulating C5a and soluble terminal complement complex C5b-9 (SC5b-9). Twenty-six (36.1%) patients carried the rs11385942 G>GA variant and 44 (66.1%) non-O blood group associated with increased risk of severe COVID-19. C5a and SC5-b9 plasma levels were higher in rs11385949 GA carriers than in non-carriers (P = 0.041 and P = 0.012, respectively), while C5a levels were higher in non-O group than in O group patients (P = 0.019). The association between rs11385949 and SC5b-9 remained significant after adjustment for ABO and disease severity (P = 0.004) and further correction for C5a (P = 0.018). There was a direct relationship between upper airways viral load and SC5b-9 in carriers of the rs11385949 risk allele (P = 0.032), which was not observed in non-carriers. The rs11385949 G>GA variant, tagging the chromosome 3 gene cluster variation and predisposing to severe COVID-19, is associated with enhanced complement activation, both with C5a and terminal complement complex, while non-O blood group with C5a levels. These findings provide a link between genetic susceptibility to more severe COVID-19 and complement activation.	
2021	Serial KL-6 measurements in COVID-19 patients.	SARS-CoV2-induced direct cytopathic effects against type II pneumocytes are suspected to play a role in mediating and perpetuating lung damage. The aim of this study was to evaluate serum KL-6 behavior in COVID-19 patients to investigate its potential role in predicting clinical course. Sixty patients (median age IQR, 65 (52-69), 43 males), hospitalized for COVID-19 at Siena COVID Unit University Hospital, were prospectively enrolled. Twenty-six patients were selected (median age IQR, 63 (55-71), 16 males); all of them underwent follow-up evaluations, including clinical, radiological, functional, and serum KL-6 assessments, after 6 (t1) and 9 (t2) months from hospital discharge. At t0, KL-6 concentrations were significantly higher than those at t1 (760 (311-1218) vs. 309 (210-408) p = 0.0208) and t2 (760 (311-1218) vs 324 (279-458), p = 0.0365). At t0, KL-6 concentrations were increased in patients with fibrotic lung alterations than in non-fibrotic group (755 (370-1023) vs. 305 (225-608), p = 0.0225). Area under the receiver operating curve (AUROC) analysis showed that basal KL-6 levels showed good accuracy in discriminating patients with fibrotic sequelae radiologically documented (AUC 85%, p = 0.0404). KL-6 concentrations in patients with fibrotic involvement were significantly reduced at t1 (755 (370-1023) vs. 290 (197-521), p = 0.0366) and t2 (755 (370-1023) vs. 318 (173-435), p = 0.0490). Serum concentrations of KL-6 in hospitalized COVID-19 patients may contribute to identify severe patients requiring mechanical ventilation and to predict those who will develop pulmonary fibrotic sequelae in the follow-up.	

2021	Plasma tissue plasminogen activator and plasminogen activator inhibitor-1 in hospitalized COVID-19 patients.	Patients with coronavirus disease-19 (COVID-19) are at high risk for thrombotic arterial and venous occlusions. However, bleeding complications have also been observed in some patients. Understanding the balance between coagulation and fibrinolysis will help inform optimal approaches to thrombosis prophylaxis and potential utility of fibrinolytic-targeted therapies. 118 hospitalized COVID-19 patients and 30 healthy controls were included in the study. We measured plasma antigen levels of tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) and performed spontaneous clot-lysis assays. We found markedly elevated tPA and PAI-1 levels in patients hospitalized with COVID-19. Both factors demonstrated strong correlations with neutrophil counts and markers of neutrophil activation. High levels of tPA and PAI-1 were associated with worse respiratory status. High levels of tPA, in particular, were strongly correlated with mortality and a significant enhancement in spontaneous ex vivo clot-lysis. While both tPA and PAI-1 are elevated among COVID-19 patients, extremely high levels of tPA enhance spontaneous fibrinolysis and are significantly associated with mortality in some patients. These data indicate that fibrinolytic homeostasis in COVID-19 is complex with a subset of patients expressing a balance of factors that may favor fibrinolysis. Further study of tPA as a biomarker is warranted.	
2021	Medium Cut-Off Dialysis Membranes: Can They Have Impact on Outcome of COVID-19 Hemodialysis Patients?	Severe acute respiratory syndrome coronavirus-2 may lead to high levels of expression of inflammatory cytokines. Medium cut-off (MCO) membranes may make greater clearances for large-middle molecules (including cytokines) than low-flux (LF) membranes. In this study, we aimed to evaluate the impact of MCO membranes on outcome of COVID-19 patients on hemodialysis (HD). Sixty COVID-19 HD patients were included in this study. The patients were categorized into 2 groups regarding type of HD membranes. Clinical data were taken from medical records. Initial crp and ferritin levels, which are surragates of cytokine storm and severity of disease in COVID-19, were significantly higher in MCO membrane group compared to LF group ($p = 0.037$ and 0.000, respectively). Although there were more patients with severe disease in MCO group, there were no significant differences regarding need for intensive care unit and death. It may be an option to use MCO membranes in HD patients with COVID-19 in order to reduce cytokine levels and prevent cytokine storm.	

2021	Inflammation and Vascular Injury as the Basis of COVID-19 Skin Changes: Preliminary Analysis of 23 Patients from the Literature.	COVID-19 can affect various organ systems including the skin. Cutaneous manifestations of COVID-19 in infected patients are poorly characterized. To summarize retrospectively the skin features of COVID-19 infection and to analyze the skin rash incidence rate, clinical onset time, cutaneous manifestations, pathological characteristics and relationship with the novel coronavirus pneumonia severity. The literature up to Sep 20, 2020, were searched and analyzed. Information on clinical features including skin manifestations, disease severity, stage and onset day, and cutaneous pathological characteristics was extracted. Data were analyzed using descriptive non-parametric statistics. For categorical data, the number and percentage of patients are presented. A Spearman correlation test was used to analyze the associations between rash type, rash onset and severity of COVID-19. All statistical analysis was performed with IBM SPSS software (version 20) using two-tailed tests. P values <0.05 were considered statistically significant. Twenty-three cases of COVID-19 patients with cutaneous manifestations from seven reports were collected. Inflammatory dermatosis, skin vasculitis and vascular dermatosis were the main lesion types of COVID-19 patients. Microvascular and endothelial cell injury, perivascular lymphocytic infiltrate, thrombosis, extremely dilated vessels and prominent deposits of C5b-9 were the main dermatologic pathological changes. The onset day analysis showed that out of 19 patients, 63.2% of cutaneous manifestations were within 10 days, 21.1% in 10-20 days and 15.8% were 20 days after the time the patient presented with COVID-19 main symptoms. Spearman rho analysis found no correlation between skin rash type, onset day and COVID-19 severity. COVID-19 induced skin changes are one of the manifestations of immune responses to the novel coronavirus. Clinical and pathological characteristics were identified as dermal inflammatory reactions and/or skin vascular injury. External or systematic use of anti-inflammatories, protection of blood vessels and circulation-improving medicines should be considered in the skin treatments for novel coronavirus pneumonia patients.	

2021	Hydroxychloroquine in the treatment of adult patients with Covid-19 infection in a primary care setting (LIBERTY): A structured summary of a study protocol for a randomised controlled trial.	The primary objective of this study is to evaluate the therapeutic potential of hydroxychloroquine (HCQ) in the treatment of adult patients with PCR-confirmed Covid-19 infection in a primary open-care setting, as compared to placebo. The study hypothesis is that treatment with HCQ will reduce the risk of hospitalization because of Covid-19 infection, and the sample size estimate of the study is based on the need to test this hypothesis. The secondary objectives of the study are: to evaluate the safety and tolerability of HCQ in the treatment of adult patients with PCR-confirmed Covid-19 infection in a primary open-care setting, as compared to placebo; to collect experience of the use of HCQ in the treatment of Covid-19 infection in outpatients, in order to be able to identify patient characteristics that predict specific treatment responses (favourable or unfavourable); this objective will also be addressed by post-hoc subgroup analysis of the study results and by meta-analysis of pooled patient data from other clinical trials of HCQ in outpatients; and to evaluate the impact of Covid-19 infection and its treatment on the mental health and well-being of the study participants. In addition, if the data allow, the study has the following exploratory objectives: to evaluate the extent and duration of SARS-CoV-2 viral shedding by PCR testing of nasopharyngeal swab samples in study subjects treated with HCQ, as compared to placebo; to evaluate the extent and time course of SARS-CoV-2 virus-specific antibody responses in serum of study subjects treated with HCQ, as compared to placebo; to evaluate other possible biomarker changes in blood in study subjects treated with HCQ, as compared to placebo; to explore the possible effects of genetic variation in drug metabolizing enzymes on HCQ-related outcomes in the study population; to explore the associations of HCQ-related outcome variables with other patient characteristics, e.g. HLA haplotypes, HCQ concentrations, demographic variables, disease history and concomitant medications. This is a phase 2, placebo-controlled, double-blind, randomized, parallel-group treatment trial comparing HCQ with placebo in outpatients with Covid-19 infection. Participants will be randomized in a 1:1 ratio to the two treatment arms. Main inclusion criteria: 1. Males and females >40 years of age, or 18-40 years of age with one or both of the following: i. diabetes mellitus (type 1 or type 2); ii. BMI > 35 kg/m 2 ; 2. Valid independent informed consent obtained; 3. Symptoms typical of Covid-19 infection, according to criteria specified in the study protocol. The onset of symptoms must be within 5 days of enrolment; 4. Positive SARS-CoV-2 PCR test result of a nasopharyngeal swab sample. Main exclusion criteria: 1. Suspected severe or moderately severe pneumonia, presenting with any of the following: respiratory rate > 26 breaths/min; significant respiratory distress; or SpO 2 ≤94% on room air; 2. Requiring treatment in the hospital, according to the treating physician's judgement; 3. Any contraindication to treatment with HCQ; 4. Pregnancy or lactation. The trial will be conducted at seven study sites in a primary public health care setting in the region of Satakunta, Finland. Participants will be randomized to receive either HCQ capsules at 300 mg twice a day for one day and then 200 mg twice a day for 6 days, or placebo capsules for 7 days. The primary endpoint of the study is the number of hospitalizations due to Covid-19 infection within four weeks of entry into the study. The secondary endpoints of the study include the following: duration and severity of Covid-19-related symptoms, as reported by daily self-assessments; number of Intensive Care Unit treatment episodes due to Covid-19 infection within four weeks of entry into the study; number of deaths due to Covid-19	

		infection within four weeks of entry into the study; number of treatment-related adverse events (AEs) and serious AEs (SAEs); all-cause hospitalizations and mortality within six months of entry into the study; and self-assessed symptoms of anxiety, as assessed with repeated administration of the Generalized Anxiety Disorder 7-item scale (GAD-7). The exploratory endpoints of the study include the following: extent and duration of SARS-CoV-2 viral shedding and virus-specific antibody responses in serum; and possible other blood biomarker changes. Eligible study participants are randomly allocated into two treatment arms (1:1 ratio). The randomization list has been generated using Viedoc™ (Viedoc Technologies AB, Uppsala, Sweden) that is used as an electronic data capture system for this study. The participants and all study personnel remain blinded to the treatment allocation by having both IMPs packed in identical containers. Masking of the treatments was performed by re-formulation of the IMPs so that the HCQ capsules and the placebo capsules have identical appearance. 600 participants are to be randomised with 300 in each arm. Protocol version 2, dated 14 July 2020; recruitment is expected to start in December, 2020, and to be completed in June, 2021. EudraCT 2020-002038-33 , registered 26 June 2020 FULL PROTOCOL: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). The protocol has been redacted to conform with privacy regulations by deleting the names and contact information of individuals mentioned in the protocol but not listed as authors in this communication. In the interest of expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.	
2021	Residence, Clinical Features, and Genetic Risk Factors Associated with Symptoms of COVID-19 in a Cohort of Older People in Madrid.	The older population has been especially affected by the severe acute respiratory syndrome coronavirus 2 pandemic (COVID-19). The aim of the study was to explore the incidence, severity, mortality rate, clinical features, and risk factors of symptoms of COVID-19 in home-dwelling older people, and its association with type of residence, cognitive deterioration, and neurodegenerative diseases. Data about symptoms of COVID-19 were collected through a telephone survey in the cohort of 913 older volunteers of the Vallecas Project, aged 75-90 years, most of them (902) home-dwelling, in Madrid, Spain. The association of demographic and anthropometric measures, genetic polymorphisms, comorbidities, life habits, type of residence, and frailty surrogates were explored as potential risk factors for the incidence, severity, and mortality of COVID-19 in the older population. Sixty-two cases reported symptoms compatible with COVID-19; 6 of them had died, 4 in their home and 2 in the nursing home. Moderate/severe cases were significantly older and more frequently males. The APOE ε4 allele was associated with the presence of symptoms of COVID-19. Higher systolic blood pressure, more intense smoking habit, more alcohol intake, lower consumption of coffee and tea, and cognitive impairment were associated with disease severity. The estimated incidence of	

		symptomatic COVID-19 in this older cohort of Madrid was 6.8%, with an overall mortality rate of 0.7% (18.2% in those living in a nursing home) and a fatality rate of 9.9%. Our exploratory study indicates that life habits, other clinical conditions and, the ε4 variant of the APOE gene are associated with the presence and clinical severity of coronavirus infection.	
2021	Unraveling the roles of vitamin D status and melanin during Covid-19 (Review).	As the coronavirus disease 2019 (COVID-19) continues to spread worldwide, it has become evident that the morbidity and mortality rates clearly vary across nations. Although several factors may account for this disparity, striking differences within and between populations indicate that ethnicity might impact COVID-19 clinical outcomes, reflecting the 'color of disease'. Therefore, the role of key biological variables that could interplay with viral spreading and severity indices has attracted increasing attention, particularly among non-Caucasian populations. Although the links between vitamin D status and the incidence and severity of COVID-19 remain elusive, several lines of emerging evidence suggest that vitamin D signaling, targeting several immune-mediated pathways, may offer potential benefits at different stages of SARS-CoV-2 infection. Given that the vitamin D status is modulated by several intrinsic and extrinsic factors, including skin type (pigmentation), melanin polymers may also play a role in variable COVID-19 outcomes among diverse population settings. Moreover, apart from the well-known limiting effects of melanin on the endogenous production of vitamin D, the potential crosstalk between the pigmentary and immune system may also require special attention concerning the current pandemic. The present review article aimed to shed light on a range of mostly overlooked host factors, such as vitamin D status and melanin pigments, that may influence the course and outcome of COVID-19.	

2021	Sputum ACE2, TMPRSS2 and FURIN gene expression in severe neutrophilic asthma.	Patients with severe asthma may have a greater risk of dying from COVID-19 disease. Angiotensin converting enzyme-2 (ACE2) and the enzyme proteases, transmembrane protease serine 2 (TMPRSS2) and FURIN, are needed for viral attachment and invasion into host cells. We examined microarray mRNA expression of ACE2, TMPRSS2 and FURIN in sputum, bronchial brushing and bronchial biopsies of the European U-BIOPRED cohort. Clinical parameters and molecular phenotypes, including asthma severity, sputum inflammatory cells, lung functions, oral corticosteroid (OCS) use, and transcriptomic-associated clusters, were examined in relation to gene expression levels. ACE2 levels were significantly increased in sputum of severe asthma compared to mild-moderate asthma. In multivariate analyses, sputum ACE2 levels were positively associated with OCS use and male gender. Sputum FURIN levels were significantly related to neutrophils (%) and the presence of severe asthma. In bronchial brushing samples, TMPRSS2 levels were positively associated with male gender and body mass index, whereas FURIN levels with male gender and blood neutrophils. In bronchial biopsies, TMPRSS2 levels were positively related to blood neutrophils. The neutrophilic molecular phenotype characterised by high inflammasome activation expressed significantly higher FURIN levels in sputum than the eosinophilic Type 2-high or the pauci-granulocytic oxidative phosphorylation phenotypes. Levels of ACE2 and FURIN may differ by clinical or molecular phenotypes of asthma. Sputum FURIN expression levels were strongly associated with neutrophilic inflammation and with inflammasome activation. This might indicate the potential for a greater morbidity and mortality outcome from SARS-CoV-2 infection in neutrophilic severe asthma.	
2021	COVID-19-neutralizing antibodies predict disease severity and survival.	Coronavirus disease 2019 (COVID-19) exhibits variable symptom severity ranging from asymptomatic to life-threatening, yet the relationship between severity and the humoral immune response is poorly understood. We examined antibody responses in 113 COVID-19 patients and found that severe cases resulting in intubation or death exhibited increased inflammatory markers, lymphopenia, pro-inflammatory cytokines, and high anti-receptor binding domain (RBD) antibody levels. Although anti-RBD immunoglobulin G (IgG) levels generally correlated with neutralization titer, quantitation of neutralization potency revealed that high potency was a predictor of survival. In addition to neutralization of wild-type SARS-CoV-2, patient sera were also able to neutralize the recently emerged SARS-CoV-2 mutant D614G, suggesting cross-protection from reinfection by either strain. However, SARS-CoV-2 sera generally lacked cross-neutralization to a highly homologous pre-emergent bat coronavirus, WIV1-CoV, which has not yet crossed the species barrier. These results highlight the importance of neutralizing humoral immunity on disease progression and the need to develop broadly protective interventions to prevent future coronavirus pandemics.	

2021	Hypoalbuminemia in COVID-19: assessing the hypothesis for underlying pulmonary capillary leakage.	Since the first observations of patients with COVID-19, significant hypoalbuminaemia was detected. Its causes have not been investigated yet. We hypothesized that pulmonary capillary leakage affects the severity of respiratory failure, causing a shift of fluids and proteins through the epithelial-endothelial barrier. One hundred seventy-four COVID-19 patients with respiratory symptoms, 92 admitted to the intermediate medicine ward (IMW) and 82 to the intensive care unit (ICU) at Luigi Sacco Hospital in Milan, were studied. Baseline characteristics at admission were considered. Proteins, interleukin 8 (IL-8) and interleukin 10 (IL-10) in bronchoalveolar lavage fluid (BALF) were analysed in 26 ICU patients. In addition, ten autopsy ultrastructural lung studies were performed in patients with COVID-19 and compared with postmortem findings in a control group (bacterial pneumonia-ARDS and H1N1-ARDS). ICU patients had lower serum albumin than IMW patients [20 (18-23) vs 28 (24-33) g L -1 , $P < 0.001$]. Serum albumin was lower in more compromised groups (lower PaO 2 -to-FiO 2 ratio and worst chest X-ray findings) and was associated with 30 days of probability of survival. Protein concentration was correlated with IL-8 and IL-10 levels in BALF. Electron microscopy examinations of eight out of ten COVID-19 lung tissues showed loosening of junctional complexes, quantitatively more pronounced than in controls, and direct viral infection of type 2 pneumocytes and endothelial cells. Hypoalbuminaemia may serve as severity marker of epithelial-endothelial damage in patients with COVID-19. There are clues that pulmonary capillary leak syndrome plays a key role in the pathogenesis of COVID-19 and might be a potential therapeutic target.	
2021	Strong Correlation between the Case Fatality Rate of COVID-19 and the rs6598045 Single Nucleotide Polymorphism (SNP) of the Interferon-Induced Transmembrane Protein 3 (IFITM3) Gene at the Population-Level.	Coronavirus disease 2019 (COVID-19) is a fatal pandemic disease that is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of 13 December, 2020, over 70,000,000 cases and 1,500,000 deaths have been reported over a period of several months; however, the mechanism underlying the pathogenesis of COVID-19 has not been elucidated. To identify the novel risk genetic biomarker for COVID-19, we evaluated the correlation between the case fatality rate of COVID-19 and the genetic polymorphisms of several potential COVID-19-related genes, including interferon-induced transmembrane protein 3 (IFITM3), the angiotensin I converting enzyme 2 (ACE2) gene, transmembrane protease, serine 2 (TMPRSS2), interleukin 6 (IL6), leucine zipper transcription factor-like protein 1 (LZTFL1), and the ABO genes, in various ethnic groups. We obtained the number of COVID-19 cases and deaths from the World Health Organization (WHO) COVID-19 dashboard and calculated the case fatality rate of each ethnic group. In addition, we obtained the allele distribution of the polymorphisms of the IFITM3, ACE2, TMPRSS2, IL6, LZTFL1, and ABO genes from the 1000 Genomes Project and performed Log-linear regression analysis using SAS version 9.4. We found different COVID-19 case fatality rates in each ethnic group. Notably, we identified a strong correlation between the case fatality rate of COVID-19 and the allele frequency of the rs6598045 single nucleotide polymorphism (SNP) of the IFITM3 gene. To the best of our knowledge, this report is the first to describe a strong correlation between the COVID-19 case fatality rate and the rs6598045 SNP of the IFITM3 gene at the population-level.	

2021	Markers Associated with COVID-19 Susceptibility, Resistance, and Severity.	In December 2019, the latest member of the coronavirus family, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China, leading to the outbreak of an unusual viral pneumonia known as coronavirus disease 2019 (COVID-19). COVID-19 was then declared as a pandemic in March 2020 by the World Health Organization (WHO). The initial mortality rate of COVID-19 declared by WHO was 2%; however, this rate has increased to 3.4% as of 3 March 2020. People of all ages can be infected with SARS-CoV-2, but those aged 60 or above and those with underlying medical conditions are more prone to develop severe symptoms that may lead to death. Patients with severe infection usually experience a hyper pro-inflammatory immune reaction (i.e., cytokine storm) causing acute respiratory distress syndrome (ARDS), which has been shown to be the leading cause of death in COVID-19 patients. However, the factors associated with COVID-19 susceptibility, resistance and severity remain poorly understood. In this review, we thoroughly explore the correlation between various host, viral and environmental markers, and SARS-CoV-2 in terms of susceptibility and severity.	
2021	Characteristic of Parkinson's disease with severe COVID-19: a study of 10 cases from Wuhan.	Information about Parkinson's disease (PD) patients with severe COVID-19 is scarce. We aimed to analyze the clinical characteristics, outcomes, and risk factors affecting the prognosis of PD patients with severe COVID-19 infection. Clinical data of severe COVID-19 patients admitted at the Union Hospital, Wuhan between 28th January and 29th February 2020 were collected and analyzed. 10 patients (1.96%) had a medical history of PD with a mean (SD) age of 72.10 (± 11.46) years. The clinical characteristics and outcomes of severe COVID-19 with and without PD patients were then compared. There was no significant difference in overall mortality between the PD and non-PD patients with severe COVID-19 ($p > 0.05$). In PD patients with severe COVID-19, the proportion of patients with critical type, disturbance of consciousness, incidence of complications, white blood cells count and neutrophils counts on admission seem higher in the non-survivors. PD patients with older age, longer PD duration, and late stage PD may be highly susceptible to critical COVID-19 infection and bad outcome. The PD patients with consciousness disorders and complications that progressed rapidly are at increased risk of death.	
2021	ACE inhibition and cardiometabolic risk factors, lung ACE2 and TMPRSS2 gene expression, and plasma ACE2 levels: a Mendelian randomization study.	Angiotensin-converting enzyme 2 (ACE2) and serine protease TMPRSS2 have been implicated in cell entry for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19). The expression of ACE2 and TMPRSS2 in the lung epithelium might have implications for the risk of SARS-CoV-2 infection and severity of COVID-19. We use human genetic variants that proxy angiotensin-converting enzyme (ACE) inhibitor drug effects and cardiovascular risk factors to investigate whether these exposures affect lung ACE2 and TMPRSS2 gene expression and circulating ACE2 levels. We observed no consistent evidence of an association of genetically predicted serum ACE levels with any of our outcomes. There was weak evidence for an association of genetically predicted serum ACE levels with ACE2 gene expression in the Lung eQTL Consortium ($p = 0.014$), but this finding did not replicate. There was evidence of a positive association of genetic liability to type 2 diabetes mellitus with lung ACE2 gene expression in the Gene-Tissue Expression (GTEx) study ($p = 4 \times 10^{-4}$) and with circulating plasma ACE2 levels in the INTERVAL study ($p = 0.03$), but not with lung ACE2 expression in the Lung eQTL Consortium study ($p = 0.68$). There were no associations of genetically proxied	

		liability to the other cardiometabolic traits with any outcome. This study does not provide consistent evidence to support an effect of serum ACE levels (as a proxy for ACE inhibitors) or cardiometabolic risk factors on lung ACE2 and TMPRSS2 expression or plasma ACE2 levels.	
2021	Current understanding of the influence of environmental factors on SARS-CoV-2 transmission, persistence, and infectivity.	Coronavirus disease 2019 (COVID-19) has emerged as a significant public health emergency in recent times. It is a respiratory illness caused by the novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was initially reported in late December 2019. In a span of 6 months, this pandemic spread across the globe leading to high morbidity and mortality rates. Soon after the identification of the causative virus, questions concerning the impact of environmental factors on the dissemination and transmission of the virus, its persistence in environmental matrices, and infectivity potential begin to emerge. As the environmental factors could have far-reaching consequences on infection dissemination and severity, it is essential to understand the linkage between these factors and the COVID-19 outbreak. In order to improve our current understanding over this topic, the present article summarizes topical and substantial observations made regarding the influences of abiotic environmental factors such as climate, temperature, humidity, wind speed, air, and water quality, solid surfaces/interfaces, frozen food, and biotic factors like age, sex, gender, blood type, population density, behavioural characteristics, etc. on the transmission, persistence, and infectivity of this newly recognized SARS-CoV-2 virus. Further, the potential pathways of virus transmission that could pose risk to population health have been discussed, and the critical areas have been identified which merits urgent research for the assessment and management of the COVID-19 outbreak. Where possible, the knowledge gaps requiring further investigation have been highlighted.	

2021	Diabetic patients with COVID-19 need more attention and better glycemic control.	Coronavirus disease 2019 (COVID-19) is a pandemic disease spreading all over the world and has aroused global concerns. The increasing mortality has revealed its severity. It is important to distinguish severe patients and provide appropriate treatment and care to prevent damages. Diabetes is reported to be a common comorbidity in COVID-19 patients and associated with higher mortality. We attempted to clarify the relationship between diabetes and COVID-19 patients' severity. To determine the role of type 2 diabetes in COVID-19 patients. To study the relationship between diabetes and COVID-19, we retrospectively collected 61 patients' data from a tertiary medical center in Wuhan. All the patients were diagnosed with laboratory-confirmed COVID-19 and admitted to the center from February 13 to March 1, 2020. Patients' age, sex, laboratory tests, chest computed tomography findings, capillary blood glucose (BG), and treatments were collected and analyzed. Fisher exact test was used for categorical data. Univariate and multivariate logistic regressions were used to explore the relationship between clinical characteristics and patients' severity. In the 61 patients, the comorbidity of type 2 diabetes, hypertension, and heart diseases were 24.6% (15 out of 61), 37.7% (23 out of 61), and 11.5% (7 out of 61), respectively. The diabetic group was related to more invasive treatments (P = 0.02) and severe status (P = 0.003). In univariate logistic regression, histories of diabetes (OR = 7.13, P = 0.003), hypertension (OR = 3.41, P = 0.039), and hepatic dysfunction (OR = 7.69, P = 0.002) were predictors of patients' severity while heart disease (OR = 4.21, P = 0.083) and large lung involvement (OR = 2.70, P = 0.093) also slightly exacerbated patients' conditions. In the multivariate analysis, diabetes (OR = 6.29, P = 0.016) and hepatic dysfunction (OR = 5.88, P = 0.018) were risk factors for severe patients. Diabetic patients showed elevated BG in 61.7% of preprandial tests and 33.3% of postprandial tests, revealing the limited control of glycemia in COVID-19 patients. A history of type 2 diabetes is correlated with invasive treatments and severe status. Suboptimal glycemic control and hepatic dysfunction have negative effects on severity status and may lead to the exacerbation of COVID-19 patients.	

2020	Differences in the Clinical and Hematological Characteristics of COVID-19 Patients with and without Type 2 Diabetes.	To examine whether comorbidity with type 2 diabetes (T2D) affects the clinical and hematological parameters of coronavirus disease 2019 (COVID-19) patients. We retrospectively investigated the clinical, imaging, and laboratory characteristics of patients with confirmed COVID-19 who were hospitalized from January 30, 2020 to March 17, 2020, at the Renmin Hospital of Wuhan University. A detailed clinical record was kept for each subject, including the medical history of COVID-19 and physical and laboratory examinations. A total of 164 subjects were eligible for the study, among which 40 patients were comorbid with T2D. Further analysis was conducted in two subcohorts of sex- and age-matched patients with and without T2D to identify hematological and biochemical differences. The laboratory tests, including routine blood tests, serum biochemistry, and coagulation function, were performed upon admission. The two groups showed no significant differences in baseline parameters, including age, sex, chest X-ray, or computed tomography (CT) findings, upon admission. However, patients with T2D showed an increased incidence of diarrhea. T2D patients required more recovery time from pneumonia, as shown by follow-up CT findings, which might contribute to the prolonged hospitalization. Comorbidity with T2D also increased risk of secondary bacterial infection during COVID-19. The T2D group had significantly higher white blood cell and neutrophil counts compared with the nondiabetic group, but T2D patients suffered from more severe lymphocytopenia and inflammation ($P < 0.05$). Most biochemical parameters showed no significant differences between the two groups ($P > 0.05$). However, patients with T2D seemed to have a significantly higher risk of developing hyperlactatemia, hyponatremia, and hypocalcemia. COVID-19 patients comorbid with T2D demonstrated distinguishing clinical features and hematological parameters during the infection. It is necessary to develop a different clinical severity scoring system for COVID-19 patients with T2D. This study may provide helpful clues for the assessment and management of COVID-19 in T2D patients.	
2020	A retrospective view of pediatric cases infected with SARS-CoV-2 of a middle-sized city in mainland China.	The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 had resulted in a global pandemic. A comprehensive analysis of pediatric COVID-19 cases is essential to decipher the natural features of children under the risk of this disease.In the epidemic period, all the children infected with SARS-CoV-2 in Wuxi, a city with a stable medical system during the COVID-19 outbreak in China, were enrolled for comprehensive data documenting their clinical, prognosis, follow-up, treatment and various tests results. Combing their family cluster characteristics, the epidemiological, hospitalization, and transmission features of children with SARS-CoV-2 were analyzed and discussed.A total of 7 children were enrolled, including 4 mild cases, 1 moderate case, and 2 asymptomatic cases. The common symptoms were fever and dry cough. The length of viral nucleic acid duration in nasopharynx varied and was irrelevant to the severity of the symptom, whether symptomatic or asymptomatic. Two cases showed viral nucleic acid positive recurrence after discharge from the hospital. A child with type 1 diabetes was also focused, for the elevated blood sugar during hospitalization. All these children had close contacts with their family members, some of those were confirmed COVID-19 cases.We provided a holistic and detailed portrayal of the pediatric COVID-19 cases in a typical city of timely response to the epidemic. While the family cluster exhibits the major transmission mode, attention should be paid for the potential risk since the expanded social space of children in future.	

2020	Independent and combined effects of hypertension and diabetes on clinical outcomes in patients with COVID-19: A retrospective cohort study of Huoshen Mountain Hospital and Guanggu Fangcang Shelter Hospital.	It is widely recognized that hypertension is one of the major risk factor for disease severity and mortality in patients with coronavirus disease 2019 (COVID-19). However, type 2 diabetes mellitus (T2DM) and hypertension are frequent comorbid conditions, complicating the assessment of hypertension's individual contribution to the risk. The aims of this study were to evaluate the contributions of hypertension alone, T2DM alone, or their combination to the risk of death, acute respiratory distress syndrome (ARDS)/respiratory failure, and severe COVID-19 infection. Additionally, we assessed risks associated with elevated blood pressure and fasting blood glucose on the same three clinical outcomes. Multivariate logistic models were used for these analyses. Among the 3400 patients, 3327(97.9%) survived and 73(2.1%) died. Compared to patients having neither hypertension nor T2DM (n = 1392), the risk of mortality was significantly higher in patients with T2DM alone (n = 226, OR 5.26 [95% CI: 2.39-11.58]) or with T2DM in combination with hypertension (n = 507, OR 3.02, [95% CI: 1.48-6.15]). Similarly, T2DM was a risk factor for development of ARDS/respiratory failure and severe infection. Hypertension alone (n = 1275) only conferred additional risk for the development of severe infection (OR 1.22 [95% CI: 1.00-1.51]). In conclusion, neither hypertension nor elevated blood pressure was independent risk factors for death or ARDS/respiratory failure but hypertension marginally increased the risk of severe COVID-19 infection. The risk associated with hypertension is accentuated through its confounding effect on T2DM.	
2020	Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity.	Immunoglobulin G (IgG) antibodies are crucial for protection against invading pathogens. A highly conserved N-linked glycan within the IgG-Fc tail, which is essential for IgG function, shows variable composition in humans. Afucosylated IgG variants are already used in anticancer therapeutic antibodies for their increased activity through Fc receptors (FcγRIIIa). Here, we report that afucosylated IgG (approximately 6% of total IgG in humans) are specifically formed against enveloped viruses but generally not against other antigens. This mediates stronger FcγRIIIa responses but also amplifies brewing cytokine storms and immune-mediated pathologies. Critically ill COVID-19 patients, but not those with mild symptoms, had high concentrations of afucosylated IgG antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), amplifying proinflammatory cytokine release and acute phase responses. Thus, antibody glycosylation plays a critical role in immune responses to enveloped viruses, including COVID-19.	

2020	Efficacy of Traditional Chinese Medicine, Maxingshigan-Weijing in the management of COVID-19 patients with severe acute respiratory syndrome: A structured summary of a study protocol for a randomized controlled trial.	We aimed to test our expectation that additional administration of Traditional Chinese medicine (TCM), maxingshigan-weijing decoction, is more effective in the management of COVID-19 patients compared to those treated with routine supportive care alone. This is a multicenter, open-label 2-arm (1:1 ratio) randomized controlled trial. Patients will be recruited from 3 hospitals in Wenzhou China: the First Affiliated Hospital of Wenzhou Medical University, the Second Affiliated Hospital of Wenzhou Medical University and Wenzhou Center Hospital. The inclusion and exclusion criteria are as follows: Inclusion criteria 1. Participants are 18-85 years of age, either male or female. 2. Diagnosed as positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 3. Symptomatic. Mild (mild clinical symptoms without signs of pneumonia in chest X-ray) and Moderate (fever or respiratory symptom with signs of pneumonia in chest X-ray) . 1. Signed the informed consent before treatment. 2. Agreed not to enroll in any other clinical trials. 3. Inpatients Exclusion criteria 1. < 18 or > 85 years old. 2. Pregnancy and lactation. 3. Serious heart, liver, kidney and hematopoietic system diseases, abnormal liver or kidney function. 4. Suffering from other known virus pneumonia. 5. Allergic to Chinese herbal medicine or suffering from allergies. 6. Critical patients (respiratory failure treated by mechanical ventilation or shock or multiple organ failure). Patients in the control group will receive routine supportive clinically care including the therapies of anti-viral, anti-bacterial and ameliorating the related symptoms, while patients in TCM group will be asked to take maxingshigan-weijing decoction (composed of 14 Chinese herbal medicines), orally 200 mL 2 times daily, for 14 consecutive days in addition to routine supportive care as mentioned above. Maxingshigan-weijing decoction consists of 10 g of Herba Ephedra (Mahuang), 10 g of Amygdalus Communis Vas (Xingren), 45 g of Gypsum Fibrosum (Shigao), 30 g of Rhizoma phragmitis (Lugen), 20 g of Peach kernel (Taoren), 20 g of Winter Melon kernel (Dongguaren), 30 g of Trichosanthes Kirilowii Maxim (Gualou), 12 g of Pericarpium Citri Reticulatae (Chenpi), 12 g of Rhizoma Pinelliae (Jiangbanxia), 12 g of caulis bambusae in taeniis (Zhuru), 30 g of semen lepidii (Tingliz), 15 g of semen lepidii (Shichangpu), 10 g of curcuma zedoary (ezhu) and 5 g of Radix Glycyrrhizae (Gancao). The primary outcome will be the number of days until the clinical symptom of fever improves in the first 14 days of treatment following randomisation. Fever will be defined as an improvement when the temperature is less than 37°C. Secondary outcomes will be TCM Syndrome Scores, the time it takes until individuals have negative test results for SARS-CoV-2 nucleic acid, the proportion of cases with chest X-ray improvements and the rate of symptom (fever, cough, malaise, shortness of breath) recovery. TCM Syndrome Scoring System is a checklist covering 4 main, 7 secondary and 13 accompanying items. The 4 main items consisting of fever, cough, malaise and shortness of breath, use a four-point scale (0, 2, 4 and 6) depending on the severity; the 7 secondary items including dysphoria, diarrhea, pharyngalgia, expectoration, muscular soreness, nasal obstruction and rhinorrhoea use 0-3-point scale; the 13 accompanying items contain chest pain, headache, aversion to cold, dizziness, nausea and vomiting, anorexia, abdominal distension, dry mouth, anxiety, spontaneous sweating, insomnia, wheezing and blood tinged sputum, and each item is rated on 0-1 scale (0 stands for asymptomatic, 1 stands for symptomatic). The total scores sum up to a range from 0 to 58, with higher scores indicating more severe levels of disease. Minimization method will be used, balancing the two arms for	

		pneumonia severity. Patients are randomized (1:1 ratio) to each group. Clinical researchers will get a random sequence number which is automatically generated by a random number generator (IBM Corp., Armonk, NY, USA), and sequentially number them in an opaque envelope. Researchers will open random allocation envelopes and assign participants accordingly. Eligible patients will be randomly divided into a routine supportive care group and a routine supportive care plus oral administration of traditional Chinese medicine group, with 70 patients in each group. This is an open-label study. The statistical analysis will be carried out by the Professor of Statistics at Wenzhou Medical University, who is blinded to patient allocation. The previous study reported the efficacy of TCM for COVID-19 and H1N1 influenza patients, the median survival time in the TCM group is estimated as 3 days; this time will be 1.5 times longer in the control group. Accordingly, Kaplan-Meier method and log-rank test will be used. And assuming a statistical power of 70% (one-sided type-1 error of $\alpha = 5\%$, $\beta = 30\%$) and a rate of withdrawal and loss to follow-up of 10%, we plan to include 140 participants in both groups (TCM group = 70, control group = 70). The trial protocol is Version 2.0, October 14, 2020. Recruitment began March, 2020, and is anticipated to be completed by December 31, 2020. Chinese Clinical Trial Registry, ChiCTR2000030759 . Registered on 13 March 2020. The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.	
2020	Non-insulin anti-diabetic agents in patients with type 2 diabetes and COVID-19: A Critical Appraisal of Literature.	Several observational studies have recently reported the outcomes of non-insulin anti-diabetic agents (ADA) in patients with T2DM and coronavirus disease 2019 (COVID-19). We sought to review the literature to appraise the clinicians on these outcomes. A literature search using the specific keywords was carried out in the database of PubMed, MedRxiv and Google Scholar up till December 11, 2020 applying Boolean method. Full text of all the relevant articles that reported the outcomes of ADA in patients with T2DM and COVID-19 were retrieved. Subsequently, an appraisal of literature report was narratively presented. Available studies that reported the outcomes of ADA are either case series or retrospective cohorts or prospective observational studies, in absence of the randomized controlled trials (RCTs). Results from these observational studies suggest that amongst all the non-insulin ADA, metformin users prior to the hospitalization had improved outcomes compared to the non-users. Data for dipeptidyl-peptidase-4 inhibitors (DPP-4i) are encouraging although inconsistent. No documentation of any harm or benefit has been observed for sulfonylureas (SUs), sodium glucose co-transporter-2 inhibitors (SGLT-2i) and glucagon-like peptide receptor agonists (GLP-1RAs). No data is yet available for pioglitazone. Metformin and DPP-4i should be	

		continued in patients with T2DM until hospitalization or unless contraindicated. No evidence of harm suggests that SUs, SGLT-2i or GLP-1RAs may not be stopped unless very sick, hospitalized or contraindicated. The results from RCTs are needed to claim any meaningful benefit with either metformin or DPP-4i in patients with T2DM and COVID-19.	
2020	Dynamics of cytokines and lymphocyte subsets associated with the poor prognosis of severe COVID-19.	We aimed to study the dynamics of cytokines and lymphocyte subsets and their correlation with the prognosis of patients with severe COVID-19. The lymphocyte subsets and cytokines of 31 patients with severe COVID-19 (7 deaths and 24 survivals) were longitudinally analyzed. The mean age of enrolled patients was 64 years, 24 (77.4%) patients were men, and 23 (74.2%) patients had comorbidities. Compared with survival group, the death group showed significant and sustained increases in the levels of IL-6, IL-8, and IL-10 from baseline to 28 days after admission (all $p<0.05$). No significant differences were observed in the levels of TNF-α, IL-1b, IL-2, IL-4, IL-5, IL-12P70, IL-17, IFN-α, and IFN-γ between the death group and survival group during the follow-up (all $p>0.05$). The absolute counts of CD3+ T cells, CD4+ T cells, CD8+ T cells, and CD45+ T cells were lower in both survival group and death group patients from hospital admission to 3 days after admission, and gradually recovered in 4 to 35 days in the survival group, but continually stayed at low levels in the death group during the follow-up. The kinetic changes of cytokines and lymphocyte subsets are related with the prognosis of patients with severe COVID-19.	

2020	[Association of D-dimer, inflammatory markers, cytokines abnormality, and disease severity in COVID-19 severe/critical patients in Wuhan].	Objective: To analyze the association of D-dimer levels, inflammatory indicators, cytokine abnormality, and disease severity in COVID-19 severe/critical type patients. Methods: The medical records of 41 patients were collected from a single center in Wuhan from February 8, 2020 to March 25, 2020. The patients were divided into severe type group (28 patients) and critical type group (13 patients) . The levels of D-dimer, WBC, ANC, PCT, hsCRP, IL-2R, IL-6, IL-8, and TNF-α were compared among patients with different clinical types of COVID-19 infection. Moreover, the changes in the cytokines were analyzed in patients with different D-dimer levels. And, the levels of D-dimer, IL-2R, IL-6, IL-8, and TNF-α before and after anticoagulant therapy were assessed. Statistical analyses were performed using Student t test, Mann-Whitney U test, and Chi-square test. Results: Among the 41 patients, 23 were men (56.1%) and 18 were women (43.9%) ; the median patient age was 57 y. The age of the critical type patients [(61.1±10.4) y] was higher than that of severe type patients [(52.8±11.7) y]; the difference was significant (t =-2.264, P =0.032) . The proportion of critical type patients with chronic diseases, especially hypertension, cardiovascular disease, and cerebrovascular disease, was higher as compared to that in those with severe type patients; the differences were significant (all P <0.05) . The prevalence of dyspnea, sweats, and fatigue symptoms in the critical type patients was higher than that in those with severe type disease; the differences were significant (χ (2)=14.898, 6.972, 7.823; P <0.001, 0.008, 0.005) . The levels of D-dimer, WBC, ANC, PCT, hsCRP, and IL-8 in critical type patients were higher than those in severe type patients; the differences were significant (all P <0.05) . The levels of IL-2R, IL-8, and TNF-α in patients with abnormal D-dimer were higher as compared to those in patients with normal D-dimer levels; the differences were significant (all P <0.05) . Eight patients were treated with prophylactic anticoagulation; the levels of D-dimer, IL-2R, IL-6 and IL-8 after anticoagulant therapy were lower than those before treatment. Conclusions: COVID-19 critical type patients have more serious coagulation-immune dysfunction and dynamic monitoring of D-dimer and cytokines levels helps in identifying critical type patients as early as possible; anticoagulant therapy may improve the patient's condition by correcting coagulation-immune dysfunction.	

2020	CT features of coronavirus disease 2019 (COVID-19) with an emphasis on the vascular enlargement pattern.	The vascular enlargement (VE) pattern differs from previously described imaging patterns for pneumonia. This study aimed to investigate the incidence, computed tomography (CT) characteristics, and diagnostic value of the VE pattern in coronavirus disease 2019 (COVID-19). The CT data of 106 patients with COVID-19 from January 19 to February 29, 2020, and 52 patients with influenza virus pneumonia (IVP) from January 2018 to February 2020 were retrospectively collected. The incidences of the VE pattern between the two groups were compared. The CT manifestations of COVID-19 were analyzed with a particular focus on the VE pattern's specific CT signs, dynamic changes, and relationships with lesion size and disease severity. Peripheral and multilobar ground-glass opacities (GGOs) or mixed GGOs with various sizes and morphologies were typical features of COVID-19 on initial CT. The VE pattern was more common in COVID-19 (88/106, 83.02 %) than in IVP (10/52, 19.23 %) on initial CT ($P < 0.001$). Three special VE-pattern-specific CT signs, including central vascular sign, ginkgo leaf sign, and comb sign, were identified. Four types of dynamic changes in the VE pattern were observed on initial and follow-up CT, which were closely associated with the evolution of lesions and the time interval from the onset of symptoms to initial CT scan. The VE pattern in COVID-19 was more commonly seen in larger lesions and patients with severe-critical type (all $P < 0.001$). The VE pattern is a valuable CT sign for differentiating COVID-19 from IVP, which correlates with more extensive or serious disease. A good understanding of the CT characteristics of the VE pattern may contribute to the early and accurate diagnosis of COVID-19 and prediction of the evolution of lesions.	

2020	Nebulised surfactant for the treatment of severe COVID-19 in adults (COV-Surf): A structured summary of a study protocol for a randomized controlled trial.	SARS-Cov-2 virus preferentially binds to the Angiotensin Converting Enzyme 2 (ACE2) on alveolar epithelial type II cells, initiating an inflammatory response and tissue damage which may impair surfactant synthesis contributing to alveolar collapse, worsening hypoxia and leading to respiratory failure. The objective of this study is to evaluate the feasibility, safety and efficacy of nebulised surfactant in COVID-19 adult patients requiring mechanical ventilation for respiratory failure. This study is a dose-escalating randomized open-label clinical trial of 20 COVID-19 patients. This study is conducted in two centres: University Hospital Southampton and University College London Hospitals. Eligible participants are aged ≥18, hospitalised with COVID-19 (confirmed by PCR), who require endotracheal intubation and are enrolled within 24 hours of mechanical ventilation. For patients unable to consent, assent is obtained from a personal legal representative (PerLR) or professional legal representative (ProfLR) prior to enrolment. The following are exclusion criteria: imminent expected death within 24 hours; specific contraindications to surfactant administration (e.g. known allergy, pneumothorax, pulmonary hemorrhage); known or suspected pregnancy; stage 4 chronic kidney disease or requiring dialysis (i.e., eGFR < 30); liver failure (Child-Pugh Class C); anticipated transfer to another hospital, which is not a study site, within 72 hours; current or recent (within 1 month) participation in another study that, in the opinion of the investigator, would prevent enrollment for safety reasons; and declined consent or assent. Intervention: The study is based on an investigational drug/device combination product. The surfactant product is Bovactant (Alveofact®), a natural animal derived (bovine) lung surfactant formulated as a lyophilized powder in 108 mg vials and reconstituted to 45 mg/mL in buffer supplied in a prefilled syringe. It is isolated by lung lavage and, by weight, is a mixture of: phospholipid (75% phosphatidylcholine, 13% phosphatidylglycerol, 3% phosphatidylethanolamine, 1% phosphatidylinositol and 1% sphingomyelin), 5% cholesterol, 1% lipid-soluble surfactant-associated proteins (SP-B and SP-C), very low levels of free fatty acid, lyso-phosphatidylcholine, water and 0.3% calcium. The Drug Delivery Device is the AeroFact-COVID™ nebulizer, an investigational device based on the Aerogen® Solo vibrating mesh nebulizer. The timing and escalation dosing plans for the surfactant are as follows. Cohort 1: Three patients will receive 10 vials (1080 mg) each of surfactant at dosing times of 0 hours, 8 hours and 24 hours. 2 controls with no placebo intervention. Cohort 2: Three patients will receive 10 vials (1080 mg) of surfactant at dosing times of 0 hours and 8 hours, and 30 vials (3240 mg) at a dosing time of 24 hours. 2 controls with no placebo intervention. Cohort 3: Three patients will receive 10 vials (1080 mg) of surfactant at a dosing time of 0 hours, and 30 vials (3240 mg) at dosing times of 8 hours and 24 hours. 2 controls with no placebo intervention. Cohort 4: Three patients will receive 30 (3240 mg) vials each of surfactant at dosing times of 0 hours, 8 hours and 24 hours. 2 controls. 2 controls with no placebo intervention. The trial steering committee, advised by the data monitoring committee, will review trial progression and dose escalation/maintenance/reduction after each cohort is completed (48-hour primary outcome timepoint reached) based on available feasibility, adverse event, safety and efficacy data. The trial will not be discontinued on the basis of lack of efficacy. The trial may be stopped early on the basis of safety or feasibility concerns. Comparator: No placebo intervention. All participants will receive usual standard of care in accordance with the local policies for mechanically	

		ventilated patients and all other treatments will be left to the discretion of the attending physician. The co-primary outcome is the improvement in oxygenation (PaO 2 /FiO 2 ratio) and pulmonary ventilation (Ventilation Index (VI), where VI = [RR x (PIP - PEEP) × PaCO 2]/1000) at 48 hours after study initiation. The secondary outcomes include frequency and severity of adverse events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Serious Adverse Device Events (SADEs), change in pulmonary compliance, change in positive end-expiratory pressure (PEEP) requirement of ventilatory support at 24 and 48 hours after study initiation, clinical improvement defined by time to one improvement point on the ordinal scale described in the WHO master protocol (2020) recorded while hospitalised, days of mechanical ventilation, mechanical ventilator free days (VFD) at day 21, length of intensive care unit stay, number of days hospitalised and mortality at day 28. Exploratory end points will include quantification of SARS-CoV-2 viral load from tracheal aspirates using PCR, surfactant dynamics (synthesis and turnover) and function (surface tension reduction) from deep tracheal aspirate samples (DTAS), surfactant phospholipid concentrations in plasma and DTAS, inflammatory markers (cellular and cytokine) in plasma and DTAS, and blood oxidative stress markers. After informed assent, patients fulfilling inclusion criteria will be randomised to 3:2 for the treatment and control arms using an internet-based block randomization service (ALEA tool for clinical trials, FormsVision BV) in combination with electronic data collection. Randomisation will be done by the recruiting centre with a unique subject identifier specific to that centre. This is an open-labelled unblinded study. The total sample size is 20 COVID-19 mechanically ventilated patients (12 intervention; 8 control). Current protocol version is V2 dated 5 th of June 2020. The recruitment is currently ongoing and started on the 14 th of October 2020. The anticipated study completion date is November 2021. ClinicalTrials.gov: NCT04362059 (Registered 24 April 2020), EUDAMED number: CIV-GB-20-06-033328, EudraCT number: 2020-001886-35 (Registered 11 May 2020) FULL PROTOCOL: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol. The study protocol has been reported in accordance with the Standard Protocol Items: Recommendations for Clinical Interventional Trials (SPIRIT) guidelines (Additional file 2).	
2020	Interferon linked to COVID-19 severity.	NA	

2020	Hyperglycemia associated with lymphopenia and disease severity of COVID-19 in type 2 diabetes mellitus.	Coronavirus disease 2019 (COVID-19) has been declared a global pandemic. COVID-19 is more severe in people with diabetes. The identification of risk factors for predicting disease severity in COVID-19 patients with type 2 diabetes mellitus (T2DM) is urgently needed. Two hundred and thirty-six patients with COVID-19 were enrolled in our study. The patients were divided into 2 groups: COVID-19 patients with or without T2DM. The patients were further divided into four subgroups according to the severity of COVID-19 as follows: Subgroup A included moderate COVID-19 patients without diabetes, subgroup B included severe COVID-19 patients without diabetes, subgroup C included moderate COVID-19 patients with diabetes, and subgroup D included severe COVID-19 patients with diabetes. The clinical features and radiological assessments were collected and analyzed. We tracked the dynamic changes in laboratory parameters and clinical outcomes during the hospitalization period. Multivariate analysis was performed using logistic regression to analyze the risk factors that predict the severity of COVID-19 with T2DM. Firstly, compared with the nondiabetic group, the COVID-19 with T2DM group had a higher erythrocyte sedimentation rate (ESR) and levels of C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and procalcitonin (PCT) but lower lymphocyte counts and T lymphocyte subsets, including CD3+ T cells, CD8+ T cells, CD4+ T cells, CD16 + CD56 cells, and CD19+ cells. Secondly, compared with group A, group C had higher levels of Fasting blood glucose (FBG), IL-6, TNF-α, and neutrophils but lower lymphocyte, CD3+ T cell, CD8+ T cell, and CD4+ T cell counts. Similarly, group D had higher FBG, IL-6 and TNF-α levels and lower lymphocyte, CD3+ T cell, CD8+ T cell, and CD4+ T cell counts than group B. Thirdly, binary logistic regression analysis showed that HbA1c, IL-6, and lymphocyte count were risk factors for the severity of COVID-19 with T2DM. Importantly, COVID-19 patients with T2DM were more likely to worsen from moderate to severe COVID-19 than nondiabetic patients. Of note, lymphopenia and inflammatory responses remained more severe throughout hospitalization for COVID-19 patients with T2DM. Our data suggested that COVID-19 patients with T2DM are more likely to develop severe COVID-19 than those without T2DM and that hyperglycemia associated with the lymphopenia and inflammatory responses in COVID-19 patients with T2DM.	

2020	Clinical Characteristics and Outcomes of Patients With Diabetes Admitted for COVID-19 Treatment in Dubai: Single-Centre Cross-Sectional Study.	Recent studies have shown that diabetes is a major risk factor that contributes to the severity of COVID-19 and resulting mortality. Poor glycemic control is also associated with poor patient outcomes (eg, hospitalization and death). This study aimed to describe the clinical characteristics and outcomes of patients with diabetes who were admitted to our hospital for COVID-19 treatment. This cross-sectional, observational study comprised patients with diabetes admitted with COVID-19 to Mediclinic Parkview Hospital in Dubai, United Arab Emirates, from March 30 to June 7, 2020. We studied the differences among characteristics, length of hospital stay, diabetes status, comorbidities, treatments, and outcomes among these patients. Of the cohort patients, 25.1% (103/410) had coexistent diabetes or prediabetes. These patients represented 17 different ethnicities, with 59.2% (61/103) from Asian countries and 35% (36/103) from Arab countries. Mean patient age was 54 (SD 12.5) years, and 66.9% (69/103) of patients were male. Moreover, 85.4% (88/103) of patients were known to have diabetes prior to admission, and 14.6% (15/103) were newly diagnosed with either diabetes or prediabetes at admission. Most cohort patients had type 2 diabetes or prediabetes, and only 2.9% (3/103) of all patients had type 1 diabetes. Furthermore, 44.6% (46/103) of patients demonstrated evidence suggesting good glycemic control during the 4-12 weeks prior to admission, as defined arbitrarily by admission hemoglobin A1 c level <7.5%, and 73.8% (76/103) of patients had other comorbidities, including hypertension, ischemic heart disease, and dyslipidemia. Laboratory data (mean and SD values) at admission for patients who needed ward-based care versus those who needed intensive care were as follows: fibrinogen, 462.8 (SD 125.1) mg/dL vs 660.0 (SD 187.6) mg/dL; D-dimer, 0.7 (SD 0.5) µg/mL vs 2.3 (SD 3.5) µg/mL; ferritin, 358.0 (SD 442.0) mg/dL vs 1762.4 (SD 2586.4) mg/dL; and C-reactive protein, 33.9 (SD 38.6) mg/L vs 137.0 (SD 111.7) mg/L. Laboratory data were all significantly higher for patients in the intensive care unit subcohort (P<.05). The average length of hospital stay was 14.55 days for all patients, with 28.2% (29/103) of patients requiring intensive care. In all, 4.9% (5/103) died during hospitalization-all of whom were in the intensive care unit. Majority of patients with diabetes or prediabetes and COVID-19 had other notable comorbidities. Only 4 patients tested negative for COVID-19 RT-PCR but showed pathognomonic changes of COVID-19 radiologically. Laboratory analyses revealed distinct abnormal patterns of biomarkers that were associated with a poor prognosis: fibrinogen, D-dimer, ferritin, and C-reactive protein levels were all significantly higher at admission in patients who subsequently needed intensive care than in those who needed ward-based care. More studies with larger sample sizes are needed to compare data of COVID-19 patients admitted with and without diabetes within the UAE region.	

2020	Untuned antiviral immunity in COVID-19 revealed by temporal type I/III interferon patterns and flu comparison.	A central paradigm of immunity is that interferon (IFN)-mediated antiviral responses precede pro-inflammatory ones, optimizing host protection and minimizing collateral damage 1,2 . Here, we report that for coronavirus disease 2019 (COVID-19) this paradigm does not apply. By investigating temporal IFN and inflammatory cytokine patterns in 32 moderate-to-severe patients with COVID-19 hospitalized for pneumonia and longitudinally followed for the development of respiratory failure and death, we reveal that IFN-λ and type I IFN production were both diminished and delayed, induced only in a fraction of patients as they became critically ill. On the contrary, pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-6 and IL-8 were produced before IFNs in all patients and persisted for a prolonged time. This condition was reflected in blood transcriptomes wherein prominent IFN signatures were only seen in critically ill patients who also exhibited augmented inflammation. By comparison, in 16 patients with influenza (flu) hospitalized for pneumonia with similar clinicopathological characteristics to those of COVID-19 and 24 nonhospitalized patients with flu with milder symptoms, IFN-λ and type I IFN were robustly induced earlier, at higher levels and independently of disease severity, whereas pro-inflammatory cytokines were only acutely produced. Notably, higher IFN-λ concentrations in patients with COVID-19 correlated with lower viral load in bronchial aspirates and faster viral clearance and a higher IFN-λ to type I IFN ratio correlated with improved outcome for critically ill patients. Moreover, altered cytokine patterns in patients with COVID-19 correlated with longer hospitalization and higher incidence of critical disease and mortality compared to flu. These data point to an untuned antiviral response in COVID-19, contributing to persistent viral presence, hyperinflammation and respiratory failure.	
2020	Viral Cultures for Coronavirus Disease 2019 Infectivity Assessment: A Systematic Review.	We aimed to review the evidence from studies relating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) culture with the results of reverse-transcription polymerase chain reaction (RT-PCR) and other variables that may influence the interpretation of the test, such as time from symptom onset. We searched LitCovid, medRxiv, Google Scholar, and the World Health Organization coronavirus disease 2019 (COVID-19) database for COVID-19 up to 10 September 2020. We included studies attempting to culture or observe SARS-CoV-2 in specimens with RT-PCR positivity. Studies were dual-extracted and the data summarized narratively by specimen type. Where necessary, we contacted corresponding authors of included papers for additional information. We assessed quality using a modified Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS 2) risk-of-bias tool. We included 29 studies reporting attempts at culturing, or observing tissue infection by, SARS-CoV-2 in sputum, nasopharyngeal or oropharyngeal, urine, stool, blood, and environmental specimens. The quality of the studies was moderate with lack of standardized reporting. The data suggest a relationship between the time from onset of symptom to the timing of the specimen test, cycle threshold (Ct), and symptom severity. Twelve studies reported that Ct values were significantly lower and log copies higher in specimens producing live virus culture. Two studies reported that the odds of live virus culture were reduced by approximately 33% for every 1-unit increase in Ct. Six of 8 studies reported detectable RNA for >14 days, but infectious potential declined after day 8 even among cases with ongoing high viral loads. Four studies reported viral culture from stool specimens. Complete live viruses are necessary for transmission, not the fragments identified by	

		PCR. Prospective routine testing of reference and culture specimens and their relationship to symptoms, signs, and patient co-factors should be used to define the reliability of PCR for assessing infectious potential. Those with high Ct are unlikely to have infectious potential.	
2020	COVID-19 and hematology findings based on the current evidences: A puzzle with many missing pieces.	In December 2019, a new type of coronavirus was detected for the first time in Wuhan, Hubei Province, China. According to the reported data, the emerging coronavirus has spread worldwide, infecting more than fifty-seven million individuals, leading to more than one million deaths. The current study aimed to review and discuss the hematological findings of COVID-19. Laboratory changes and hematologic abnormalities have been reported repeatedly in COVID-19 patients. WBC count and peripheral blood lymphocytes are normal or slightly reduced while these indicators may change with the progression of the disease. In addition, several studies demonstrated that decreased hemoglobin levels in COVID-19 patients were associated with the severity of the disease. Moreover, thrombocytopenia, which is reported in 5%-40% of patients, is known to be associated with poor prognosis of the disease. COVID-19 can present with various hematologic manifestations. In this regard, accurate evaluation of laboratory indicators at the beginning and during COVID-19 can help physicians to adjust appropriate treatment and provide special and prompt care for those in need.	

2020	The influence of ABO blood groups on COVID-19 susceptibility and severity: A molecular hypothesis based on carbohydrate-carbohydrate interactions.	The world is experiencing one of the most difficult moments in history with the COVID-19 pandemic, a disease caused by SARS-CoV-2, a new type of coronavirus. Virus infectivity is mediated by the binding of Spike transmembrane glycoprotein to specific protein receptors present on cell host surface. Spike is a homotrimer that emerges from the virion, each monomer containing two subunits named S1 and S2, which are related to cell recognition and membrane fusion, respectively. S1 is subdivided in domains S1A (or NTD) and S1B (or RBD), with experimental and in silico studies suggesting that the former binds to sialic acid-containing glycoproteins, such as CD147, whereas the latter binds to ACE2 receptor. Recent findings indicate that the ABO blood system modulates susceptibility and progression of infection, with type-A individuals being more susceptible to infection and/or manifestation of a severe condition. Seeking to understand the molecular mechanisms underlying this susceptibility, we carried out an extensive bibliographic survey on the subject. Based on this survey, we hypothesize that the correlation between the ABO blood system and susceptibility to SARS-CoV-2 infection can be presumably explained by the modulation of sialic acid-containing receptors distribution on host cell surface induced by ABO antigens through carbohydrate-carbohydrate interactions, which could maximize or minimize the virus Spike protein binding to the host cell. This model could explain previous sparse observations on the molecular mechanism of infection and can direct future research to better understand of COVID-19 pathophysiology.	
2020	The Urgent Need for Recommending Physical Activity for the Management of Diabetes During and Beyond COVID-19 Outbreak.	Diabetes is the second most prevalent non-communicable chronic diseases (NCDs) in patients with coronavirus disease 2019 (COVID-19) and is highly associated with increased incidence of disease severity and mortality. Individuals with diabetes and poor glycemic control have an even worse prognosis. Despite of the need/effectiveness of social distancing measures (i.e.: home confinement, quarantine and/or lockdown) during COVID-19 outbreak, preliminary findings showed an increase in negative behaviors during COVID-19 home confinement (i.e.: ~33.5% reduction in physical activity, ~28.6% (~3.10h) increase in sedentary behavior (i.e.: daily sitting, reclining and lying down time), and more unhealthy food consumption and meal pattern), which may have important clinical implications. For example, we estimated that this reduction in physical activity can increase the cases of type 2 diabetes (from ~7.2% to ~9.6%; ~11.1 million cases per year) and all-cause mortality (from ~9.4% to ~12.5%; ~1.7 million deaths per year) worldwide. Few weeks of reduction in physical activity levels result in deleterious effects on several cardiometabolic (i.e.: glycemic control, body composition, inflammatory cytokines, blood pressure, vascular function…) and functional parameters (i.e.: cardiorespiratory/muscle fitness, balance, agility…). In contrast, physical activity and exercise are important tools for preventing and treating diabetes and others NCDs. Home-based exercise programs are useful, safe and effective for the management of diabetes, and could be widely used during COVID-19 outbreak. In this context, there is an urgent need for recommending physical activity/exercise, during and beyond COVID-19 outbreak, for improving the management of diabetes, as well as to prevent the increase in global burden of COVID-19, diabetes and others NCDs.	

2020	Levels of Soluble CD14 and Tumor Necrosis Factor Receptors 1 and 2 May Be Predictive of Death in Severe Coronavirus Disease 2019.	People infected with severe acute respiratory syndrome coronavirus 2 display a wide range of illness, from asymptomatic infection to severe respiratory distress resulting in death. We measured serum biomarkers in uninfected individuals and in individuals with mild, moderate, or critical coronavirus disease 2019 (COVID-19) disease. Levels of monocyte activation (soluble CD14 and fatty acid-binding protein 4) and inflammation (tumor necrosis factor receptors 1 and 2 [TNFR1 and TNFR2]) were increased in COVID-19 individuals, regardless of disease severity. Among patients with critical disease, individuals who recovered from COVID-19 had lower levels of TNFR1 and TNFR2 at hospital admission compared to these levels in patients with critical disease who ultimately died.	
2020	Could KL-6 levels in COVID-19 help to predict lung disease?	Coronavirus disease COVID-19 has become a public health emergency of international concern. Together with the quest for an effective treatment, the question of the post-infectious evolution of affected patients in healing process remains uncertain. Krebs von den Lungen 6 (KL-6) is a high molecular weight mucin-like glycoprotein produced by type II pneumocytes and bronchial epithelial cells. Its production is raised during epithelial lesions and cellular regeneration. In COVID-19 infection, KL-6 serum levels could therefore be of interest for diagnosis, prognosis and therapeutic response evaluation. Our study retrospectively compared KL-6 levels between a cohort of 83 COVID-19 infected patients and two other groups: healthy subjects (n = 70) on one hand, and a heterogenous group of patients suffering from interstitial lung diseases (n = 31; composed of 16 IPF, 4 sarcoidosis, 11 others) on the other hand. Demographical, clinical and laboratory indexes were collected. Our study aims to compare KL-6 levels between a COVID-19 population and healthy subjects or patients suffering from interstitial lung diseases (ILDs). Ultimately, we ought to determine whether KL-6 could be a marker of disease severity and bad prognosis. Our results showed that serum KL-6 levels in COVID-19 patients were increased compared to healthy subjects, but to a lesser extent than in patients suffering from ILD. Increased levels of KL-6 in COVID-19 patients were associated with a more severe lung disease. Our results suggest that KL-6 could be a good biomarker to assess ILD severity in COVID-19 infection. Concerning the therapeutic response prediction, more studies are necessary.	

2020	An immune-based biomarker signature is associated with mortality in COVID-19 patients.	Immune and inflammatory responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) contribute to disease severity of coronavirus disease 2019 (COVID-19). However, the utility of specific immune-based biomarkers to predict clinical outcome remains elusive. Here, we analyzed levels of 66 soluble biomarkers in 175 Italian patients with COVID-19 ranging from mild/moderate to critical severity and assessed type I IFN-, type II IFN-, and NF-κB-dependent whole-blood transcriptional signatures. A broad inflammatory signature was observed, implicating activation of various immune and nonhematopoietic cell subsets. Discordance between IFN-α2a protein and IFNA2 transcript levels in blood suggests that type I IFNs during COVID-19 may be primarily produced by tissue-resident cells. Multivariable analysis of patients' first samples revealed 12 biomarkers (CCL2, IL-15, soluble ST2 [sST2], NGAL, sTNFRSF1A, ferritin, IL-6, S100A9, MMP-9, IL-2, sVEGFR1, IL-10) that when increased were independently associated with mortality. Multivariate analyses of longitudinal biomarker trajectories identified 8 of the aforementioned biomarkers (IL-15, IL-2, NGAL, CCL2, MMP-9, sTNFRSF1A, sST2, IL-10) and 2 additional biomarkers (lactoferrin, CXCL9) that were substantially associated with mortality when increased, while IL-1α was associated with mortality when decreased. Among these, sST2, sTNFRSF1A, IL-10, and IL-15 were consistently higher throughout the hospitalization in patients who died versus those who recovered, suggesting that these biomarkers may provide an early warning of eventual disease outcome.	
2020	Association Between ABO and Rh Blood Groups and SARS-CoV-2 Infection or Severe COVID-19 Illness : A Population-Based Cohort Study.	The ABO and rhesus (Rh) blood groups may influence risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. To determine whether ABO and Rh blood groups are associated with risk for SARS-CoV-2 infection and severe coronavirus disease 2019 (COVID-19) illness. Population-based cohort study. Ontario, Canada. All adults and children who had ABO blood group assessed between January 2007 and December 2019 and who subsequently had SARS-CoV-2 testing between 15 January and 30 June 2020. The main study outcome was SARS-CoV-2 infection, determined by viral RNA polymerase chain reaction testing. A second outcome was severe COVID-19 illness or death. Adjusted relative risks (aRRs) and absolute risk differences (ARDs) were adjusted for demographic characteristics and comorbidities. A total of 225 556 persons were included, with a mean age of 54 years. The aRR of SARS-CoV-2 infection for O blood group versus A, AB, and B blood groups together was 0.88 (95% CI, 0.84 to 0.92; ARD, -3.9 per 1000 [CI, -5.4 to -2.5]). Rhesus-negative (Rh-) blood type was protective against SARS-CoV-2 infection (aRR, 0.79 [CI, 0.73 to 0.85]; ARD, -6.8 per 1000 [CI, -8.9 to -4.7]), especially for those who were O-negative (O-) (aRR, 0.74 [CI, 0.66 to 0.83]; ARD, -8.2 per 1000 [CI, -10.8 to -5.3]). There was also a lower risk for severe COVID-19 illness or death associated with type O blood group versus all others (aRR, 0.87 [CI, 0.78 to 0.97]; ARD, -0.8 per 1000 [CI, -1.4 to -0.2]) and with Rh- versus Rh-positive (aRR, 0.82 [CI, 0.68 to 0.96]; ARD, -1.1 per 1000 [CI, -2.0 to -0.2]). Persons who rapidly died of severe COVID-19 illness may not have had SARS-CoV-2 testing. The O and Rh- blood groups may be associated with a slightly lower risk for SARS-CoV-2 infection and severe COVID-19 illness. Ontario Academic Health Sciences Centre AFP Innovation Fund and the Ontario Ministry of Health and Long-Term Care.	

2020	Peripheral blood inflammatory markers in predicting prognosis in patients with COVID-19. Some differences with influenza A.	To evaluate the ability of peripheral blood inflammatory markers in predicating the typing of COVID-19, prognosis, and some differences between COVID-19 and influenza A patients. Clinical data on 285 cases laboratory-confirmed as SARS-CoV-2 infection were obtained from a Wuhan local hospital's electronic medical records according to previously designed standardized data collection forms. Additional 446 Influenza A outpatients' hematologic data were enrolled for comparison. NLR, SII, RLR, PLR, HsCRP, and IL-6 were significant higher and LMR was lower in severe COVID-19 patients than in mild COVID-19 patients ($p < .001$). PLR and LMR were lower in the individuals with influenza A than those with COVID-19 ($p < .01$). COVID-19 patients with higher levels of NLR, SII, RLR, PLR, HsCRP, and IL-6 and lower LMR were significantly associated with the severe type. AUC of NLR (0.76) was larger while the specificity of IL-6 (86%) and sensitivity of HsCRP (89%) were higher than other inflammatory markers in predicating the typing of COVID-19. PT had obvious correlation with all the inflammatory markers except RPR. NLR showed positive correlations with AST, TP, BUN, CREA, PT, and D-dimer. Patients with high IL-6 levels have a relatively worse prognosis (HR = 2.30). Peripheral blood inflammatory markers reflected the intensity of inflammation and associated with severity of COVID-19.NLR was more useful to predict severity as well as IL-6 to predict prognosis of COVID-19. PLR and LMR were initially found to be higher in SARS-CoV-2 virus-infected group than in influenza A.	
2020	Association of glycosylated hemoglobin and outcomes in patients with COVID-19 and pre-existing type 2 diabetes: A protocol for systematic review and meta-analysis.	The impact of glycosylated hemoglobin on mortality in patients with coronavirus disease 2019 (COVID-19) and type 2 diabetes (T2D) remains uncertain. In this study, we aim to assess the effect of pre-hospital blood glucose regulation on patients with COVID-19 and pre-existing T2D. All randomized controlled trials (RCTs) and cohort studies of association of glycosylated hemoglobin and outcomes in patients with COVID-19 and T2D will be included in this review. PubMed, Embase, and CNKI will be searched for relevant literature, up to August 20, 2020 in English and Chinese language. Two reviewers will select trials independently for inclusion and assess trial quality. Two pairs of authors will independently extract information for each included trials. Primary outcomes are death and composite adverse outcomes: the number of participants who died or remained severely disabled. Revman 5.3 will be used for heterogeneity assessment, data synthesis, subgroup analysis, sensitivity analysisa and generating funnel-plots. We will provide practical results about the association of glycosylated hemoglobin and outcomes in patients with COVID-19 and T2D. The stronger evidence about the association of glycosylated hemoglobin and outcomes in patients with COVID-19 and T2D will be provided for clinical practice. PROSPERO CRD42020200574. There is no need for ethical approval, and the review will be reported in a peer-reviewed journal.	

2020	Decreased GLUT1/NHE1 RNA expression in whole blood predicts disease severity in patients with COVID-19.	We aimed to assess whether expression of whole-blood RNA of sodium proton exchanger 1 (NHE1) and glucose transporter 1 (GLUT1) is associated with COVID-19 infection and outcome in patients presenting to the emergency department with respiratory infections. Furthermore, we investigated NHE1 and GLUT1 expression in the myocardium of deceased COVID-19 patients. Whole-blood quantitative assessment of NHE1 and GLUT1 RNA was performed using quantitative PCR in patients with respiratory infection upon first contact in the emergency department and subsequently stratified by SARS-CoV-2 infection status. Assessment of NHE1 and GLUT1 RNA using PCR was also performed in left ventricular myocardium of deceased COVID-19 patients. NHE1 expression is up-regulated in whole blood of patients with COVID-19 compared with other respiratory infections at first medical contact in the emergency department (control: 0.0021 ± 0.0002, COVID-19: 0.0031 ± 0.0003, P = 0.01). The ratio of GLUT1 to NHE1 is significantly decreased in the blood of COVID-19 patients who are subsequently intubated and/or die (severe disease) compared with patients with moderate disease (moderate disease: 0.497 ± 0.083 vs. severe disease: 0.294 ± 0.0336, P = 0.036). This ratio is even further decreased in the myocardium of patients who deceased from COVID-19 in comparison with the myocardium of non-infected donors. NHE1 and GLUT1 may be critically involved in the disease progression of SARS-CoV-2 infection. We show here that SARS-CoV-2 infection critically disturbs ion channel expression in the heart. A decreased ratio of GLUT1/NHE1 could potentially serve as a biomarker for disease severity in patients with COVID-19.	
2020	Diabetes and COVID-19: a major challenge in pandemic period?	Diabetes is a lifestyle disease and it has become an epidemic worldwide in recent decades. In the ongoing COVID-19 pandemic situation, diabetes has become a serious health concern since large numbers of patients are vulnerable to die from the virus. Thus, diabetic patients affected by COVID-19 cause a major health crisis now. Reports show that large occurrence of diabetes makes it a serious comorbidity in COVID-19 patients. It is crucial to understand how COVID-19 affects diabetes patients. This paper has reviewed published literature extensively to understand the pattern, importance, care, and medication. This review summarizes the association between COVID-19 and diabetes in terms of susceptibility for pneumonia and other diseases. It also discusses the harshness of COVID-19 with diabetes populations and immunological impacts. It further adds the ACE2 receptor role in diabetes with COVID-19 patients. Finally, this paper illustrates different types of diabetes management techniques, such as blood glucose management, self-management, mental health management, and therapeutic management. It also summarizes the current knowledge about diabetic patients with COVID-19 to fight this pandemic.	

2020	Prevalence of readily detected amyloid blood clots in 'unclotted' Type 2 Diabetes Mellitus and COVID-19 plasma: a preliminary report.	Type 2 Diabetes Mellitus (T2DM) is a well-known comorbidity to COVID-19 and coagulopathies are a common accompaniment to both T2DM and COVID-19. In addition, patients with COVID-19 are known to develop micro-clots within the lungs. The rapid detection of COVID-19 uses genotypic testing for the presence of SARS-Cov-2 virus in nasopharyngeal swabs, but it can have a poor sensitivity. A rapid, host-based physiological test that indicated clotting severity and the extent of clotting pathologies in the individual who was infected or not would be highly desirable. Platelet poor plasma (PPP) was collected and frozen. On the day of analysis, PPP samples were thawed and analysed. We show here that microclots can be detected in the native plasma of twenty COVID-19, as well as ten T2DM patients, without the addition of any clotting agent, and in particular that such clots are amyloid in nature as judged by a standard fluorogenic stain. Results were compared to ten healthy age-matched individuals. In COVID-19 plasma these microclots are significantly increased when compared to the levels in T2DM. This fluorogenic test may provide a rapid and convenient test with 100% sensitivity ($P < 0.0001$) and is consistent with the recognition that the early detection and prevention of such clotting can have an important role in therapy.	
2020	An Immediate and Long-Term Complication of COVID-19 May Be Type 2 Diabetes Mellitus: The Central Role of β-Cell Dysfunction, Apoptosis and Exploration of Possible Mechanisms.	The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was declared a pandemic by the WHO on 19 March 2020. This pandemic is associated with markedly elevated blood glucose levels and a remarkable degree of insulin resistance, which suggests pancreatic islet β-cell dysfunction or apoptosis and insulin's inability to dispose of glucose into cellular tissues. Diabetes is known to be one of the top pre-existing co-morbidities associated with the severity of COVID-19 along with hypertension, cardiocerebrovascular disease, advanced age, male gender, and recently obesity. This review focuses on how COVID-19 may be responsible for the accelerated development of type 2 diabetes mellitus (T2DM) as one of its acute and suspected long-term complications. These observations implicate an active role of metabolic syndrome, systemic and tissue islet renin-angiotensin-aldosterone system, redox stress, inflammation, islet fibrosis, amyloid deposition along with β-cell dysfunction and apoptosis in those who develop T2DM. Utilizing light and electron microscopy in preclinical rodent models and human islets may help to better understand how COVID-19 accelerates islet and β-cell injury and remodeling to result in the long-term complications of T2DM.	

2020	Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review.	The objective of our systematic review is to identify prognostic factors that may be used in decision-making related to the care of patients infected with COVID-19. We conducted highly sensitive searches in PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and Embase. The searches covered the period from the inception date of each database until April 28, 2020. No study design, publication status or language restriction were applied. We included studies that assessed patients with confirmed or suspected SARS-CoV-2 infectious disease and examined one or more prognostic factors for mortality or disease severity. Reviewers working in pairs independently screened studies for eligibility, extracted data and assessed the risk of bias. We performed meta-analyses and used GRADE to assess the certainty of the evidence for each prognostic factor and outcome. We included 207 studies and found high or moderate certainty that the following 49 variables provide valuable prognostic information on mortality and/or severe disease in patients with COVID-19 infectious disease: Demographic factors (age, male sex, smoking), patient history factors (comorbidities, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, cardiovascular disease, cardiac arrhythmia, arterial hypertension, diabetes, dementia, cancer and dyslipidemia), physical examination factors (respiratory failure, low blood pressure, hypoxemia, tachycardia, dyspnea, anorexia, tachypnea, haemoptysis, abdominal pain, fatigue, fever and myalgia or arthralgia), laboratory factors (high blood procalcitonin, myocardial injury markers, high blood White Blood Cell count (WBC), high blood lactate, low blood platelet count, plasma creatinine increase, high blood D-dimer, high blood lactate dehydrogenase (LDH), high blood C-reactive protein (CRP), decrease in lymphocyte count, high blood aspartate aminotransferase (AST), decrease in blood albumin, high blood interleukin-6 (IL-6), high blood neutrophil count, high blood B-type natriuretic peptide (BNP), high blood urea nitrogen (BUN), high blood creatine kinase (CK), high blood bilirubin and high erythrocyte sedimentation rate (ESR)), radiological factors (consolidative infiltrate and pleural effusion) and high SOFA score (sequential organ failure assessment score). Identified prognostic factors can help clinicians and policy makers in tailoring management strategies for patients with COVID-19 infectious disease while researchers can utilise our findings to develop multivariable prognostic models that could eventually facilitate decision-making and improve patient important outcomes. Prospero registration number: CRD42020178802. Protocol available at: https://www.medrxiv.org/content/10.1101/2020.04.08.20056598v1.	

2020	Clinical, regional, and genetic characteristics of Covid-19 patients from UK Biobank.	Coronavirus disease 2019 (Covid-19) has rapidly infected millions of people worldwide. Recent studies suggest that racial minorities and patients with comorbidities are at higher risk of Covid-19. In this study, we analyzed the effects of clinical, regional, and genetic factors on Covid-19 positive status. The UK Biobank is a longitudinal cohort study that recruited participants from 2006 to 2010 from throughout the United Kingdom. Covid-19 test results were provided to UK Biobank starting on March 16, 2020. The main outcome measure in this study was Covid-19 positive status, determined by the presence of any positive test for a single individual. Clinical risk factors were derived from UK Biobank at baseline, and regional risk factors were imputed using census features local to each participant's home zone. We used robust adjusted Poisson regression with clustering by testing laboratory to estimate relative risk. Blood types were derived using genetic variants rs8176719 and rs8176746, and genomewide tests of association were conducted using logistic-Firth hybrid regression. This prospective cohort study included 397,064 UK Biobank participants, of whom 968 tested positive for Covid-19. The unadjusted relative risk of Covid-19 for Black participants was 3.66 (95% CI 2.83-4.74), compared to White participants. Adjusting for Townsend deprivation index alone reduced the relative risk to 2.44 (95% CI 1.86-3.20). Comorbidities that significantly increased Covid-19 risk included chronic obstructive pulmonary disease (adjusted relative risk [ARR] 1.64, 95% CI 1.18-2.27), ischemic heart disease (ARR 1.48, 95% CI 1.16-1.89), and depression (ARR 1.32, 95% CI 1.03-1.70). There was some evidence that angiotensin converting enzyme inhibitors (ARR 1.48, 95% CI 1.13-1.93) were associated with increased risk of Covid-19. Each standard deviation increase in the number of total individuals living in a participant's locality was associated with increased risk of Covid-19 (ARR 1.14, 95% CI 1.08-1.20). Analyses of genetically inferred blood types confirmed that participants with type A blood had increased odds of Covid-19 compared to participants with type O blood (odds ratio [OR] 1.16, 95% CI 1.01-1.33). A meta-analysis of genomewide association studies across ancestry groups did not reveal any significant loci. Study limitations include confounding by indication, bias due to limited information on early Covid-19 test results, and inability to accurately gauge disease severity. When assessing the association of Black race with Covid-19, adjusting for deprivation reduced the relative risk of Covid-19 by 33%. In the context of sociological research, these findings suggest that discrimination in the labor market may play a role in the high relative risk of Covid-19 for Black individuals. In this study, we also confirmed the association of blood type A with Covid-19, among other clinical and regional factors.	

2020	Relationship between the ABO blood group and COVID-19 susceptibility, severity and mortality in two cohorts of patients.	Several articles reported the existence of an association between ABO blood groups and COVID-19 susceptibility. Group A and group O individuals showed a higher and lower risk, respectively, of becoming infected. No association was observed between ABO groups and mortality. To verify this association, we performed a retrospective study of two cohorts of patients with different demographic and clinical characteristics. A total of 854 regular blood donors were recruited for convalescent plasma donation after recovering from a mild COVID-19 infection, and a group of 965 patients more severely affected who were transfused during hospitalisation were also included. We also investigated the potential role of the different risk factors on patient outcome and death. To eliminate the confounding effect of risk factors on mortality, a propensity score analysis was performed. Blood group A and blood group O COVID-19 blood donors showed a higher and lower risk, respectively, for acquiring COVID-19. In contrast, this association was not found in the group of patients transfused during hospitalisation, probably due to the great differences in demographic and clinical characteristics between the two groups. Regarding severity, age was one of the most significant risk factors. ABO blood groups were also seen to represent important risk factors for COVID-19 severity and mortality. Mortality risk in group A individuals was significantly higher than in group O individuals (OR: 1.75, 95% CI: 1.22-2.51). The association between the ABO blood groups and the susceptibility to acquire COVID-19 infection was confirmed in the group of blood donors. ABO blood groups were also associated to COVID-19 severity and mortality in the group of patients transfused during hospitalisation. Therefore, blood groups A and O are two important factors to be considered when evaluating the prognosis of patients with COVID-19.	
2020	Major reduction of NKT cells in patients with severe COVID-19 pneumonia.	NK cells seem to be mainly involved in COVID-19 pneumonia. Little is known about NKT cells which represent a bridge between innate and adaptive immunity. We characterized peripheral blood T, NK and NKT cells in 45 patients with COVID-19 pneumonia (COVID-19 subjects) and 19 healthy donors (HDs). According to the severity of the disease, we stratified COVID-19 subjects into severe and non-severe groups. Compared to HDs, COVID-19 subjects showed higher percentages of NK CD57+ and CD56dim NK cells and lower percentages of NKT and CD56bright cells. In the severe group we found a significantly lower percentage of NKT cells. In a multiple logistic regression analysis, NKT cell was independently associated with the severity of the disease. The low percentage of NKT cells in peripheral blood of COVID-19 subjects and the independent association with the severity of the disease suggests a potential role of this subset.	

2020	COVID-19 and diabetes mellitus: from pathophysiology to clinical management.	Initial studies found increased severity of coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in patients with diabetes mellitus. Furthermore, COVID-19 might also predispose infected individuals to hyperglycaemia. Interacting with other risk factors, hyperglycaemia might modulate immune and inflammatory responses, thus predisposing patients to severe COVID-19 and possible lethal outcomes. Angiotensin-converting enzyme 2 (ACE2), which is part of the renin-angiotensin-aldosterone system (RAAS), is the main entry receptor for SARS-CoV-2; although dipeptidyl peptidase 4 (DPP4) might also act as a binding target. Preliminary data, however, do not suggest a notable effect of glucose-lowering DPP4 inhibitors on SARS-CoV-2 susceptibility. Owing to their pharmacological characteristics, sodium-glucose cotransporter 2 (SGLT2) inhibitors might cause adverse effects in patients with COVID-19 and so cannot be recommended. Currently, insulin should be the main approach to the control of acute glycaemia. Most available evidence does not distinguish between the major types of diabetes mellitus and is related to type 2 diabetes mellitus owing to its high prevalence. However, some limited evidence is now available on type 1 diabetes mellitus and COVID-19. Most of these conclusions are preliminary, and further investigation of the optimal management in patients with diabetes mellitus is warranted.	
2020	COVID-19 in the Developing World: Is the Immune Response to α-Gal an Overlooked Factor Mitigating the Severity of Infection?	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which has affected millions of people worldwide. Considerably lower prevalence and fatality rates resulting from COVID-19 are reported in Africa and Asia than in the industrialized world. In this Viewpoint, we discuss the possibility that this intriguing phenomenon could be, among other factors, due to protective immunity of the oligosaccharide galactose-α-1,3-galactose (α-Gal). The α-Gal immunity induced by gut microbiota that express the same glycan modification may prevent COVID-19 through the activation of different mechanisms involved in SARS-CoV-2 neutralization and the downregulation of the inflammatory response in the lungs of infected patients.	
2020	The hematology laboratory's response to the COVID-19 pandemic: A scoping review.	The ongoing COVID-19 pandemic has had a profound worldwide impact on the laboratory hematology community. Nevertheless, the pace of COVID-19 hematology-related research has continued to accelerate and has established the role of laboratory hematology data for many purposes including disease prognosis and outcome. The purpose of this scoping review was to assess the current state of COVID-19 laboratory hematology research. A comprehensive search of the literature published between December 1, 2019, and July 3, 2020, was performed, and we analyzed the sources, publication dates, study types, and topics of the retrieved studies. Overall, 402 studies were included in this scoping review. Approximately half of these studies (n = 202, 50.37%) originated in China. Retrospective cohort studies comprised the largest study type (n = 176, 43.89%). Prognosis/ risk factors, epidemiology, and coagulation were the most common topics. The number of studies published per day has increased through the end of May. The studies were heavily biased in favor of papers originating in China and on retrospective clinical studies with limited use of and reporting of laboratory data. Despite the major improvements in our understanding of the role of coagulation, automated hematology, and cell morphology in COVID-19, there are gaps in the literature, including biosafety and the laboratory role in screening and prevention of COVID-19. There is a gap in the publication of papers focused on guidelines for the laboratory.	

		Our findings suggest that, despite the large number of publications related to laboratory data and their use in COVID-19 disease, many areas remain unexplored or under-reported.	
2020	Cardiac damage in patients with the severe type of coronavirus disease 2019 (COVID-19).	Coronavirus disease 2019 (COVID-19) has become a global pandemic. Studies showed COVID-19 affected not only the lung but also other organs. In this study, we aimed to explore the cardiac damage in patients with COVID-19. We collected data of 100 patients diagnosed as severe type of COVID-19 from February 8 to April 10, 2020, including demographics, illness history, physical examination, laboratory test, and treatment. In-hospital mortality were observed. Cardiac damage was defined as plasma hypersensitive troponin I (hsTnI) over 34.2 pg/ml and/or N-terminal-pro brain natriuretic peptide (NTproBNP) above 450 pg/ml at the age < 50, above 900 pg/ml at the age < 75, or above 1800 pg/ml at the age ≥ 75. The median age of the patients was 62.0 years old. 69 (69.0%) had comorbidities, mainly presenting hypertension, diabetes, and cardiovascular disease. Fever (69 [69.0%]), cough (63 [63.0%]), chest distress (13 [13.0%]), and fatigue (12 [12.0%]) were the common initial symptoms. Cardiac damage occurred in 25 patients. In the subgroups, hsTnI was significantly higher in elder patients (≥ 60 years) than in the young (median [IQR], 5.2 [2.2-12.8] vs. 1.9 [1.9-6.2], p = 0.018) and was higher in men than in women (4.2 [1.9-12.8] vs. 2.9 [1.9-7.4], p = 0.018). The prevalence of increased NTproBNP was significantly higher in men than in women (32.1% vs. 9.1%, p = 0.006), but was similar between the elder and young patients (20.0% vs. 25.0%, p = 0.554). After multivariable analysis, male and hypertension were the risk factors of cardiac damage. The mortality was 4.0%. Cardiac damage exists in patients with the severe type of COVID-19, especially in male patients with hypertension. Clinicians should pay more attention to cardiac damage.	

2020	Diagnostic accuracy of serological tests and kinetics of severe acute respiratory syndrome coronavirus 2 antibody: A systematic review and meta-analysis.	This study aimed to assess the diagnostic test accuracy (DTA) of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) serological test methods and the kinetics of antibody positivity. Systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. We included articles evaluating the diagnostic accuracy of serological tests and the kinetics of antibody positivity. MEDLINE through PubMed, Scopus, medRxiv and bioRxiv were sources of articles. Methodological qualities of included articles were appraised using QUADAS-2 while Metandi performs bivariate meta-analysis of DTA using a generalized linear mixed-model approach. Stata 14 and Review Manager 5.3 were used for data analysis. The summary sensitivity/specificity of chemiluminescence immunoassay (CLIA), enzyme-linked immunosorbent assay (ELISA) and lateral flow immunoassay (LFIA) were 92% (95% CI: 86%-95%)/99% (CI: 97%-99%), 86% (CI: 82%-89%)/99% (CI: 98%-100%) and 78% (CI: 71%-83%)/98% (95% CI: 96%-99%), respectively. Moreover, CLIA-based assays produced nearly 100% sensitivity within 11-15 days post-symptom onset (DPSO). Based on antibody type, the sensitivity of ELISA-total antibody, CLIA-IgM/G and CLIA-IgG gauged at 94%, 92% and 92%, respectively. The sensitivity of CLIA-RBD assay reached 96%, while LFIA-S demonstrated the lowest sensitivity, 71% (95% CI: 58%-80%). CLIA assays targeting antibodies against RBD considered the best DTA. The antibody positivity rate increased corresponding with DPSO, but there was some decrement when moving from acute phase to convalescent phase of infection. As immunoglobulin isotope-related DTA was heterogeneous, our data have insufficient evidence to recommend CLIA/ELISA for clinical decision-making, but likely to have comparative advantage over RT-qPCR in certain circumstances and geographic regions.	
2020	HLA and AB0 Polymorphisms May Influence SARS-CoV-2 Infection and COVID-19 Severity.	SARS-CoV-2 infection is heterogeneous in clinical presentation and disease evolution. To investigate whether immune response to the virus can be influenced by genetic factors, we compared HLA and AB0 frequencies in organ transplant recipients and waitlisted patients according to presence or absence of SARS-CoV-2 infection. A retrospective analysis was performed on an Italian cohort composed by transplanted and waitlisted patients in a January 2002 to March 2020 time frame. Data from this cohort were merged with the Italian registry of COVID+ subjects, evaluating infection status of transplanted and waitlisted patients. A total of 56 304 cases were studied with the aim of comparing HLA and AB0 frequencies according to the presence (n = 265, COVID+) or absence (n = 56 039, COVID-) of SARS-CoV-2 infection. The cumulative incidence rate of COVID-19 was 0.112% in the Italian population and 0.462% in waitlisted/transplanted patients (OR = 4.2; 95% CI, 3.7-4.7; P < 0.0001). HLA-DRB1*08 was more frequent in COVID+ (9.7% and 5.2%: OR = 1.9, 95% CI, 1.2-3.1; P = 0.003; Pc = 0.036). In COVID+ patients, HLA-DRB1*08 was correlated to mortality (6.9% in living versus 17.5% in deceased: OR = 2.9, 95% CI, 1.15-7.21; P = 0.023). Peptide binding prediction analyses showed that these DRB1*08 alleles were unable to bind any of the viral peptides with high affinity. Finally, blood group A was more frequent in COVID+ (45.5%) than COVID- patients (39.0%; OR = 1.3; 95% CI, 1.02-1.66; P = 0.03). Although preliminary, these results suggest that HLA antigens may influence SARS-CoV-2 infection and clinical evolution of COVID-19 and confirm that blood group A individuals are at greater risk of infection, providing clues on the spread	

		of the disease and indications about infection prognosis and vaccination strategies.	
2020	Complement activation and endothelial perturbation parallel COVID-19 severity and activity.	Animal models and few clinical reports suggest the involvement of the complement system in the onset of severe manifestations of coronavirus disease-2019 (COVID-19). However, complement contribution to endotheliopathy and hypercoagulability has not been elucidated yet. To evaluate the association among complement activation, endothelial damage and disease severity or activity in COVID-19 patients. In this single-centre cohort study, 148 patients with COVID-19 of different severity were evaluated upon hospital admission and 30 days later. Markers of complement activation (SC5b-9 and C5a) and endothelial perturbation (von Willebrand factor [vWF], tissue-type plasminogen activator [t-PA], plasminogen activator inhibitor-1 [PAI-1], soluble thrombomodulin [sTM], and soluble endothelial selectin [sE-selectin]) were measured in plasma. The patients had high plasma levels of SC5b-9 and C5a ($p = 0.0001$ for both) and vWF, t-PA and PAI-1 ($p = 0.0001$ for all). Their SC5b-9 levels correlated with those of vWF ($r = 0.517$, $p = 0.0001$) and paralleled disease severity (severe vs mild $p = 0.0001$, severe vs moderate $p = 0.026$ and moderate vs mild $p = 0.001$). The levels of sE-selectin were significantly increased only in the patients with severe disease. After 30 days, plasma SC5b-9, C5a and vWF levels had significantly decreased ($p = 0.0001$ for all), and 43% of the evaluated patients had normal levels. Complement activation is boosted during the progression of COVID-19 and dampened during remission, thus indicating its role in the pathophysiology of the disease. The association between complement activation and the biomarkers of endothelial damage suggests that complement may contribute to tissue injury and could be the target of specific therapy.	

2020	Clinical analysis of 132 cases COVID-19 from Wuhan.	Numerous cases of pneumonia from a novel coronavirus (SARS-CoV-2) emerged in Wuhan, China during December 2019.We determined the correlations of patient parameters with disease severity in patients with COVID-19.A total of 132 patients from Wuhan Fourth Hospital who had COVID-19 from February 1 to February 29 in 2020 were retrospectively analyzed.Ninety patients had mild disease, 32 had severe disease, and 10 had critical disease. The severe/critical group was older (P<.05), had a higher proportion of males (P<.05), and had a greater mortality rate (0% vs 61.9%, P<.05). The main symptoms were fever (n=112, 84.8%) and cough (n=96, 72.7%). Patients were treated with antiviral agents (n=94, 71.2%), antibiotics (n=92, 69.7%), glucocorticoids (n=46, 34.8%), intravenous immunoglobulin (n=38, 27.3%), and/or traditional Chinese medicine (n=40, 30.3%). Patients in the severe/critical group received mechanical ventilation (n=22, 16.7%) or high-flow nasal can-nula oxygen therapy (n=6, 4.5%). Chest computed tomography (CT) indicated bilateral pneumonia in all patients. Relative to the mild group, the severe/critical group had higher levels of leukocytes, C-reactive protein (CRP), procalcitonin (PCT), D-dimer, B-type natriuretic peptide (BNP), liver enzymes, and myocardial enzymes (P<.05), and decreased levels of lymphocytes and blood oxygen partial pressure (P<.05).The main clinical symptoms of patients from Wuhan who had COVID-19 were fever and cough. Patients with severe/critical disease were more likely to be male and elderly. Disease severity correlated with increased leukocytes, CRP, PCT, BNP, D-dimer, liver enzymes, and myocardial enzymes, and with decreased lymphocytes and blood oxygen partial pressure.	
2020	An 89-Year-Old Man with COVID-19-Associated Coagulopathy Presenting with a Prolonged Partial Thromboplastin Time, Lupus Anticoagulant, and a High Titer of Factor VIII Inhibitor.	BACKGROUND Coagulation abnormalities are frequently encountered in patients with coronavirus disease 2019 (COVID-19), especially in those with more severe disease. These hematologic abnormalities are suspected to occur in the context of underlying immune dysregulation and endothelial dysfunction. Elevated D-dimer levels, COVID-19-associated coagulopathy (CAC), disseminated intravascular coagulation (DIC), and positive lupus anticoagulants are the most common findings to date. Current guidelines suggest that all patients with COVID-19 should receive pharmacologic thromboprophylaxis. CASE REPORT An 89-year-old man with a medical history of hypertension, type 2 diabetes, and advanced prostate cancer in remission presented with generalized weakness. At our center, a reverse transcription-polymerase chain reaction test was positive for severe acute respiratory syndrome coronavirus 2, but the patient did not have symptoms of COVID-19. He was also found to have a prolonged activated partial thromboplastin time, secondary to both a high titer of factor VIII inhibitor and a lupus anticoagulant. He eventually developed respiratory compromise, during which his disease manifested as a bleeding rather than a prothrombotic state. CONCLUSIONS This report highlights the importance of a comprehensive evaluation of prolonged partial thromboplastin time, rather than making an assumption based on a positive lupus anticoagulant result. In the case presented, the concomitant factor VIII inhibitor caused the patient to have a greater bleeding tendency. It is imperative that physicians balance the risk of bleeding and clotting in patients with COVID-19 because patients seem to have varying presentations based on disease severity and level of immune dysregulation.	

2020	IP-10 and MCP-1 as biomarkers associated with disease severity of COVID-19.	COVID-19 is a viral respiratory disease caused by the severe acute respiratory syndrome-Coronavirus type 2 (SARS-CoV-2). Patients with this disease may be more prone to venous or arterial thrombosis because of the activation of many factors involved in it, including inflammation, platelet activation and endothelial dysfunction. Interferon gamma inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein 1-alpha (MIP1α) are cytokines related to thrombosis. Therefore, this study focused on these three indicators in COVID-19, with the hope to find biomarkers that are associated with patients' outcome. This is a retrospective single-center study involving 74 severe and critically ill COVID-19 patients recruited from the ICU department of the Tongji Hospital in Wuhan, China. The patients were divided into two groups: severe patients and critically ill patients. The serum IP-10, MCP-1 and MIP1α level in both groups was detected using the enzyme-linked immunosorbent assay (ELISA) kit. The clinical symptoms, laboratory test results, and the outcome of COVID-19 patients were retrospectively analyzed. The serum IP-10 and MCP-1 level in critically ill patients was significantly higher than that in severe patients ($P < 0.001$). However, no statistical difference in MIP1α between the two groups was found. The analysis of dynamic changes showed that these indicators remarkably increased in patients with poor prognosis. Since the selected patients were severe or critically ill, no significant difference was observed between survival and death. IP-10 and MCP-1 are biomarkers associated with the severity of COVID-19 disease and can be related to the risk of death in COVID-19 patients.	
2020	Chronic lung diseases are associated with gene expression programs favoring SARS-CoV-2 entry and severity.	Patients with chronic lung disease (CLD) have an increased risk for severe coronavirus disease-19 (COVID-19) and poor outcomes. Here, we analyzed the transcriptomes of 605,904 single cells isolated from healthy and CLD lungs to identify molecular characteristics of lung cells that may account for worse COVID-19 outcomes in patients with chronic lung diseases. We observed a similar cellular distribution and relative expression of SARS-CoV-2 entry factors in control and CLD lungs. CLD epithelial cells expressed higher levels of genes linked directly to the efficiency of viral replication and innate immune response. Additionally, we identified basal differences in inflammatory gene expression programs that highlight how CLD alters the inflammatory microenvironment encountered upon viral exposure to the peripheral lung. Our study indicates that CLD is accompanied by changes in cell-type-specific gene expression programs that prime the lung epithelium for and influence the innate and adaptive immune responses to SARS-CoV-2 infection.	
2020	The potential use of ABO blood group system for risk stratification of COVID-19.	ABO blood groups is a cheap and affordable test that can be immediately retrieved from COVID-19 patients at the diagnosis. There is increasing evidence that non-O blood groups have both higher susceptibility and higher severity of COVID-19 infections. The reason behind such relationship seems elusive. Regarding susceptibility, Non-O individuals have Anti-A antibodies which can prevent viral entry across ACE-2 receptors, moreover, Non-O individuals are at higher risk of autoimmunity, hypercoagulable state, and dysbiosis resulting in an augmented tendency for vascular inflammatory sequelae of COVID-19. We can conclude, on the diagnostic level, that ABO blood groups can be potentially used for risk stratification of affected COVID-19 patients, to anticipate the deterioration of patients at higher risk for complications. On a therapeutic level, plasma from normal O blood group individuals might potentially replace the use of convalescent serum for the treatment of COVID-19.	

2020	Abnormal antibodies to self-carbohydrates in SARS-CoV-2 infected patients.	SARS-CoV-2 is a deadly virus that is causing the global pandemic coronavirus disease 2019 (COVID-19). Our immune system plays a critical role in preventing, clearing, and treating the virus, but aberrant immune responses can contribute to deleterious symptoms and mortality. Many aspects of immune responses to SARS-CoV-2 are being investigated, but little is known about immune responses to carbohydrates. Since the surface of the virus is heavily glycosylated, pre-existing antibodies to glycans could potentially recognize the virus and influence disease progression. Furthermore, antibody responses to carbohydrates could be induced, affecting disease severity and clinical outcome. In this study, we used a carbohydrate antigen microarray with over 800 individual components to profile serum anti-glycan antibodies in COVID-19 patients and healthy control subjects. In COVID-19 patients, we observed abnormally high IgG and IgM antibodies to numerous self-glycans, including gangliosides, N -linked glycans, LacNAc-containing glycans, blood group H, and sialyl Lewis X. Some of these anti-glycan antibodies are known to play roles in autoimmune diseases and neurological disorders, which may help explain some of the unusual and prolonged symptoms observed in COVID-19 patients. The detection of antibodies to self-glycans has important implications for using convalescent serum to treat patients, developing safe and effective SARS-CoV-2 vaccines, and understanding the risks of infection. In addition, this study provides new insight into the immune responses to SARS-CoV-2 and illustrates the importance of including host and viral carbohydrate antigens when studying immune responses to viruses.	
2020	Decentralized COVID-19 measures in Brazil were ineffective to protect people with diabetes.	COVID-19 severity and mortality are elevated in individuals with diabetes. During the pandemic, interventions recommended globally for people with diabetes were to keep blood glucose on target whilst staying at home to curb the spread of the virus. In Brazil, similar measures were proposed. The aim of our observational study was to assess whether these measures achieved their objectives. An anonymous and untraceable survey was shared from April 22nd to May 4th. States with more than 30 respondents were included in the analysis and Fisher's exact test was performed to identify associations, with $p < 0.05$ considered significant. Type 1 diabetes and female participants were prevalent, 60.76% and 76.12% respectively. 10 out of 26 states were included, in addition to the Federal District (1562 responses). Only in three states (Bahia, Goiás and Pernambuco) less than 50% of the respondents experienced higher glycemia or higher variability during the pandemic. Goiás state, where almost half of the respondents (49.12%) have private insurance, presented the highest percentage of individuals receiving medicines for three months (35.48%) and one of the lowest percentages of blood glucose deterioration (47.17%). In the large states of Minas Gerais, Rio de Janeiro and São Paulo, consultations and/or lab exams were postponed by 37.14%, 34.33% and 40.88%, respectively. The decentralized measures implemented by states in Brazil left most people with diabetes unprotected. Many were forced to venture outside to collect or to purchase their medical supplies monthly and reported increased glycemic levels and/or variability.	

2020	Increased Serum Levels of sCD14 and sCD163 Indicate a Preponderant Role for Monocytes in COVID-19 Immunopathology.	Emerging evidence indicates a potential role for monocytes in COVID-19 immunopathology. We investigated two soluble markers of monocyte activation, sCD14 and sCD163, in COVID-19 patients, with the aim of characterizing their potential role in monocyte-macrophage disease immunopathology. To the best of our knowledge, this is the first study of its kind. Fifty-nine SARS-Cov-2 positive hospitalized patients, classified according to ICU or non-ICU admission requirement, were prospectively recruited and analyzed by ELISA for levels of sCD14 and sCD163, along with other laboratory parameters, and compared to a healthy control group. sCD14 and sCD163 levels were significantly higher among COVID-19 patients, independently of ICU admission requirement, compared to the control group. We found a significant correlation between sCD14 levels and other inflammatory markers, particularly Interleukin-6, in the non-ICU patients group. sCD163 showed a moderate positive correlation with the time lapsed from admission to sampling, independently of severity group. Treatment with corticoids showed an interference with sCD14 levels, whereas hydroxychloroquine and tocilizumab did not. Monocyte-macrophage activation markers are increased and correlate with other inflammatory markers in SARS-Cov-2 infection, in association to hospital admission. These data suggest a preponderant role for monocyte-macrophage activation in the development of immunopathology of COVID-19 patients.	
2020	Risk Factors for Poor Outcomes of Diabetes Patients With COVID-19: A Single-Center, Retrospective Study in Early Outbreak in China.	Background: Diabetes has been found to increase severity and mortality under the current pandemic of coronavirus disease of 2019 (COVID-19). Up to date, the clinical characteristics of diabetes patients with COVID-19 and the risk factors for poor clinical outcomes are not clearly understood. Methods: The study was retrospectively carried out on enrolled diabetes patients with laboratory confirmed COVID-19 infection from a designated medical center for COVID-19 from January 25th, 2020 to February 14th, 2020 in Wuhan, China. The medical record was collected and reviewed. Univariate and multivariate analyses were performed to assess the risk factors associated with the severe events which were defined as a composite endpoint of admission to intensive care unit, the use of mechanical ventilation, or death. Results: A total of 52 diabetes patients with COVID-19 were finally included in the study. 21 (40.4%) patients had developed severe events in 27.50 (IQR 12.25-35.75) days follow-up, 15 (28.8%) patients experienced life-threatening complications and 8 patients died with a recorded mortality rate of 15.4%. Only 13 patients (41.9%) were in optimal glycemic control with HbA1c value of <7.0%. In addition to general clinical characteristics of COVID-19, the severe events diabetes patients showed higher counts of white blood cells and neutrophil, lower lymphocytes (40, 76.9%), high levels of hs-CRP, erythrocyte sedimentation rate (ESR) and procalcitonin (PCT) as compared to the non-severe diabetes patients. Mild higher level of cardiac troponin I (cTNI) (32.0 pg/ml; IQR 16.80-55.00) and D-dimer (1.70 μg/L, IQR 0.70-2.40) were found in diabetes patients with severe events as compared to the non-severe patients (cTNI:20.00 pg/ml, IQR5.38-30.00, $p = 0.019$; D-dimer: 0.70 μg/L, IQR 0.30-2.40, $p = 0.037$). After adjusting age and sex, increased level of cTNI was found to significantly associate with the incidence of severe events (HR: 1.007; 95% CI: 1.000-1.013; $p = 0.048$), Furthermore, using of α-glucosidase inhibitors was found to be the potential protectant for severe events (HR: 0.227; 95% CI: 0.057-0.904; $p = 0.035$). Conclusion: Diabetes patients with COVID-19 showed poor clinical outcomes. Vigorous monitoring of cTNI should be	

		recommended for the diabetes patients with COVID-19. Usage of α-glucosidase inhibitors could be a potential protectant for the diabetes patients with COVID-19.	
2020	Rotational thromboelastometry results are associated with care level in COVID-19.	High prevalence of thrombotic events in severely ill COVID-19 patients have been reported. Pulmonary embolism as well as microembolization of vital organs may in these individuals be direct causes of death. The identification of patients at high risk of developing thrombosis may lead to targeted, more effective prophylactic treatment. The primary aim of this study was to test whether rotational thromboelastometry (ROTEM) at admission indicates hypercoagulopathy and predicts the disease severity, assessed as care level, in COVID-19 patients. The study was designed as a prospective, observational study where COVID-19 patients over 18 years admitted to hospital were eligible for inclusion. Patients were divided into two groups depending on care level: (1) regular wards or (2) wards with specialized ventilation support. Conventional coagulation tests, blood type and ROTEM were taken at admission. 60 patients were included; age 61 (median), 67% men, many with comorbidities (e.g. hypertension, diabetes). The ROTEM variables Maximum Clot Firmness (EXTEM-/FIBTEM-MCF) were higher in COVID-19 patients compared with in healthy controls ($p < 0.001$) and higher in severely ill patients compared with in patients at regular wards ($p < 0.05$). Our results suggest that hypercoagulopathy is present early in patients with mild to moderate disease, and more pronounced in severe COVID-19 pneumonia. Non-O blood types were not overrepresented in COVID-19 positive patients. ROTEM variables showed hypercoagulopathy at admission and this pattern was more pronounced in patients with increased disease severity. If this feature is to be used to predict the risk of thromboembolic complications further studies are warranted.	

2020	Clinical Features of COVID-19 Patients with Diabetes and Secondary Hyperglycemia.	People with diabetes have higher risks of various infections. Therefore, these diabetic patients might be at increased risk of COVID-19 and have a poorer prognosis. Up until now, little is known about critical role in the pathogenesis. This study aims to investigate the clinical characteristics of COVID-19 patients with diabetes and secondary hyperglycemia, as well as to explore the purported mechanisms. 80 confirmed COVID-19 subjects were classified into the euglycemia group, secondary hyperglycemia group, and diabetes group. Severity of COVID-19 was defined based on the diagnostic and treatment guideline for SARS-CoV-2 issued by Chinese National Health Committee. According to the severity of the disease, patients of the mild type and common type were registered as mild cases (patients with minimal symptoms and negative CT findings), while patients of the severe type and critical type were enrolled as severe cases (patients with positive CT findings and different extent of clinical manifestations). Patients in the diabetes group were older than those in the euglycemia group, and most of them were male. In the diabetes group, the proportion of severe cases was 57.14%, which was significantly higher than those in the other two groups, and 32% of the COVID-19 patients diagnosed as severe cases were with diabetes. The CD4+ cell counts in the diabetes group were lower than those in the other two groups, while the levels of LDH and hs-CRP were higher. Compared with the euglycemia group, the CD3+ cell counts and the CD4+/CD8+ ratio were decreased, whereas the levels of IL-6 were increased in the secondary hyperglycemia group and diabetes group, with the diversities in the diabetes group being especially more significant. The Spearman correlation analysis revealed that the presence of diabetes was positively correlated with age, hs-CRP, LDH, IL-6, CD8+ cells, and severity of COVID-19 and negatively correlated with CD3+ cell counts, CD4+ cell counts, and CD4+/CD8+ ratio. Compared with the other two groups, the diabetes group exhibited more diverse and multifocal features in CT imagings. Diabetes is a risk factor for influence of the progression and prognosis of COVID-19 due to ongoing inflammation and impaired immune response.	

2020	Distinguishable Immunologic Characteristics of COVID-19 Patients with Comorbid Type 2 Diabetes Compared with Nondiabetic Individuals.	COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has threatened every civilian as a global pandemic. The immune system poses the critical interactive chain between the human body and the virus. Here, we make efforts to examine whether comorbidity with type 2 diabetes (T2D) affects the immunological response in COVID-19 patients. We conducted a retrospective pilot study investigating immunological characteristics of confirmed cases of COVID-19 with or without comorbid T2D. Two subcohorts of sex- and age-matched participants were eligible for data analysis, of which 33 participants were with T2D and the remaining 37 were nondiabetic (NDM). Cellular immunity was assessed by flow cytometric determination of surface markers including CD3, CD4, CD8, CD19, CD16, and CD56 in peripheral blood. Levels of C reactive protein, immunoglobulin (IgG, IgM, IgA, and IgE), and complements (C3, C4) were detected by rate nephelometry immunoassay. And Th1/Th2 cytokines (IL-2, IL-4, IL-6, IL-10, TNF- α , and IFN- γ) were detected by Cytometric Bead Array. Neutrophil counts were found to be significantly higher in the T2D group than in the NDM group and had a significant relevance with clinical severity. Lymphocyte frequencies showed no significant differences in the two groups. However, the proportions and absolute counts of T, Tc, Th, and NK cells decreased in both groups to different degrees. An abnormal increase in neutrophil count and a decrease in lymphocyte subpopulations may represent risk factors of COVID-19 severity. The level of IgG, IgM, IgA, C3, and C4 showed no significant difference between the two groups, while the IgE levels were higher in the T2D group than in the NDM group ($p < 0.05$). Th1 cytokines including IFN- γ , TNF- α , and IL-6, as well as CRP, appeared significantly higher in the T2D group. The COVID-19 patients comorbid with T2D demonstrated distinguishable immunological parameters, which represented clinical relevancies with the predisposed disease severity in T2D.	
2020	Unique immunological profile in patients with COVID-19.	The relationship between severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and host immunity is poorly understood. We performed an extensive analysis of immune responses in 32 patients with severe COVID-19, some of whom succumbed. A control population of healthy subjects was included. Patients with COVID-19 had an altered distribution of peripheral blood lymphocytes, with an increased proportion of mature natural killer (NK) cells and low T-cell numbers. NK cells and $CD8^+$ T cells overexpressed T-cell immunoglobulin and mucin domain-3 (TIM-3) and CD69. NK cell exhaustion was attested by increased frequencies of programmed cell death protein 1 (PD-1) positive cells and reduced frequencies of natural killer group 2 member D (NKG2D)-, DNAX accessory molecule-1 (DNAM-1)- and sialic acid-binding Ig-like lectin 7 (Siglec-7)-expressing NK cells, associated with a reduced ability to secrete interferon (IFN)γ. Patients with poor outcome showed a contraction of immature $CD56^{bright}$ and an expansion of mature $CD57^+$ $Fc\varepsilon RI\gamma^{neg}$ adaptive NK cells compared to survivors. Increased serum levels of IL-6 were also more frequently identified in deceased patients compared to survivors. Of note, monocytes secreted abundant quantities of IL-6, IL-8, and IL-1β which persisted at lower levels several weeks after recovery with concomitant normalization of CD69, PD-1 and TIM-3 expression and restoration of $CD8^+$ T cell numbers. A hyperactivated/exhausted immune response dominate in severe SARS-CoV-2 infection, probably driven by an uncontrolled secretion of inflammatory cytokines by monocytes. These findings unveil a unique	

		immunological profile in COVID-19 patients that will help to design effective stage-specific treatments for this potentially deadly disease.	
2020	Deciphering the COVID-19 cytokine storm: Systematic review and meta-analysis.	The coronavirus pandemic has affected more than 20 million people so far. Elevated cytokines and suppressed immune responses have been hypothesized to set off a cytokine storm, contributing to ARDS, multiple-organ failure and, in the most severe cases, death. We aimed to quantify the differences in the circulating levels of major inflammatory and immunological markers between severe and nonsevere COVID-19 patients. Relevant studies were identified from PubMed, EMBASE, Web of Science, SCOPUS and preprint servers. Risk of bias was assessed for each study, using appropriate checklists. All studies were described qualitatively and a subset was included in the meta-analysis, using forest plots. Based on 23 studies, mean cytokine levels were significantly higher (IL-6: MD, 19.55 pg/mL; CI, 14.80, 24.30; IL-8: MD, 19.18 pg/mL; CI, 2.94, 35.43; IL-10: MD, 3.66 pg/mL; CI, 2.41, 4.92; IL-2R: MD, 521.36 U/mL; CI, 87.15, 955.57; and TNF-alpha: MD, 1.11 pg/mL; CI, 0.07, 2.15) and T-lymphocyte levels were significantly lower (CD4+ T cells: MD, -165.28 cells/μL; CI, -207.58, -122.97; CD8+ T cells: MD, -106.51 cells/μL; CI, -128.59, -84.43) among severe cases as compared to nonsevere ones. There was heterogeneity across studies due to small sample sizes and nonuniformity in outcome assessment and varied definitions of disease severity. The overall quality of studies was sub-optimal. Severe COVID-19 is characterized by significantly increased levels of pro-inflammatory cytokines and reduced T lymphocytes. Well-designed and adequately powered prospective studies are needed to amplify the current evidence and provide definitive answers to dilemmas regarding timing and type of anti-COVID-19 therapy particularly in severe patients.	

2020	The association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19.	Studies on severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) suggest a protective effect of anti-A antibodies against viral cell entry that may hold relevance for SARS-CoV-2 infection. Therefore, we aimed to determine whether ABO blood groups are associated with different severities of COVID-19. We conducted a multicenter retrospective analysis and nested prospective observational substudy of critically ill patients with COVID-19. We collected data pertaining to age, sex, comorbidities, dates of symptom onset, hospital admission, intensive care unit (ICU) admission, mechanical ventilation, continuous renal replacement therapy (CRRT), standard laboratory parameters, and serum inflammatory cytokines. National (N = 398 671; P = .38) and provincial (n = 62 246; P = .60) ABO blood group distributions did not differ from our cohort (n = 95). A higher proportion of COVID-19 patients with blood group A or AB required mechanical ventilation (P = .02) and CRRT (P = .004) and had a longer ICU stay (P = .03) compared with patients with blood group O or B. Blood group A or AB also had an increased probability of requiring mechanical ventilation and CRRT after adjusting for age, sex, and presence of ≥1 comorbidity. Inflammatory cytokines did not differ between patients with blood group A or AB (n = 11) vs O or B (n = 14; P > .10 for all cytokines). Collectively, our data indicate that critically ill COVID-19 patients with blood group A or AB are at increased risk for requiring mechanical ventilation, CRRT, and prolonged ICU admission compared with patients with blood group O or B. Further work is needed to understand the underlying mechanisms.	
2020	Predictive Models of Mortality for Hospitalized Patients With COVID-19: Retrospective Cohort Study.	The novel coronavirus SARS-CoV-2 and its associated disease, COVID-19, have caused worldwide disruption, leading countries to take drastic measures to address the progression of the disease. As SARS-CoV-2 continues to spread, hospitals are struggling to allocate resources to patients who are most at risk. In this context, it has become important to develop models that can accurately predict the severity of infection of hospitalized patients to help guide triage, planning, and resource allocation. The aim of this study was to develop accurate models to predict the mortality of hospitalized patients with COVID-19 using basic demographics and easily obtainable laboratory data. We performed a retrospective study of 375 hospitalized patients with COVID-19 in Wuhan, China. The patients were randomly split into derivation and validation cohorts. Regularized logistic regression and support vector machine classifiers were trained on the derivation cohort, and accuracy metrics (F1 scores) were computed on the validation cohort. Two types of models were developed: the first type used laboratory findings from the entire length of the patient's hospital stay, and the second type used laboratory findings that were obtained no later than 12 hours after admission. The models were further validated on a multicenter external cohort of 542 patients. Of the 375 patients with COVID-19, 174 (46.4%) died of the infection. The study cohort was composed of 224/375 men (59.7%) and 151/375 women (40.3%), with a mean age of 58.83 years (SD 16.46). The models developed using data from throughout the patients' length of stay demonstrated accuracies as high as 97%, whereas the models with admission laboratory variables possessed accuracies of up to 93%. The latter models predicted patient outcomes an average of 11.5 days in advance. Key variables such as lactate dehydrogenase, high-sensitivity C-reactive protein, and percentage of lymphocytes in the blood were indicated by the models. In line with previous studies, age was also found to be an important variable in predicting mortality. In particular, the mean age of patients	

		who survived COVID-19 infection (50.23 years, SD 15.02) was significantly lower than the mean age of patients who died of the infection (68.75 years, SD 11.83; P<.001). Machine learning models can be successfully employed to accurately predict outcomes of patients with COVID-19. Our models achieved high accuracies and could predict outcomes more than one week in advance; this promising result suggests that these models can be highly useful for resource allocation in hospitals.	
2020	Pharmacotherapeutic considerations for the management of diabetes mellitus among hospitalized COVID-19 patients.	Diabetes mellitus is one of the most prevalent comorbidities identified in patients with coronavirus disease 2019 (COVID-19). This article aims to discuss the pharmacotherapeutic considerations for the management of diabetes in hospitalized patients with COVID-19. We discussed various aspects of pharmacotherapeutic management in hospitalized patients with COVID-19: (i) susceptibility and severity of COVID-19 among individuals with diabetes, (ii) glycemic goals for hospitalized patients with COVID-19 and concurrent diabetes, (iii) pharmacological treatment considerations for hospitalized patients with COVID-19 and concurrent diabetes. The glycemic goals in patients with COVID-19 and concurrent type 1 (T1DM) or type 2 diabetes (T2DM) are to avoid disruption of stable metabolic state, maintain optimal glycemic control, and prevent adverse glycemic events. Patients with T1DM require insulin therapy at all times to prevent ketosis. The management strategies for patients with T2DM include temporary discontinuation of certain oral antidiabetic agents and consideration for insulin therapy. Patients with T2DM who are relatively stable and able to eat regularly may continue with oral antidiabetic agents if glycemic control is satisfactory. Hyperglycemia may develop in patients with systemic corticosteroid treatment and should be managed upon accordingly.	

2020	Fasting Blood Glucose and COVID-19 Severity: Nonlinearity Matters.	Fasting blood glucose (FBG) could be an independent predictor for coronavirus disease 2019 (COVID-19) morbidity and mortality. However, when included as a predictor in a model, it is conventionally modeled linearly, dichotomously, or categorically. We comprehensively examined different ways of modeling FBG to assess the risk of being admitted to the intensive care unit (ICU). Utilizing COVID-19 data from Kuwait, we fitted conventional approaches to modeling FBG as well as a nonlinear estimation using penalized splines. For 417 patients, the conventional linear, dichotomous, and categorical approaches to modeling FBG missed key trends in the exposure-response relationship. A nonlinear estimation showed a steep slope until about 10 mmol/L before flattening. Our results argue for strict glucose management on admission. Even a small incremental increase within the normal range of FBG was associated with a substantial increase in risk of ICU admission for COVID-19 patients.	
2020	Validation and clinical evaluation of a SARS-CoV-2 surrogate virus neutralisation test (sVNT).	To understand SARS-CoV-2 immunity after natural infection or vaccination, functional assays such as virus neutralising assays are needed. So far, assays to detect SARS-CoV-2 neutralising antibodies rely on cell-culture based infection assays either using wild type SARS-CoV-2 or pseudotyped viruses. Such assays are labour-intensive, require appropriate biosafety facilities and are difficult to standardize. Recently, a new surrogate virus neutralisation test (sVNT) was described that uses the principle of an ELISA to measure the neutralisation capacity of anti-SARS-CoV-2 antibodies directed against the receptor binding domain. Here, we performed an independent evaluation of the robustness, specificity and sensitivity on an extensive panel of sera from 269 PCR-confirmed COVID-19 cases and 259 unmatched samples collected before 2020 and compared it to cell-based neutralisation assays. We found a high specificity of 99.2 (95%CI: 96.9-99.9) and overall sensitivity of 80.3 (95%CI: 74.9-84.8) for the sVNT. Clinical sensitivity increased between early (<14 days post symptom onset or post diagnosis, dpos/dpd) and late sera (>14 dpos/dpd) from 75.0 (64.7-83.2) to 83.1 (76.5-88.1). Also, higher severity was associated with an increase in clinical sensitivity. Upon comparison with cell-based neutralisation assays we determined an analytical sensitivity of 74.3 (56.4-86.9) and 98.2 (89.4-99.9) for titres ≥10 to <40 and ≥40 to <160, respectively. Only samples with a titre ≥160 were always positive in the sVNT. In conclusion, the sVNT can be used as an additional assay to determine the immune status of COVID-19 infected of vaccinated individuals but its value needs to be assessed for each specific context.	

2020	Interleukin-6 role in the severity of COVID-19 and intensive care unit stay length.	Evaluation of cytokine production in COVIID-19 disease, in which the cytokine storm is one of the most important pathological features in complicated cases, especially interleukin 6 as a pre-inflammatory cytokine that exacerbates the immune response, could help determine the pathophysiology of the disease. Examining the level of this cytokine along with other related factors can help to better understand the pathogenesis of this disease. In this cross-sectional study, 48 patients with COVID-19 whose disease was confirmed by swap testing were evaluated. The demographic information of the individuals, the symptoms of the disease, and the ward in which they were admitted were recorded. Blood samples were taken from patients to test for interleukin-6 levels by electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics). Due to the lack of specific treatment protocols for patients and the use of supportive treatments based on meeting the nutritional needs for all patients, blood albumin levels and nutritional status of patients were also evaluated using Subjective Global Assessment (SGA) Form. Their calorie intake was assessed by calculating the number of calories received based on the type of nutrition and compared to the required amount calculated through the Harris-Benedict equation. 48 laboratory-confirmed 2019-nCoV infected patients were included in the study with the mean age of 46.4 ± 8.3 years. 21 patients were admitted to the intensive care unit (ICU). There was no significant difference between the ICU admitted and patients admitted inward in terms of demographic characteristics, and history of previous diseases (p > 0.05). The average interleukin 6 (IL-6) in patients was 72.3±34.4 pg/ml. ICU admitted patients had higher IL6 levels (p=0.001). The mean interleukin 6 level was 89.04±34.1 pg/ml in patients admitted for less than 7 days and it was significantly higher (119.2±28.3) in patients hospitalized for more than 7 days (p=0.001). there was no significant difference in terms of nutritional status and albumin level between ICU admitted and ward admitted patients (p >0.05). Our study shows that there may be possible associations of IL6 and disease severity and ICU stay length.	
2020	Elevated fasting blood glucose within the first week of hospitalization was associated with progression to severe illness of COVID-19 in patients with preexisting diabetes: A multicenter observational study.	Highlights Fasting blood glucose < 10 mmol/L was proposed as a target of glycemic control during the first week of hospitalization in patients with preexisting diabetes. Poor HbA1c levels prior to coronavirus disease 2019 (COVID-19) might not be associated with severity among patients with preexisting diabetes. Mean blood glucose seemed not to be associated with poor prognosis of COVID-19.	

2020	Children and Adolescents With SARS-CoV-2 Infection: Epidemiology, Clinical Course and Viral Loads.	There is limited information on severe acute respiratory syndrome virus 2 (SARS-CoV-2) infection in children. We retrieved data from the national database on SARS-CoV-2 infections. We studied in-family transmission. The level of viral load was categorized as high, moderate, or low based on the cycle threshold values. We studied 203 SARS-CoV-2-infected children (median age: 11 years; range: 6 days to 18.4 years); 111 (54.7%) had an asymptomatic infection. Among the 92 children (45.3%) with coronavirus disease 2019 (COVID-19), 24 (26.1%) were hospitalized. Infants <1 year were more likely to develop COVID-19 (19.5% of all COVID-19 cases) (P-value = 0.001). There was no significant difference between viral load and age, sex, underlying condition, fever and hospitalization, as well as between type of SARS-CoV-2 infection and age, sex, underlying condition and viral load. Transmission from a household member accounted for 132 of 178 (74.2%) children for whom the source of infection was identified. An adult member with COVID-19 was the first case in 125 (66.8%) family clusters. Child-to-adult transmission was found in one occasion only. SARS-CoV-2 infection is mainly asymptomatic or mild during childhood. Adults appear to play a key role in spread of the virus in families. Most children have moderate or high viral loads regardless of age, symptoms or severity of infection. Further studies are needed to elucidate the role of children in the ongoing pandemic and particularly in light of schools reopening and the need to prioritize groups for vaccination, when COVID-19 vaccines will be available.	
2020	Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults.	Testing of vaccine candidates to prevent infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in an older population is important, since increased incidences of illness and death from coronavirus disease 2019 (Covid-19) have been associated with an older age. We conducted a phase 1, dose-escalation, open-label trial of a messenger RNA vaccine, mRNA-1273, which encodes the stabilized prefusion SARS-CoV-2 spike protein (S-2P) in healthy adults. The trial was expanded to include 40 older adults, who were stratified according to age (56 to 70 years or ≥71 years). All the participants were assigned sequentially to receive two doses of either 25 μg or 100 μg of vaccine administered 28 days apart. Solicited adverse events were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site. Such adverse events were dose-dependent and were more common after the second immunization. Binding-antibody responses increased rapidly after the first immunization. By day 57, among the participants who received the 25-μg dose, the anti-S-2P geometric mean titer (GMT) was 323,945 among those between the ages of 56 and 70 years and 1,128,391 among those who were 71 years of age or older; among the participants who received the 100-μg dose, the GMT in the two age subgroups was 1,183,066 and 3,638,522, respectively. After the second immunization, serum neutralizing activity was detected in all the participants by multiple methods. Binding- and neutralizing-antibody responses appeared to be similar to those previously reported among vaccine recipients between the ages of 18 and 55 years and were above the median of a panel of controls who had donated convalescent serum. The vaccine elicited a strong CD4 cytokine response involving type 1 helper T cells. In this small study involving older adults, adverse events associated with the mRNA-1273 vaccine were mainly mild or moderate. The 100-μg dose induced higher binding- and neutralizing-antibody titers than the 25-μg dose, which supports the use of the 100-μg dose in a phase 3 vaccine trial. (Funded by the National Institute of Allergy and	

		Infectious Diseases and others; mRNA-1273 Study ClinicalTrials.gov number, NCT04283461.).	
2020	Clinical and Proteomic Correlates of Plasma ACE2 (Angiotensin-Converting Enzyme 2) in Human Heart Failure.	ACE2 (angiotensin-converting enzyme 2) is a key component of the renin-angiotensin-aldosterone system. Yet, little is known about the clinical and biologic correlates of circulating ACE2 levels in humans. We assessed the clinical and proteomic correlates of plasma (soluble) ACE2 protein levels in human heart failure. We measured plasma ACE2 using a modified aptamer assay among PHFS (Penn Heart Failure Study) participants (n=2248). We performed an association study of ACE2 against ≈5000 other plasma proteins measured with the SomaScan platform. Plasma ACE2 was not associated with ACE inhibitor and angiotensin-receptor blocker use. Plasma ACE2 was associated with older age, male sex, diabetes mellitus, a lower estimated glomerular filtration rate, worse New York Heart Association class, a history of coronary artery bypass surgery, and higher pro-BNP (pro-B-type natriuretic peptide) levels. Plasma ACE2 exhibited associations with 1011 other plasma proteins. In pathway overrepresentation analyses, top canonical pathways associated with plasma ACE2 included clathrin-mediated endocytosis signaling, actin cytoskeleton signaling, mechanisms of viral exit from host cells, EIF2 (eukaryotic initiation factor 2) signaling, and the protein ubiquitination pathway. In conclusion, in humans with heart failure, plasma ACE2 is associated with various clinical factors known to be associated with severe coronavirus disease 2019 (COVID-19), including older age, male sex, and diabetes mellitus, but is not associated with ACE inhibitor and angiotensin-receptor blocker use. Plasma ACE2 protein levels are prominently associated with multiple cellular pathways involved in cellular endocytosis, exocytosis, and intracellular protein trafficking. Whether these have a causal relationship with ACE2 or are relevant to novel coronavirus-2 infection remains to be assessed in future studies.	

2020	Elevated plasma sTIM-3 levels in patients with severe COVID-19.	The pathogenesis of coronavirus disease 2019 (COVID-19) is still incompletely understood, but it seems to involve immune activation and immune dysregulation. We examined the parameters of activation of different leukocyte subsets in COVID-19-infected patients in relation to disease severity. We analyzed plasma levels of myeloperoxidase (a marker of neutrophil activation), soluble (s) CD25 (sCD25) and soluble T-cell immunoglobulin mucin domain-3 (sTIM-3) (markers of T-cell activation and exhaustion), and sCD14 and sCD163 (markers of monocyte/macrophage activation) in 39 COVID-19-infected patients at hospital admission and 2 additional times during the first 10 days in relation to their need for intensive care unit (ICU) treatment. Our major findings were as follows: (1) severe clinical outcome (ICU treatment) was associated with high plasma levels of sTIM-3 and myeloperoxidase, suggesting activated and potentially exhausted T cells and activated neutrophils, respectively; (2) in contrast, sCD14 and sCD163 showed no association with need for ICU treatment; and (3) levels of sCD25, sTIM-3, and myeloperoxidase were inversely correlated with degree of respiratory failure, as assessed by the ratio of Pao 2 to fraction of inspired oxygen, and were positively correlated with the cardiac marker N-terminal pro-B-type natriuretic peptide. Our findings suggest that neutrophil activation and, in particular, activated T cells may play an important role in the pathogenesis of COVID-19 infection, suggesting that T-cell-targeted treatment options and downregulation of neutrophil activation could be of importance in this disorder.	
2020	Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines.	Coronavirus disease 2019 (COVID-19) has swept the world, unlike any other pandemic in the last 50 years. Our understanding of the disease has evolved rapidly since the outbreak; disease prognosis is influenced mainly by multi-organ involvement. Acute respiratory distress syndrome, heart failure, renal failure, liver damage, shock and multi-organ failure are strongly associated with morbidity and mortality. The COVID-19 disease pathology is plausibly linked to the hyperinflammatory response of the body characterized by pathological cytokine levels. The term 'cytokine storm syndrome' is perhaps one of the critical hallmarks of COVID-19 disease severity. In this review, we highlight prominent cytokine families and their potential role in COVID-19, the type I and II interferons, tumour necrosis factor and members of the Interleukin family. We address various changes in cellular components of the immune response corroborating with changes in cytokine levels while discussing cytokine sources and biological functions. Finally, we discuss in brief potential therapies attempting to modulate the cytokine storm.	

2020	Risk of Metformin in Patients With Type 2 Diabetes With COVID-19: A Preliminary Retrospective Report.	The current outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread across the world. No specific antiviral agents have been adequately evidenced for the treatment of coronavirus disease 2019 (COVID-19). Although metformin has been recommended as a host-directed therapy for COVID-19, there are some opposite views. The effects of metformin on the disease severity of patients with COVID-19 with diabetes during hospitalization remains unclear. This study aimed to determine the effect of metformin on disease severity. We enrolled 110 hospitalized patients with COVID-19 with diabetes prescribed either metformin or non-metformin hypoglycemic treatment for a case-control study. The primary outcome was the occurrence of life-threatening complications. There were no differences between the two groups in age, sex, comorbidities, and clinical severity at admission. Blood glucose and lactate dehydrogenase levels of the metformin group were higher than those of the non-metformin group at admission. Other laboratory parameters at admission and treatments after admission were not different between the two groups. Strikingly, the percentage of patients who experienced life-threatening complications was significantly higher in the metformin group (28.6% (16/56) vs. 7.4% (4/54), P = 0.004). Antidiabetic therapy with metformin was associated with a higher risk of disease progression in patients with COVID-19 with diabetes during hospitalization (adjusted odds ratio = 3.964, 95% confidence interval 1.034-15.194, P = 0.045). This retrospective analysis suggested a potential safety signal for metformin, the use of which was associated with a higher risk of severe COVID-19. We propose that metformin withdrawal in patients with COVID-19 be considered to prevent disease progression.	
2020	Clinical considerations in patients with diabetes during times of COVID19: An update on lifestyle factors and antihyperglycemic drugs with focus on India.	Diabetes is recognized as an important comorbidity in patients with COVID-19 and a large amount of literature has become available regarding this. The aim of this article is to review the literature regarding various aspects of association between diabetes and COVID-19 and to highlight clinically relevant points with focus on India. We searched Pubmed and Google Scholar databases for articles regarding diabetes and COVID-19 published between March 19, 2020 and August 30, 2020. Diabetes and poor glycemic control are associated with increased severity and mortality in patients with COVID-19. Several clinical scenarios about hyperglycemia and COVID-19 are identified and each of these needs specific management strategies. It is prudent to maintain good glycemic control in patients with diabetes in order to minimize the complications of COVID-19. There is a need for well conducted studies to asses the role of individual antihyperglycemic therapies in COVID-19 and also the behavior of new onset diabetes diagnosed either after COVID-19 infection or during this time.	

2020	Impact of Vitamin D Deficiency on COVID-19-A Prospective Analysis from the CovILD Registry.	The novel Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is a global health concern. Vitamin D (VITD) deficiency has been suggested to alter SARS-CoV-2 susceptibility and the course of disease. Thus, we aimed to investigate associations of VITD status to disease presentation within the CovILD registry. This prospective, multicenter, observational study on long-term sequelae includes patients with COVID-19 after hospitalization or outpatients with persistent symptoms. Eight weeks after PCR confirmed diagnosis, a detailed questionnaire, a clinical examination, and laboratory testing, including VITD status, were evaluated. Furthermore, available laboratory specimens close to hospital admission were used to retrospectively analyze 25-hydroxyvitamin D levels at disease onset. A total of 109 patients were included in the analysis (60% males, 40% females), aged 58 ± 14 years. Eight weeks after the onset of COVID-19, a high proportion of patients presented with impaired VITD metabolism and elevated parathyroid hormone (PTH) levels. PTH concentrations were increased in patients who needed intensive care unit (ICU) treatment, while VITD levels were not significantly different between disease severity groups. Low VITD levels at disease onset or at eight-week follow-up were not related to persistent symptom burden, lung function impairment, ongoing inflammation, or more severe CT abnormalities. VITD deficiency is frequent among COVID-19 patients but not associated with disease outcomes. However, individuals with severe disease display a disturbed parathyroid-vitamin-D axis within their recovery phase. The proposed significance of VITD supplementation in the clinical management of COVID-19 remains elusive.	
2020	Cytokine release syndrome in COVID-19: Innate immune, vascular, and platelet pathogenic factors differ in severity of disease and sex.	COVID-19 rapidly emerged as a crippling public health crisis in the last few months, which has presented a series health risk. Understanding of the immune response and biomarker analysis is needed to progress toward understanding disease pathology and developing improved treatment options. The goal of this study is to identify pathogenic factors that are linked to disease severity and patient characteristics. Patients with COVID-19 who were hospitalized from March 17 to June 5, 2020 were analyzed for clinical features of disease and soluble plasma cytokines in association with disease severity and sex. Data from COVID-19 patients with acute illness were examined along with an age- and gender-matched control cohort. We identified a group of 16 soluble factors that were found to be increased in COVID-19 patients compared to controls, whereas 2 factors were decreased. In addition to inflammatory cytokines, we found significant increases in factors known to mediate vasculitis and vascular remodeling (PDGF-AA, PDGF-AB-BB, soluble CD40L (sCD40L), FGF, and IP10). Four factors such as platelet-derived growth factors, fibroblast growth factor-2, and IFN-γ-inducible protein 10 were strongly associated with severe disease and ICU admission. Th2-related factors (IL-4 and IL-13) were increased with IL-4 and sCD40L present at increased levels in males compared with females. Our analysis revealed networking clusters of cytokines and growth factors, including previously unknown roles of vascular and stromal remodeling, activation of the innate immunity, as well activation of type 2 immune responses in the immunopathogenesis of COVID-19. These data highlight biomarker associations with disease severity and sex in COVID-19 patients.	

2020	Prevalence, clinical manifestations, and biochemical data of type 2 diabetes mellitus versus nondiabetic symptomatic patients with COVID-19: A comparative study.	There is a scarcity of data regarding the effect of Type 2 diabetes mellitus (T2DM) and associated comorbidities on the clinical presentation and outcome of symptomatic patients with -COVID-19 infection in comparison with non-diabetic patients. We described and compared the clinical presentation and radiological and hematological data of a cohort of symptomatic COVID19 positive T2DM diabetic patients (n = 59) versus another cohort of non-diabetic symptomatic COVID19 positive patients (n =244) diagnosed at the same time from January 2020 to May 2020. Associated comorbidities were -assessed, and the Charlson Comorbidity Index was calculated. The outcomes including duration of hospitalization, duration of Intensive Care Unit (ICU) stay, duration of mechanical ventilation, and duration of O2 -supplementation were assessed. Prevalence of T2DM in symptomatic COVID19 positive patients was 59/303 (=19.5%). Diabetic patients had higher prevalence of hypertension, chronic kidney disease (CKD) and cardiac dysfunction [coronary heart disease (CHD)], and congestive heart failure (CHF). Charlson Comorbidity score was significantly higher in the T2DM patients (2.4± 1.6) versus the non-diabetic -patients (0.28 ± 0.8; p: < 0.001). Clinically and radiologically, T2DM patients had significantly higher percentage of pneumonia, severe pneumonia and ARDS versus the non-diabetic patients. Hematologically, diabetic patients had significantly higher C-reactive protein (CRP), higher absolute neutrophilic count (ANC) and lower counts of lymphocytes and eosinophils compared to non-diabetic patients. They had significantly higher systolic and diastolic blood pressures, longer duration of hospitalization, ICU stay, mechanical ventilation and oxygen therapy. CRP was correlated significantly with the duration of stay in the ICU and the duration for oxygen supplementation (r = 0.37 and 0.42 respectively; p: <0.01). T2DM patients showed higher inflammatory response to COVID 19 with higher absolute neutrophilic count (ANC) and CRP with lower lymphocytic and eosinophilic counts. Diabetic patients had more comorbidities and more aggressive course of the disease with higher rate of ICU admission and longer need for hospitalization and oxygen use.	

2020	Genetic Hypothesis and Pharmacogenetics Side of Renin-Angiotensin-System in COVID-19.	The importance of host genetics and demography in coronavirus disease 2019 (COVID-19) is a crucial aspect of infection, prognosis and associated case fatality rate. Individual genetic landscapes can contribute to understand Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) burden and can give information on how to fight virus spreading and the associated severe acute respiratory distress syndrome (ARDS). The spread and pathogenicity of the virus have become pandemic on specific geographic areas and ethnicities. Interestingly, SARS-CoV-2 firstly emerged in East Asia and next in Europe, where it has caused higher morbidity and mortality. This is a peculiar feature of SARS-CoV-2, different from past global viral infections (i.e., SARS-1 or MERS); it shares with the previous pandemics strong age- and sex-dependent gaps in the disease outcome. The observation that the severest COVID-19 patients are more likely to have a history of hypertension, diabetes and/or cardiovascular disease and receive Renin-Angiotensin-System (RAS) inhibitor treatment raised the hypothesis that RAS-unbalancing may have a crucial role. Accordingly, we recently published a genetic hypothesis on the role of RAS-pathway genes (ACE1 , rs4646994, rs1799752, rs4340, rs13447447; and ACE2 , rs2285666, rs1978124, rs714205) and ABO -locus (rs495828, rs8176746) in COVID-19 prognosis, suspecting inherited genetic predispositions to be predictive of COVID-19 severity. In addition, recently, Genome-Wide Association Studies (GWAS) found COVID-19-association signals at locus 3p21.31 (rs11385942) comprising the solute carrier SLC6A20 (Na+ and Cl- coupled transporter family) and at locus 9q34.2 (rs657152) coincident with ABO -blood group (rs8176747, rs41302905, rs8176719), and interestingly, both loci are associated to RAS-pathway. Finally, ACE1 and ACE2 haplotypes seem to provide plausible explanations for why SARS-CoV-2 have affected more heavily some ethnic groups, namely people with European ancestry, than Asians.	
2020	Phenotypical and functional alteration of unconventional T cells in severe COVID-19 patients.	COVID-19 includes lung infection ranging from mild pneumonia to life-threatening acute respiratory distress syndrome (ARDS). Dysregulated host immune response in the lung is a key feature in ARDS pathophysiology. However, cellular actors involved in COVID-19-driven ARDS are poorly understood. Here, in blood and airways of severe COVID-19 patients, we serially analyzed unconventional T cells, a heterogeneous class of T lymphocytes (MAIT, γδT, and iNKT cells) with potent antimicrobial and regulatory functions. Circulating unconventional T cells of COVID-19 patients presented with a profound and persistent phenotypic alteration. In the airways, highly activated unconventional T cells were detected, suggesting a potential contribution in the regulation of local inflammation. Finally, expression of the CD69 activation marker on blood iNKT and MAIT cells of COVID-19 patients on admission was predictive of clinical course and disease severity. Thus, COVID-19 patients present with an altered unconventional T cell biology, and further investigations will be required to precisely assess their functions during SARS-CoV-2-driven ARDS.	

2020	Antibody response and the clinical presentation of patients with COVID-19 in Croatia: the importance of a two-step testing approach.	According to anti-SARS-CoV-2 seroresponse in patients with COVID-19 from Croatia, we emphasised the issue of different serological tests and need for combining diagnostic methods for COVID-19 diagnosis. Anti-SARS-CoV-2 IgA and IgG ELISA and IgM/IgG immunochromatographic assay (ICA) were used for testing 60 sera from 21 patients (6 with severe, 10 moderate, and 5 with mild disease). The main clinical, demographic, and haemato-biochemical data were analysed. The most common symptoms were cough (95.2%), fever (90.5%), and fatigue and shortness of breath (42.9%). Pulmonary opacities showed 76.2% of patients. Within the first 7 days of illness, seropositivity for ELISA IgA and IgG was 42.9% and 7.1%, and for ICA IgM and IgG 25% and 10.7%, respectively. From day 8 after onset, ELISA IgA and IgG seropositivity was 90.6% and 68.8%, and for ICA IgM and IgG 84.4% and 75%, respectively. In general, sensitivity for ELISA IgA and IgG was 68.3% and 40%, and for ICA IgM and IgG 56.7% and 45.0%, respectively. The anti-SARS-CoV-2 antibody distributions by each method were statistically different (ICA IgM vs. IgG, $p = 0.016$; ELISA IgG vs. IgA, $p < 0.001$). Antibody response in COVID-19 varies and depends on the time the serum is taken, on the severity of disease, and on the type of test used. IgM and IgA antibodies as early-stage disease markers are comparable, although they cannot replace each other. Simultaneous IgM/IgG/IgA anti-SARS-CoV-2 antibody testing followed by the confirmation of positive findings with another test in a two-tier testing is recommended.	
2020	Age and Location in Severity of COVID-19 Pathology: Do Lactoferrin and Pneumococcal Vaccination Explain Low Infant Mortality and Regional Differences?	Two conundrums puzzle COVID-19 investigators: 1) morbidity and mortality is rare among infants and young children and 2) rates of morbidity and mortality exhibit large variances across nations, locales, and even within cities. It is found that the higher the rate of pneumococcal vaccination in a nation (or city) the lower the COVID-19 morbidity and mortality. Vaccination rates with Bacillus Calmette-Guerin, poliovirus, and other vaccines do not correlate with COVID-19 risks, nor do COVID-19 case or death rates correlate with number of people in the population with diabetes, obesity, or adults over 65. Infant protection may be due to maternal antibodies and antiviral proteins in milk such as lactoferrin that are known to protect against coronavirus infections. Subsequent protection might then be conferred (and correlate with) rates of Haemophilus influenzae type B (Hib) (universal in infants) and pneumococcal vaccination, the latter varying widely by geography among infants, at-risk adults, and the elderly. Also see the video abstract here https://youtu.be/GODBYRbPL00.	

2020	Current Use of Cardiac Biomarkers in Various Heart Conditions.	Biomarkers are increasingly recognized to have significant clinical value in early identification and progression of various cardiovascular diseases. There are many heart conditions, such as congestive heart failure (CHF), ischemic heart diseases (IHD), and diabetic cardiomyopathy (DCM), and cardiac remodeling, in which the severity of the cardiac pathology can be mirrored through these cardiac biomarkers. From the emergency department (ED) evaluation of acute coronary syndromes (ACS) or suspected acute myocardial infarction (AMI) with cardiac marker Troponin to the diagnosis of chronic conditions like Heart Failure (HF) with natriuretic peptides, like B-type natriuretic peptide (BNP), N-terminal pro-B- type natriuretic peptide (Nt-proBNP) and mid regional pro-atrial natriuretic peptide (MR-proANP), their use is continuously increasing. Their clinical importance has led to the discovery of newer biomarkers, such as the soluble source of tumorigenicity 2 (sST2), galectin-3 (Gal-3), growth differentiation factor-15 (GDF-15), and various micro ribonucleic acids (miRNAs). Since cardiac pathophysiology involves a complex interplay between inflammatory, genetic, neurohormonal, and biochemical levels, these biomarkers could be enzymes, hormones, and biologic substances showing cardiac injury, stress, and malfunction. Therefore, multi-marker approaches with different combinations of novel cardiac biomarkers, and continual assessment of cardiac biomarkers are likely to improve cardiac risk prediction, stratification, and overall patient wellbeing. On the other hand, these biomarkers may reflect coexisting or isolated disease processes in different organ systems other than the cardiovascular system. Therefore, knowledge of cardiac biomarkers is imperative. In this article, we have reviewed the role of cardiac biomarkers and their use in the diagnosis and prognosis of various cardiovascular diseases from different investigations conducted in recent years.	
2020	The role of neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio in the prognosis of type 2 diabetics with COVID-19.	To assess the prognostic value of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio and red cell distribution width in type 2 diabetics with COVID-19. We collected the data of type 2 diabetics with COVID-19 treated in our hospital from January 28 to March 15, 2020 and performed a retrospective analysis. Using severity, duration of hospital stay, and the time required for nucleic acid results became negative as prognostic indicators, we explored the relationship between these inflammation-based markers and prognosis of type 2 diabetics with COVID-19. A total of 134 type 2 diabetics with COVID-19 were selected for this study. Correlation analysis showed that NLR, LMR and RDW were correlated with prognosis ($P < 0.05$). In multivariate regression analysis after controlling for the relevant confounding factors, COVID-19 diabetes patients with higher NLR had heavier severity, longer duration of hospital stay, more time required for nucleic acid results became negative, and heavier hospital expenses ($P < 0.05$). ROC curve result displayed that higher NLR predicted all prognostic indicators with statistical significance, and lower LMR predicted severe and extremely severe with statistical significance ($P < 0.05$). NLR is a more powerful and practical marker for predicting the prognosis of type 2 diabetic COVID-19 patients that is simple and fast.	

2020	Prevalence of phenotypes of acute respiratory distress syndrome in critically ill patients with COVID-19: a prospective observational study.	In acute respiratory distress syndrome (ARDS) unrelated to COVID-19, two phenotypes, based on the severity of systemic inflammation (hyperinflammatory and hypoinflammatory), have been described. The hyperinflammatory phenotype is known to be associated with increased multiorgan failure and mortality. In this study, we aimed to identify these phenotypes in COVID-19-related ARDS. In this prospective observational study done at two UK intensive care units, we recruited patients with ARDS due to COVID-19. Demographic, clinical, and laboratory data were collected at baseline. Plasma samples were analysed for interleukin-6 (IL-6) and soluble tumour necrosis factor receptor superfamily member 1A (TNFR1) using a novel point-of-care assay. A parsimonious regression classifier model was used to calculate the probability for the hyperinflammatory phenotype in COVID-19 using IL-6, soluble TNFR1, and bicarbonate levels. Data from this cohort was compared with patients with ARDS due to causes other than COVID-19 recruited to a previous UK multicentre, randomised controlled trial of simvastatin (HARP-2). Between March 17 and April 25, 2020, 39 patients were recruited to the study. Median ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air (PaO 2 /FiO 2) was 18 kpa (IQR 15-21) and acute physiology and chronic health evaluation II score was 12 (10-16). 17 (44%) of 39 patients had died by day 28 of the study. Compared with survivors, patients who died were older and had lower PaO 2 /FiO 2 . The median probability for the hyperinflammatory phenotype was 0·03 (IQR 0·01-0·2). Depending on the probability cutoff used to assign class, the prevalence of the hyperinflammatory phenotype was between four (10%) and eight (21%) of 39, which is lower than the proportion of patients with the hyperinflammatory phenotype in HARP-2 (186 [35%] of 539). Using the Youden index cutoff (0·274) to classify phenotype, five (63%) of eight patients with the hyperinflammatory phenotype and 12 (39%) of 31 with the hypoinflammatory phenotype died. Compared with matched patients recruited to HARP-2, levels of IL-6 were similar in our cohort, whereas soluble TNFR1 was significantly lower in patients with COVID-19-associated ARDS. In this exploratory analysis of 39 patients, ARDS due to COVID-19 was not associated with higher systemic inflammation and was associated with a lower prevalence of the hyperinflammatory phenotype than that observed in historical ARDS data. This finding suggests that the excess mortality observed in COVID-19-related ARDS is unlikely to be due to the upregulation of inflammatory pathways described by the parsimonious model. US National Institutes of Health, Innovate UK, and Randox.	

2020	Blood use and transfusion needs at a large health care system in Washington state during the SARS-CoV-2 pandemic.	This report evaluates hospital blood use trends during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, and identifies factors associated with the need for transfusion and risk of death in patients with coronavirus 2019 (COVID-19). Overall hospital blood use and medical records of adult patients with COVID-19 were extracted for two institutions. Multivariate logistic regression models were conducted to estimate associations between the outcomes transfusion and mortality and patient factors. Daily blood use decreased compared to pre-COVID-19 levels; the effect was more significant for platelets (29% and 34%) compared to red blood cells (25% and 20%) at the two institutions, respectively. Surgical and oncologic services had a decrease in average daily use of platelets of 52% and 30%, and red blood cells of 39% and 25%, respectively. A total of 128 patients with COVID-19 were hospitalized, and 13 (10%) received at least one transfusion due to anemia secondary to chronic illness (n = 7), recent surgery (n = 3), and extracorporeal membrane oxygenation (n = 3). Lower baseline platelet count and admission to the intensive care unit were associated with increased risk of transfusion. The blood group distribution in patients with COVID-19 was 37% group O, 40% group A, 18% group B, and 5% group AB. Non-type O was not associated with increased risk of mortality. The response to the SARS-CoV-2 pandemic included changes in routine hospital operations that allowed for the provision of a sufficient level of care for patients with and without COVID-19. Although blood type may play a role in COVID-19 susceptibility, it did not seem to be associated with patient mortality.	
2020	Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes.	Poor outcomes of coronavirus disease 2019 (COVID-19) have been linked to diabetes, but its relation to pre-infection glycaemic control is still unclear. To address this question, we report here the association between pre-infection Haemoglobin A1c (HbA1c) levels and COVID-19 severity as assessed by need for hospitalization in a cohort of 2068 patients with diabetes tested for COVID-19 in Leumit Health Services (LHSs), Israel, between 1 February and 30 April 2020. Using the LHS-integrated electronic medical records system, we were able to collect a large amount of clinical information including age, sex, socio-economic status, weight, height, body mass index, HbA1c, prior diagnosis of ischaemic heart disease, depression/anxiety, schizophrenia, dementia, hypertension, cerebrovascular accident, congestive heart failure, smoking, and chronic lung disease. Of the patients included in the cohort, 183 (8.85%) were diagnosed with COVID-19 and 46 were admitted to hospital. More hospitalized patients were female, came from higher socio-economic background and had a higher baseline HbA1c. A prior diagnosis of cerebrovascular accident and chronic lung disease conferred an increased risk of hospitalization but not obesity or smoking status. In a multivariate analysis, controlling for multiple prior clinical conditions, the only parameter associated with a significantly increased risk for hospitalization was HbA1c $\geq$ 9%. Using pre-infection glycaemic control data, we identify HbA1c as a clear predictor of COVID-19 severity. Pre-infection risk stratification is crucial to successfully manage this disease, efficiently allocate resources, and minimize the economic and social burden associated with an undiscriminating approach.	

2020	Effects of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: an observational cohort study.	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants with a 382-nucleotide deletion (Δ382) in the open reading frame 8 (ORF8) region of the genome have been detected in Singapore and other countries. We investigated the effect of this deletion on the clinical features of infection. We retrospectively identified patients who had been screened for the Δ382 variant and recruited to the PROTECT study-a prospective observational cohort study conducted at seven public hospitals in Singapore. We collected clinical, laboratory, and radiological data from patients' electronic medical records and serial blood and respiratory samples taken during hospitalisation and after discharge. Individuals infected with the Δ382 variant were compared with those infected with wild-type SARS-CoV-2. Exact logistic regression was used to examine the association between the infection groups and the development of hypoxia requiring supplemental oxygen (an indicator of severe COVID-19, the primary endpoint). Follow-up for the study's primary endpoint is completed. Between Jan 22 and March 21, 2020, 278 patients with PCR-confirmed SARS-CoV-2 infection were screened for the Δ382 deletion and 131 were enrolled onto the study, of whom 92 (70%) were infected with the wild-type virus, ten (8%) had a mix of wild-type and Δ382-variant viruses, and 29 (22%) had only the Δ382 variant. Development of hypoxia requiring supplemental oxygen was less frequent in the Δ382 variant group (0 [0%] of 29 patients) than in the wild-type only group (26 [28%] of 92; absolute difference 28% [95% CI 14-28]). After adjusting for age and presence of comorbidities, infection with the Δ382 variant only was associated with lower odds of developing hypoxia requiring supplemental oxygen (adjusted odds ratio 0·07 [95% CI 0·00-0·48]) compared with infection with wild-type virus only. The Δ382 variant of SARS-CoV-2 seems to be associated with a milder infection. The observed clinical effects of deletions in ORF8 could have implications for the development of treatments and vaccines. National Medical Research Council Singapore.	
2020	Is Blood Type Associated with COVID-19 Severity?	Blood type purportedly influences susceptibility to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, but whether it affects severity of coronavirus disease 2019 (COVID-19) is unclear. Therefore, we examined the association of blood type and rhesus with hospitalization and disease severity among 428 COVID-19 patients diagnosed at the University of Cincinnati health system. In the sample, 50.2% of participants had the blood type O, 38.7% had the blood type A, 17.5% had the blood type B, and 3.5% had the blood type AB. In analysis adjusted for sociodemographic characteristics and comorbidities, the blood types A (OR: 0.90, 95% CI: 0.54, 1.50), B (OR: 0.93, 95% CI: 0.51, 1.69), AB (OR: 0.69, 95% CI: 0.20, 2.41), and O (OR: 1.18, 95%: 0.74, 1.98) were not associated with hospitalization for COVID-19. Similarly, the blood types A (OR: 0.93, 95% CI: 0.52, 1.65), B (OR: 0.92, 95% CI: 0.46, 1.84), AB (OR: 0.30, 95% CI: 0.04, 2.44), and O (OR: 1.25, 95%: 0.73, 2.14) were not associated with admission to intensive care unit or death in COVID-19. In conclusion, blood type is not associated with hospitalization or disease severity in COVID-19; therefore, it may not be useful marker for identifying patients at risk for severe COVID-19.	

2020	Elevated Calprotectin and Abnormal Myeloid Cell Subsets Discriminate Severe from Mild COVID-19.	Blood myeloid cells are known to be dysregulated in coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2. It is unknown whether the innate myeloid response differs with disease severity and whether markers of innate immunity discriminate high-risk patients. Thus, we performed high-dimensional flow cytometry and single-cell RNA sequencing of COVID-19 patient peripheral blood cells and detected disappearance of non-classical CD14 Low CD16 High monocytes, accumulation of HLA-DR Low classical monocytes (Human Leukocyte Antigen - DR isotype), and release of massive amounts of calprotectin (S100A8/S100A9) in severe cases. Immature CD10 Low CD101 - CXCR4 +/- neutrophils with an immunosuppressive profile accumulated in the blood and lungs, suggesting emergency myelopoiesis. Finally, we show that calprotectin plasma level and a routine flow cytometry assay detecting decreased frequencies of non-classical monocytes could discriminate patients who develop a severe form of COVID-19, suggesting a predictive value that deserves prospective evaluation.	
2020	The Predictive Effectiveness of Blood Biochemical Indexes for the Severity of COVID-19.	We aimed to explore the predictive effectiveness of blood biochemical indexes for COVID-19 severity. We retrospectively analyzed the clinical data of COVID-19 patients who were cured and discharged from the Public Health Treatment Center of Changsha from January 30, 2020, to February 19, 2020. According to the clinical classification of the disease, the patients were divided into severe and nonsevere groups. General clinical data and underlying medical conditions were recorded through the electronic medical record (EMR) system. Laboratory examination results of the patients during their hospitalization were collected, including the first results for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), peripheral blood lymphocyte ratio and count, and peripheral blood white blood cell (WBC) count. Univariate and multivariate logistic regression models were used to analyze the predictive effectiveness of blood biochemical indexes and other related factors for COVID-19 severity. In all, 108 COVID-19 patients (median age: 43.9 years (range: 1-75); male patients: 56 (51.85%)) were enrolled, of whom 24 (22.22%) showed severe disease and 84 (77.78%) showed nonsevere disease, and two in 24 patients with severe disease developed into a critically severe type and died. Fever was the most common onset symptom (67.59%), followed by cough (48.15%) and fatigue (37.04%). Comorbidities were important factors affecting the severity of COVID-19, and among the patients with severe disease, the proportion with comorbidities was 70.83%, and the proportion without comorbidities was 29.17%. The intergroup difference was significant ($P < 0.05$). In patients with CRP levels (mg/L) of ≤ 8, >8-≤ 20, >20-≤ 40, and >40, the proportions of those with severe and nonsevere disease were 0 to 32, 7 to 19, 6 to 23, and 11 to 10, respectively; the intergroup difference was significant ($P < 0.05$). The presence or absence of comorbidities and CRP elevation were independent significant predictors of COVID-19 severity, and hypertension was found as the most common comorbidity in patients with severe disease.	

2020	Gastrointestinal Bleeding in Patients With Coronavirus Disease 2019: A Matched Case-Control Study.	Although current literature has addressed gastrointestinal presentations including nausea, vomiting, diarrhea, abnormal liver chemistries, and hyperlipasemia as possible coronavirus disease 2019 (COVID-19) manifestations, the risk and type of gastrointestinal bleeding (GIB) in this population is not well characterized. This is a matched case-control (1:2) study with 41 cases of GIB (31 upper and 10 lower) in patients with COVID-19 and 82 matched controls of patients with COVID-19 without GIB. The primary objective was to characterize bleeding etiologies, and our secondary aim was to discuss outcomes and therapeutic approaches. There was no difference in the presenting symptoms of the cases and controls, and no difference in severity of COVID-19 manifestations ($P > 0.05$) was observed. Ten (32%) patients with upper GIB underwent esophagogastroduodenoscopy and 5 (50%) patients with lower GIBs underwent flexible sigmoidoscopy or colonoscopy. The most common upper and lower GIB etiologies were gastric or duodenal ulcers (80%) and rectal ulcers related to rectal tubes (60%), respectively. Four of the esophagogastroduodenoscopies resulted in therapeutic interventions, and the 3 patients with rectal ulcers were referred to colorectal surgery for rectal packing. Successful hemostasis was achieved in all 7 cases that required interventions. Transfusion requirements between patients who underwent endoscopic therapy and those who were conservatively managed were not significantly different. Anticoagulation and rectal tube usage trended toward being a risk factor for GIB, although it did not reach statistical significance. In COVID-19 patients with GIB, compared with matched controls of COVID-19 patients without GIB, there seemed to be no difference in initial presenting symptoms. Of those with upper and lower GIB, the most common etiology was peptic ulcer disease and rectal ulcers from rectal tubes, respectively. Conservative management seems to be a reasonable initial approach in managing these complex cases, but larger studies are needed to guide management.	
2020	COVID-19: Underlying Adipokine Storm and Angiotensin 1-7 Umbrella.	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third coronavirus leading to a global health outbreak. Despite the high mortality rates from SARS-CoV-1 and Middle-East respiratory syndrome (MERS)-CoV infections, which both sparked the interest of the scientific community, the underlying physiopathology of the SARS-CoV-2 infection, remains partially unclear. SARS-CoV-2 shares similar features with SARS-CoV-1, notably the use of the angiotensin conversion enzyme 2 (ACE2) as a receptor to enter the host cells. However, some features of the SARS-CoV-2 pandemic are unique. In this work, we focus on the association between obesity, metabolic syndrome, and type 2 diabetes on the one hand, and the severity of COVID-19 infection on the other, as it seems greater in these patients. We discuss how adipocyte dysfunction leads to a specific immune environment that predisposes obese patients to respiratory failure during COVID-19. We also hypothesize that an ACE2-cleaved protein, angiotensin 1-7, has a beneficial action on immune deregulation and that its low expression during the SARS-CoV-2 infection could explain the severity of infection. This introduces angiotensin 1-7 as a potential candidate of interest in therapeutic research on CoV infections.	

2020	Single-cell landscape of immunological responses in patients with COVID-19.	In coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the relationship between disease severity and the host immune response is not fully understood. Here we performed single-cell RNA sequencing in peripheral blood samples of 5 healthy donors and 13 patients with COVID-19, including moderate, severe and convalescent cases. Through determining the transcriptional profiles of immune cells, coupled with assembled T cell receptor and B cell receptor sequences, we analyzed the functional properties of immune cells. Most cell types in patients with COVID-19 showed a strong interferon-α response and an overall acute inflammatory response. Moreover, intensive expansion of highly cytotoxic effector T cell subsets, such as CD4 + effector-GNLY (granulysin), CD8 + effector-GNLY and NKT CD160, was associated with convalescence in moderate patients. In severe patients, the immune landscape featured a deranged interferon response, profound immune exhaustion with skewed T cell receptor repertoire and broad T cell expansion. These findings illustrate the dynamic nature of immune responses during disease progression.	
2020	Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans.	Coronavirus disease 2019 (COVID-19) represents a global crisis, yet major knowledge gaps remain about human immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We analyzed immune responses in 76 COVID-19 patients and 69 healthy individuals from Hong Kong and Atlanta, Georgia, United States. In the peripheral blood mononuclear cells (PBMCs) of COVID-19 patients, we observed reduced expression of human leukocyte antigen class DR (HLA-DR) and proinflammatory cytokines by myeloid cells as well as impaired mammalian target of rapamycin (mTOR) signaling and interferon-α (IFN-α) production by plasmacytoid dendritic cells. By contrast, we detected enhanced plasma levels of inflammatory mediators-including EN-RAGE, TNFSF14, and oncostatin M-which correlated with disease severity and increased bacterial products in plasma. Single-cell transcriptomics revealed a lack of type I IFNs, reduced HLA-DR in the myeloid cells of patients with severe COVID-19, and transient expression of IFN-stimulated genes. This was consistent with bulk PBMC transcriptomics and transient, low IFN-α levels in plasma during infection. These results reveal mechanisms and potential therapeutic targets for COVID-19.	

2020	[Correlation between hyponatremia and the severity of coronavirus disease 2019].	To investigate the correlation between hyponatremia and the severity of coronavirus disease 2019 (COVID-19). Clinical data of 12 patients with COVID-19 admitted to Shantou Central Hospital from January 23 to February 5 in 2020 were retrospectively analyzed, including gender, age, symptoms, lab test and clinical outcomes, to analyze the change trend of blood Na + level in the patients with COVID-19. Among the 12 patients with COVID-19, there were 8 males and 4 females with the mean age of (38.0±16.3) years old, most of them were admitted to the hospital with cough and/or fever. All patients had a positive nucleic acid test for 2019 novel coronavirus (2019-nCoV), and were discharged after clinical treatment with oxygen therapy, antiviral, antibacterial, anti-inflammatory, and nutritional support. All patients were of ordinary type when they were admitted to the hospital. Among them, 1 patient turned into a severe case during the course of the disease, and 1 patient showed a tendency to become severe case. It was found that 10 patients without severe conversion had an average blood Na + of (138.3±1.3) mmol/L at admission, and the lowest blood Na + during the course of disease was (135.9±3.1) mmol/L. However, 2 patients who became severe and had a tendency to become severe disease (Na + levels at admission were 140.0 mmol/L and 138.0 mmol/L, respectively) experienced hyponatremia during the course of the disease (the lowest blood Na + levels were 129.0 mmol/L and 122.0 mmol/L). Further analysis showed that the lower serum Na + level, the higher level of white blood cell count (WBC) and C-reactive protein (CRP), but serum Na + level was consistent with the change trend of lymphocytes, suggesting that hyponatremia was closely correlated with severe inflammation reaction. Serum Na + showed decreasing tendency during the development of COVID-19, and hyponatremia was closely related to the severity of COVID-19. It was necessary to pay great attention to the change trend of blood Na + level. However, further research was needed to obtain more reliable conclusions and explorer the pathophysiological mechanisms.	
2020	Blood type A associates with critical COVID-19 and death in a Swedish cohort.	NA	

2020	The differing pathophysiologies that underlie COVID-19-associated perniosis and thrombotic retiform purpura: a case series.	There are two distinctive acral manifestations of COVID-19 embodying disparate clinical phenotypes. One is perniosis occurring in mildly symptomatic patients, typically children and young adults; the second is the thrombotic retiform purpura of critically ill adults with COVID-19. To compare the clinical and pathological profiles of these two different cutaneous manifestations of COVID-19. We compared the light microscopic, phenotypic, cytokine and SARS-CoV-2 protein and RNA profiles of COVID-19-associated perniosis with that of thrombotic retiform purpura in critical patients with COVID-19. Biopsies of COVID-19-associated perniosis exhibited vasocentric and eccrinotropic T-cell- and monocyte-derived CD11c + , CD14 + and CD123 + dendritic cell infiltrates. Both COVID-associated and idiopathic perniosis showed striking expression of the type I interferon-inducible myxovirus resistance protein A (MXA), an established marker for type I interferon signalling in tissue. SARS-CoV-2 RNA, interleukin-6 and caspase 3 were minimally expressed and confined to mononuclear inflammatory cells. The biopsies from livedo/retiform purpura showed pauci-inflammatory vascular thrombosis without any MXA decoration. Blood vessels exhibited extensive complement deposition with endothelial cell localization of SARS-CoV-2 protein, interleukin-6 and caspase 3; SARS-CoV-2 RNA was not seen. COVID-19-associated perniosis represents a virally triggered exaggerated immune reaction with significant type I interferon signaling. This is important to SARS-CoV-2 eradication and has implications in regards to a more generalized highly inflammatory response. We hypothesize that in the thrombotic retiform purpura of critically ill patients with COVID-19, the vascular thrombosis in the skin and other organ systems is associated with a minimal interferon response. This allows excessive viral replication with release of viral proteins that localize to extrapulmonary endothelium and trigger extensive complement activation.	

2020	Clinical characteristics of patients with uremia undergoing maintenance hemodialysis complicated with COVID-19.	This study aimed to evaluate the onset characteristics of patients with uremia undergoing maintenance hemodialysis complicated with COVID-19, so as to improve the understanding, diagnosis, and treatment.26 cases were confirmed cases of COVID-19. Confirmed patients with COVID-19 undergoing maintenance hemodialysis in the blood purification center were recruited. The general data of patients, including age, sex, duration of dialysis, and basic diseases, were analyzed. The clinical features included fever, respiratory symptoms, and gastrointestinal symptoms. The items for laboratory tests included blood routine examination, liver function, C-reactive protein, procalcitonin, creatine kinase, creatine kinase-MB, markers of myocardial injury, B-type natriuretic peptide, D-dimer, and so forth. The imaging examinations referred mainly to computed tomography imaging findings of the lungs.Twenty-one cases were complicated with chronic basic diseases, such as hypertension or diabetes. In terms of clinical manifestations, 13 cases had fever, which was close to the number of cases without fever (13 cases). The respiratory symptoms included dry cough (19 cases), shortness of breath (9 cases), fatigue (11 cases), and so forth. Further, 15 patients had hypoxemia, indicating more severe patients. Sore throat (2 cases) was not significant, and a few patients reported gastrointestinal symptoms (3 cases). The results of blood routine examination showed decreased absolute lymphocyte count (0.7±0.4×10∼9/L), lower hemoglobin level (105.2±20 g/L), and normal absolute neutrophil count 4.2 (3.0, 5.9)×10∼9/L. Of the inflammatory indexes, procalcitonin was 0.69 (0.24, 2.73) ng/mL; C reactive protein was 17.2 (5.2, 181.6) mg/L, which was higher than normal. Blood biochemistry revealed lower albumin level (38.0±4.0 g/L) and higher troponin 0.11(0.035, 6.658) ng/mL and myoglobin levels (538.5±240.5 ng/mL), suggesting myocardial injury.The patients with uremia and confirmed COVID-19 undergoing maintenance hemodialysis are more common in males. Although the proportion of fever patients is 50%, the proportion of hypoxemia patients is high (58%). With poor cardiac function. They were prone to respiratory failure complicated with heart failure. According to the onset characteristics of this population, early diagnosis and treatment could help reduce the risk of developing a critical illness and control the spread of the COVID-19 epidemic.	

2020	Analysis of clinical features and imaging signs of COVID-19 with the assistance of artificial intelligence.	To explore the CT imaging features/signs of patients with different clinical types of Coronavirus Disease 2019 (COVID-19) via the application of artificial intelligence (AI), thus improving the understanding of COVID-19. Clinical data and chest CT imaging features of 58 patients confirmed with COVID-19 in the Fifth Medical Center of PLA General Hospital were retrospectively analyzed. According to the Guidelines on Novel Coronavirus-Infected Pneumonia Diagnosis and Treatment (Provisional 6th Edition), COVID-19 patients were divided into mild type (7), common type (34), severe type (7) and critical type (10 patients). The CT imaging features of the patients with different clinical types of COVID-19 types were analyzed, and the volume percentage of pneumonia lesions with respect to the lung lobes (where the lesion was located) and to the whole lung was calculated with the use of AI software. SPSS 21.0 software was used for statistical analysis. Common clinical manifestations of COVID-19 patients: fever was found in 47 patients (81.0%), cough in 31 (53.4%) and weakness in 10 (17.2%). Laboratory examinations: normal or decreased white blood cell (WBC) counts were observed in 52 patients (89.7%), decreased lymphocyte counts (LCs) in 14 (24.1%) and increased C-reactive protein (CRP) levels in 18 (31.0%). CT imaging features: there were 48 patients (94.1%) with lesions distributed in both lungs and 46 patients (90.2%) had lesions most visible in the lower lungs; the primary manifestations in patients with common type COVID-19 were ground-glass opacities (GGOs) (23/34, 67.6%) or mixed type (17/34, 50.0%), with lesions mainly distributed in the periphery of the lungs (28/34, 82.4%); the primary manifestations of patients with severe/critical type COVID-19 were consolidations (13/17, 76.5%) or mixed type (14/17, 82.4%), with lesions distributed in both the peripheral and central areas of lungs (14/17,82.4%); other common signs, including pleural parallel signs, halo signs, vascular thickening signs, crazy-paving signs and air bronchogram signs, were visible in patients with different clinical types, and pleural effusion was found in 5 patients with severe/critical COVID-19. AI software was used to calculate the volume percentages of pneumonia lesions with respect to the lung lobes (where the lesion was located) and to the whole lung. There were significant differences in the volume percentages of pneumonia lesions for the superior lobe of the left lung, the inferior lobe of the left lung, the superior lobe of the right lung, the inferior lobe of the right lung and the whole lung among patients with different clinical types ($p<0.05$). The area under the ROC curve (AUC) of the volume percentage of pneumonia lesions for the whole lung for the diagnosis of severe/critical type COVID-19 was 0.740, with sensitivity and specificity of 91.2% and 58.8%, respectively. The clinical and CT imaging features of COVID-19 patients were characteristic to a certain degree; thus, the clinical course and severity of COVID-19 could be evaluated with a combination of an analysis of clinical features and CT imaging features and assistant diagnosis by AI software.	

2020	Immune complement and coagulation dysfunction in adverse outcomes of SARS-CoV-2 infection.	Understanding the pathophysiology of SARS-CoV-2 infection is critical for therapeutic and public health strategies. Viral-host interactions can guide discovery of disease regulators, and protein structure function analysis points to several immune pathways, including complement and coagulation, as targets of coronaviruses. To determine whether conditions associated with dysregulated complement or coagulation systems impact disease, we performed a retrospective observational study and found that history of macular degeneration (a proxy for complement-activation disorders) and history of coagulation disorders (thrombocytopenia, thrombosis and hemorrhage) are risk factors for SARS-CoV-2-associated morbidity and mortality-effects that are independent of age, sex or history of smoking. Transcriptional profiling of nasopharyngeal swabs demonstrated that in addition to type-I interferon and interleukin-6-dependent inflammatory responses, infection results in robust engagement of the complement and coagulation pathways. Finally, in a candidate-driven genetic association study of severe SARS-CoV-2 disease, we identified putative complement and coagulation-associated loci including missense, eQTL and sQTL variants of critical complement and coagulation regulators. In addition to providing evidence that complement function modulates SARS-CoV-2 infection outcome, the data point to putative transcriptional genetic markers of susceptibility. The results highlight the value of using a multimodal analytical approach to reveal determinants and predictors of immunity, susceptibility and clinical outcome associated with infection.	
2020	Severe COVID-19 patients with liver injury: a seven-case series.	We present the case details of seven patients diagnosed with severe novel coronavirus disease 2019 (2019-nCoV, hereafter COVID-19) with hepatic injury. Most of these patients were elderly and had hypertension, diabetes mellitus, coronary heart disease, and other underlying health conditions prior to admission for COVID-19. Liver injury occurred in all seven cases during the course of the disease. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels initially increased (1.2-times to 2.0-times the normal value, respectively) in the second week. The liver function recovered in all patients within one week of conventional liver protection treatment. Elevated serum transaminase levels in these patients were due to the COVID-19 infection but could also be related to systemic immune response caused by cytokine storm syndrome (CSS) and hepatocyte damage caused by ischemia and hypoxia. COVID-19 is highly infectious and mainly affects the lungs. In some cases, especially in patients with severe disease type, COVID-19 may also cause liver injury. The liver function of patients with severe COVID-19 should be very carefully monitored, especially if the patients are elderly and have underlying comorbidities.	

2020	Association between ABO blood groups and COVID-19 infection, severity and demise: A systematic review and meta-analysis.	The COVID-19 spreads rapidly around the world which has brought a global health crisis. The pathogen of COVID-19 is SARS-COV-2, and previous studies have proposed the relationship between ABO blood group and coronavirus. Here, we aim to delve into the association between ABO blood group and COVID-19 infection, severity and demise. The relevant studies were retrieved from five databases: PubMed, MedRxiv, BioRxiv,Web of Science and CNKI. Members of cases(symptomatic cases, severe cases, died cases) and controls(asymptomatic controls, non-severe controls, alive controls) were extracted from collected studies. Odds ratios (OR) and 95% confidence intervals (CI) were calculated and interpreted from extracted data. Publication bias and sensitivity analysis were also applied to confirm our discovery. Overall 31,100 samples were included in the analysis. Compared to other ABO blood type, an increased odds of infecting COVID-19 among individuals with A blood group (OR: 1.249, 95%CI: 1.114-1.440, P < 0.001) and a decreased odds of infecting COVID-19 among individuals with blood group O (OR: 0.699, 95%CI: 0.635-0.770, P < 0.001) were found. Besides, individuals with blood group AB seems to link a higher risk to COVID-19 severity (OR: 2.424, 95%CI: 0.934-6.294) and demise (OR: 1.348, 95%CI: 0.507-3.583). Meantime, individuals with O blood group might had lower risk to COVID-19 severity (OR: 0.748, 95%CI: 0.556-1.007), and individuals with B blood group were likely to relate a lower risk to COVID-19 demise. The current meta-analysis suggest that blood type A might be more susceptible to infect COVID-19 while blood type O might be less susceptible to infect COVID-19; there were no correlation between ABO blood group and severity or demise of COVID-19. However, more investigation and research are warranted to clarify the relationship between COVID-19 and ABO blood type.	
2020	Lipoprotein(a) and Its Potential Association with Thrombosis and Inflammation in COVID-19: a Testable Hypothesis.	The COVID-19 pandemic has infected over > 11 million as of today people worldwide and is associated with significant cardiovascular manifestations, particularly in subjects with preexisting comorbidities and cardiovascular risk factors. Recently, a predisposition for arterial and venous thromboses has been reported in COVID-19 infection. We hypothesize that besides conventional risk factors, subjects with elevated lipoprotein(a) (Lp(a)) may have a particularly high risk of developing cardiovascular complications. The Lp(a) molecule has the propensity for inhibiting endogenous fibrinolysis through its apolipoprotein(a) component and for enhancing proinflammatory effects such as through its content of oxidized phospholipids. The LPA gene contains an interleukin-6 (IL-6) response element that may induce an acute phase-type increase in Lp(a) levels following a cytokine storm from COVID-19. Thus, subjects with either baseline elevated Lp(a) or those who have an increase following COVID-19 infection, or both, may be at very high risk of developing thromboses. Elevated Lp(a) may also lead to acute destabilization of preexisting but quiescent atherosclerotic plaques, which might induce acute myocardial infarction and stroke. Ongoing studies with IL-6 antagonists may be informative in understanding this relationship, and registries are being initiated to measure Lp(a) in subjects infected with COVID-19. If indeed an association is suggestive of being causal, consideration can be given to systematic testing of Lp(a) and prophylactic systemic anticoagulation in infected inpatients. Therapeutic lipid apheresis and pharmacotherapy for the reduction of Lp(a) levels may minimize thrombogenic potential and proinflammatory effects. We propose studies to test the hypothesis that Lp(a) may contribute to cardiovascular complications of COVID-19.	

2020	SARS-CoV2 drives JAK1/2-dependent local and systemic complement hyper-activation.	Patients with coronavirus disease 2019 (COVID-19) present with a range of devastating acute clinical manifestations affecting the lungs, liver, kidneys and gut. The best-characterized entry receptor for the disease-causing virus SARS-CoV2, angiotensin converting enzyme (ACE) 2, is highly expressed in these tissues. However, the pathways that underlie the disease are still poorly understood. Here we show that the complement system is unexpectedly one of the intracellular pathways most highly induced by SARS-CoV2 infection in lung epithelial and liver cells. Within cells of the bronchoalveolar lavage of patients, distinct signatures of complement activation in myeloid, lymphoid and epithelial cells tracked with disease severity. Modelling the regulome of host genes induced by COVID-19 and the drugs that could normalize these genes both implicated the JAK1/2-STAT1 signaling system downstream of type I interferon receptors, and NF-kB. Ruxolitinib, a JAK1/2 inhibitor and the top predicted pharmaceutical candidate, normalized interferon signature genes, IL-6 (the best characterized severity marker in COVID-19) and all complement genes induced by SARS-CoV2, but did not affect NF-kB-regulated genes. We predict that combination therapy with JAK inhibitors and other agents with the potential to normalize NF-kB-signaling, such as anti-viral agents, may serve as an effective clinical strategy.	
2020	Mortality in COVID-19 disease patients: Correlating the association of major histocompatibility complex (MHC) with severe acute respiratory syndrome 2 (SARS-CoV-2) variants.	Genetic factors such as the HLA type of patients may play a role in regard to disease severity and clinical outcome of patients with COVID-19. Taking the data deposited in the GISAID database, we made predictions using the IEDB analysis resource (TepiTool) to gauge how variants in the SARS-CoV-2 genome may change peptide binding to the most frequent MHC-class I and -II alleles in Africa, Asia and Europe. We caracterized how a single mutation in the wildtype sequence of of SARS-CoV-2 could influence the peptide binding of SARS-CoV-2 variants to MHC class II, but not to MHC class I alleles. Assuming the ORF8 (L84S) mutation is biologically significant, selective pressure from MHC class II alleles may select for viral varients and subsequently shape the quality and quantity of cellular immune responses aginast SARS-CoV-2. MHC 4-digit typing along with viral sequence analysis should be considered in studies examining clinical outcomes in patients with COVID-19.	

2020	High Thrombus Burden in Patients With COVID-19 Presenting With ST-Segment Elevation Myocardial Infarction.	Coronavirus disease-2019 (COVID-19) is thought to predispose patients to thrombotic disease. To date there are few reports of ST-segment elevation myocardial infarction (STEMI) caused by type 1 myocardial infarction in patients with COVID-19. The aim of this study was to describe the demographic, angiographic, and procedural characteristics alongside clinical outcomes of consecutive cases of COVID-19-positive patients with STEMI compared with COVID-19-negative patients. This was a single-center, observational study of 115 consecutive patients admitted with confirmed STEMI treated with primary percutaneous coronary intervention at Barts Heart Centre between March 1, 2020, and May 20, 2020. Patients with STEMI presenting with concurrent COVID-19 infection had higher levels of troponin T and lower lymphocyte count, but elevated D-dimer and C-reactive protein. There were significantly higher rates of multivessel thrombosis, stent thrombosis, higher modified thrombus grade post first device with consequently higher use of glycoprotein IIb/IIIa inhibitors and thrombus aspiration. Myocardial blush grade and left ventricular function were significantly lower in patients with COVID-19 with STEMI. Higher doses of heparin to achieve therapeutic activated clotting times were also noted. Importantly, patients with STEMI presenting with COVID-19 infection had a longer in-patient admission and higher rates of intensive care admission. In patients presenting with STEMI and concurrent COVID-19 infection, there is a strong signal toward higher thrombus burden and poorer outcomes. This supports the need for establishing COVID-19 status in all STEMI cases. Further work is required to understand the mechanism of increased thrombosis and the benefit of aggressive antithrombotic therapy in selected cases.	
2020	COVID-19: the role of excessive cytokine release and potential ACE2 down-regulation in promoting hypercoagulable state associated with severe illness.	The novel coronavirus disease (COVID-19) has become a universally prevalent infectious disease. The causative virus of COVID-19 is severe acute respiratory syndrome coronavirus type 2. Recent retrospective clinical studies have established a significant association between the incidence of vascular thrombotic events and the severity of COVID-19. The enhancement in serum levels of markers that reflect a hypercoagulable state has been suggested to indicate a poor prognosis. Therefore, at present, it is crucial to understand the mechanisms that foster the hypercoagulable state in COVID-19. Over-activated inflammatory response, which is manifested as excessive cytokine release in COVID-19 patients, is also associated with COVID-19 severity. This review discusses the immuno-pathological basis of the excessive cytokine release in COVID-19. Besides, this article reviews the role of pro-inflammatory or anti-inflammatory cytokines, whose significant elevations in their serum levels have been consistently detected in multiple different clinical studies, in promoting the hypercoagulable state. Since the expression of angiotensin-converting enzyme 2 (ACE2) is potentially down-regulated in COVID-19, as proposed by a recent bio-informatic analysis, mechanisms through which reduced ACE2 expressions promote vascular thrombosis are summarized. In addition, the reciprocal-enhancing effects of the excessive cytokine release and the downregulated ACE2 expression on their pro-thrombotic activities are further discussed. Here, based on currently available evidence, we review the pathogenic mechanisms of the hypercoagulable state associated with severe cases of COVID-19 to give insights into prevention and treatment of the vascular thrombotic events in COVID-19.	

2020	"Small" Intestinal Immunopathology Plays a "Big" Role in Lethal Cytokine Release Syndrome, and Its Modulation by Interferon-γ, IL-17A, and a Janus Kinase Inhibitor.	Chimeric antigen receptor T cell (CART) therapy, administration of certain T cell-agonistic antibodies, immune check point inhibitors, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) and Toxic shock syndrome (TSS) caused by streptococcal as well as staphylococcal superantigens share one common complication, that is T cell-driven cytokine release syndrome (CRS) accompanied by multiple organ dysfunction (MOD). It is not understood whether the failure of a particular organ contributes more significantly to the severity of CRS. Also not known is whether a specific cytokine or signaling pathway plays a more pathogenic role in precipitating MOD compared to others. As a result, there is no specific treatment available to date for CRS, and it is managed only symptomatically to support the deteriorating organ functions and maintain the blood pressure. Therefore, we used the superantigen-induced CRS model in HLA-DR3 transgenic mice, that closely mimics human CRS, to delineate the immunopathogenesis of CRS as well as to validate a novel treatment for CRS. Using this model, we demonstrate that (i) CRS is characterized by a rapid rise in systemic levels of several Th1/Th2/Th17/Th22 type cytokines within a few hours, followed by a quick decline. (ii) Even though multiple organs are affected, small intestinal immunopathology is the major contributor to mortality in CRS. (iii) IFN-γ deficiency significantly protected from lethal CRS by attenuating small bowel pathology, whereas IL-17A deficiency significantly increased mortality by augmenting small bowel pathology. (iv) RNA sequencing of small intestinal tissues indicated that IFN-γ-STAT1-driven inflammatory pathways combined with enhanced expression of pro-apoptotic molecules as well as extracellular matrix degradation contributed to small bowel pathology in CRS. These pathways were further enhanced by IL-17A deficiency and significantly down-regulated in mice lacking IFN-γ. (v) Ruxolitinib, a selective JAK-1/2 inhibitor, attenuated SAg-induced T cell activation, cytokine production, and small bowel pathology, thereby completely protecting from lethal CRS in both WT and IL-17A deficient HLA-DR3 mice. Overall, IFN-γ-JAK-STAT-driven pathways contribute to lethal small intestinal immunopathology in T cell-driven CRS.	

2020	Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes.	Coronavirus disease 2019 (COVID-19) is a recent pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus. Diabetes (mostly type 2 diabetes mellitus, T2DM) and hyperglycemia are among the major comorbidities in patients with COVID-19 leading to poor outcomes. Reports show that patients with diabetes and COVID-19 are at an increased risk for developing severe complications including acute respiratory distress syndrome, multi-organ failure, and death. Here we explore potential mechanistic links that could explain the observed higher morbidity and mortality in this patient population. Patients with T2DM have an underlying increased level of inflammation associated with obesity and insulin resistance in addition to other comorbidities including hypertension, obesity, cardiovascular disease, dyslipidemia, and being older. We review evidence that T2DM with hyperglycemia are among factors that lead to elevated expression of angiotensin-converting enzyme 2 (ACE2) in lungs and other tissues; ACE2 is the cellular "receptor" and port of viral entry. The preexisting chronic inflammation with augmented inflammatory response to the infection and the increasing viral load leads to extreme systemic immune response ("cytokine storm") that is strongly associated with increased severity of COVID-19. Based on the available evidence, it is recommended by a panel of experts that safe but stringent control of blood glucose, blood pressure, and lipids be carried out in patients with T2DM, measures that could potentially serve to decrease the severity of COVID-19 should these patients contract the viral infection. Once the infection occurs, then attention should be directed to proper glycemic control with use of insulin and frequent monitoring of blood glucose levels.	
2020	Next-Generation Sequencing of T and B Cell Receptor Repertoires from COVID-19 Patients Showed Signatures Associated with Severity of Disease.	We profiled adaptive immunity in COVID-19 patients with active infection or after recovery and created a repository of currently >14 million B and T cell receptor (BCR and TCR) sequences from the blood of these patients. The B cell response showed converging IGHV3-driven BCR clusters closely associated with SARS-CoV-2 antibodies. Clonality and skewing of TCR repertoires were associated with interferon type I and III responses, early CD4 + and CD8 + T cell activation, and counterregulation by the co-receptors BTLA, Tim-3, PD-1, TIGIT, and CD73. Tfh, Th17-like, and nonconventional (but not classical antiviral) Th1 cell polarizations were induced. SARS-CoV-2-specific T cell responses were driven by TCR clusters shared between patients with a characteristic trajectory of clonotypes and traceability over the disease course. Our data provide fundamental insight into adaptive immunity to SARS-CoV-2 with the actively updated repository providing a resource for the scientific community urgently needed to inform therapeutic concepts and vaccine development.	
2020	Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients.	Coronavirus disease 2019 (COVID-19) is characterized by distinct patterns of disease progression that suggest diverse host immune responses. We performed an integrated immune analysis on a cohort of 50 COVID-19 patients with various disease severity. A distinct phenotype was observed in severe and critical patients, consisting of a highly impaired interferon (IFN) type I response (characterized by no IFN-β and low IFN-α production and activity), which was associated with a persistent blood viral load and an exacerbated inflammatory response. Inflammation was partially driven by the transcriptional factor nuclear factor-κB and characterized by increased tumor necrosis factor-α and interleukin-6 production and signaling. These data suggest that type I IFN deficiency in the blood could be a hallmark of severe	

		COVID-19 and provide a rationale for combined therapeutic approaches.	
2020	Blood type and outcomes in patients with COVID-19.	This study aimed to determine if there is an association between ABO blood type and severity of COVID-19 defined by intubation or death as well as ascertain if there is variability in testing positive for COVID-19 between blood types. In a multi-institutional study, all adult patients who tested positive for COVID-19 across five hospitals were identified and included from March 6th to April 16th, 2020. Hospitalization, intubation, and death were evaluated for association with blood type. Univariate analysis was conducted using standard techniques and logistic regression was used to determine the independent effect of blood type on intubation and/or death and positive testing. During the study period, there were 7648 patients who received COVID-19 testing throughout the institutions. Of these, 1289 tested positive with a known blood type. A total of 484 (37.5%) were admitted to hospital, 123 (9.5%) were admitted to the ICU, 108 (8.4%) were intubated, 3 (0.2%) required ECMO, and 89 (6.9%) died. Of the 1289 patients who tested positive, 440 (34.2%) were blood type A, 201 (15.6%) were blood type B, 61 (4.7%) were blood type AB, and 587 (45.5%) were blood type O. On univariate analysis, there was no association between blood type and any of the peak inflammatory markers (peak WBC, $p = 0.25$; peak LDH, $p = 0.40$; peak ESR, $p = 0.16$; peak CRP, $p = 0.14$) nor between blood type and any of the clinical outcomes of severity (admission $p = 0.20$, ICU admission $p = 0.94$, intubation $p = 0.93$, proning while intubated $p = 0.58$, ECMO $p = 0.09$, and death $p = 0.49$). After multivariable analysis, blood type was not independently associated with risk of intubation or death (referent blood type A; blood type B: AOR: 0.72, 95% CI: 0.42-1.26, blood type AB: AOR: 0.78, CI: 0.33-1.87, blood type O: AOR: 0.77, CI: 0.51-1.16), rhesus factor positive (Rh+): AOR: 1.03, CI: 0.93-1.86. Blood type A had no correlation with positive testing (AOR: 1.00, CI: 0.88-1.13), blood type B was associated with higher odds of testing positive for disease (AOR: 1.28, CI: 1.08-1.52), AB was also associated with higher odds of testing positive (AOR: 1.37, CI: 1.02-1.83), and O was associated with a lower risk of testing positive (AOR: 0.84, CI: 0.75-0.95). Rh+ status was associated with higher odds of testing positive (AOR: 1.23, CI: 1.003-1.50). Blood type was not associated with risk of intubation or death in patients with COVID-19. Patients with blood types B and AB who received a test were more likely to test positive and blood type O was less likely to test positive. Rh+ patients were more likely to test positive.	

2020	Cardiac Troponin for Assessment of Myocardial Injury in COVID-19: JACC Review Topic of the Week.	Increases in cardiac troponin indicative of myocardial injury are common in patients with coronavirus disease-2019 (COVID-19) and are associated with adverse outcomes such as arrhythmias and death. These increases are more likely to occur in those with chronic cardiovascular conditions and in those with severe COVID-19 presentations. The increased inflammatory, prothrombotic, and procoagulant responses following severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection increase the risk for acute nonischemic myocardial injury and acute myocardial infarction, particularly type 2 myocardial infarction, because of respiratory failure with hypoxia and hemodynamic instability in critically ill patients. Myocarditis, stress cardiomyopathy, acute heart failure, and direct injury from SARS-CoV-2 are important etiologies, but primary noncardiac conditions, such as pulmonary embolism, critical illness, and sepsis, probably cause more of the myocardial injury. The structured use of serial cardiac troponin has the potential to facilitate risk stratification, help make decisions about when to use imaging, and inform stage categorization and disease phenotyping among hospitalized COVID-19 patients.	
2020	Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19.	Although most SARS-CoV-2-infected individuals experience mild coronavirus disease 2019 (COVID-19), some patients suffer from severe COVID-19, which is accompanied by acute respiratory distress syndrome and systemic inflammation. To identify factors driving severe progression of COVID-19, we performed single-cell RNA-seq using peripheral blood mononuclear cells (PBMCs) obtained from healthy donors, patients with mild or severe COVID-19, and patients with severe influenza. Patients with COVID-19 exhibited hyper-inflammatory signatures across all types of cells among PBMCs, particularly up-regulation of the TNF/IL-1β-driven inflammatory response as compared to severe influenza. In classical monocytes from patients with severe COVID-19, type I IFN response co-existed with the TNF/IL-1β-driven inflammation, and this was not seen in patients with milder COVID-19. Interestingly, we documented type I IFN-driven inflammatory features in patients with severe influenza as well. Based on this, we propose that the type I IFN response plays a pivotal role in exacerbating inflammation in severe COVID-19.	

2020	Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review.	Convalescent plasma and hyperimmune immunoglobulin may reduce mortality in patients with viral respiratory diseases, and are currently being investigated in trials as potential therapy for coronavirus disease 2019 (COVID-19). A thorough understanding of the current body of evidence regarding the benefits and risks is required. OBJECTIVES: To continually assess, as more evidence becomes available, whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in treatment of people with COVID-19. We searched the World Health Organization (WHO) COVID-19 Global Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, Centers for Disease Control and Prevention COVID-19 Research Article Database and trial registries to identify completed and ongoing studies on 4 June 2020. We followed standard Cochrane methodology. We included studies evaluating convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, irrespective of study design, disease severity, age, gender or ethnicity. We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)) and studies evaluating standard immunoglobulin. We followed standard Cochrane methodology. To assess bias in included studies, we used the Cochrane 'Risk of bias' tool for randomised controlled trials (RCTs), the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool for controlled non-randomised studies of interventions (NRSIs), and the assessment criteria for observational studies, provided by Cochrane Childhood Cancer for non-controlled NRSIs. MAIN RESULTS: This is the first living update of our review. We included 20 studies (1 RCT, 3 controlled NRSIs, 16 non-controlled NRSIs) with 5443 participants, of whom 5211 received convalescent plasma, and identified a further 98 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin, of which 50 are randomised. We did not identify any completed studies evaluating hyperimmune immunoglobulin. Overall risk of bias of included studies was high, due to study design, type of participants, and other previous or concurrent treatments. Effectiveness of convalescent plasma for people with COVID-19 We included results from four controlled studies (1 RCT (stopped early) with 103 participants, of whom 52 received convalescent plasma; and 3 controlled NRSIs with 236 participants, of whom 55 received convalescent plasma) to assess effectiveness of convalescent plasma. Control groups received standard care at time of treatment without convalescent plasma. All-cause mortality at hospital discharge (1 controlled NRSI, 21 participants) We are very uncertain whether convalescent plasma has any effect on all-cause mortality at hospital discharge (risk ratio (RR) 0.89, 95% confidence interval (CI) 0.61 to 1.31; very low-certainty evidence). Time to death (1 RCT, 103 participants; 1 controlled NRSI, 195 participants) We are very uncertain whether convalescent plasma prolongs time to death (RCT: hazard ratio (HR) 0.74, 95% CI 0.30 to 1.82; controlled NRSI: HR 0.46, 95% CI 0.22 to 0.96; very low-certainty evidence). Improvement of clinical symptoms, assessed by need for respiratory support (1 RCT, 103 participants; 1 controlled NRSI, 195 participants) We are very uncertain whether convalescent plasma has any effect on improvement of clinical symptoms at seven days (RCT: RR 0.98, 95% CI 0.30 to 3.19), 14 days (RCT: RR 1.85, 95% CI 0.91 to 3.77; controlled NRSI: RR 1.08, 95% CI 0.91 to 1.29), and 28 days (RCT: RR 1.20, 95% CI 0.80 to 1.81; very low-certainty evidence). Quality of life No studies reported this outcome. Safety of convalescent plasma for people with COVID-19 We	

		included results from 1 RCT, 3 controlled NRSIs and 10 non-controlled NRSIs assessing safety of convalescent plasma. Reporting of adverse events and serious adverse events was variable. The controlled studies reported on adverse events and serious adverse events only in participants receiving convalescent plasma. The duration of follow-up varied. Some, but not all, studies included death as a serious adverse event. Grade 3 or 4 adverse events (13 studies, 201 participants) The studies did not report the grade of adverse events. Thirteen studies (201 participants) reported on adverse events of possible grade 3 or 4 severity. The majority of these adverse events were allergic or respiratory events. We are very uncertain whether or not convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence). Serious adverse events (14 studies, 5201 participants) Fourteen studies (5201 participants) reported on serious adverse events. The majority of participants were from one non-controlled NRSI (5000 participants), which reported only on serious adverse events limited to the first four hours after convalescent plasma transfusion. This study included death as a serious adverse event; they reported 15 deaths, four of which they classified as potentially, probably or definitely related to transfusion. Other serious adverse events reported in all studies were predominantly allergic or respiratory in nature, including anaphylaxis, transfusion-associated dyspnoea, and transfusion-related acute lung injury (TRALI). We are very uncertain whether or not convalescent plasma affects the number of serious adverse events. We are very uncertain whether convalescent plasma is beneficial for people admitted to hospital with COVID-19. For safety outcomes we also included non-controlled NRSIs. There was limited information regarding adverse events. Of the controlled studies, none reported on this outcome in the control group. There is only very low-certainty evidence for safety of convalescent plasma for COVID-19. While major efforts to conduct research on COVID-19 are being made, problems with recruiting the anticipated number of participants into these studies are conceivable. The early termination of the first RCT investigating convalescent plasma, and the multitude of studies registered in the past months illustrate this. It is therefore necessary to critically assess the design of these registered studies, and well-designed studies should be prioritised. Other considerations for these studies are the need to report outcomes for all study arms in the same way, and the importance of maintaining comparability in terms of co-interventions administered in all study arms. There are 98 ongoing studies evaluating convalescent plasma and hyperimmune immunoglobulin, of which 50 are RCTs. This is the first living update of the review, and we will continue to update this review periodically. These updates may show different results to those reported here.	

2020	Immune responses and pathogenesis in persistently PCR-positive patients with SARS-CoV-2 infection.	Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 emerged in China in December 2019 and then rapidly spread worldwide. Why COVID-19 patients with the same clinical condition have different outcomes remains unclear. This study aimed to examine the differences in the phenotype and functions of major populations of immune cells between COVID-19 patients with same severity but different outcomes. Four common type adult inpatients with laboratory confirmed COVID-19 from Beijing YouAn Hospital, Capital Medical University were included in this study. The patients were divided into two groups based on whether or not COVID-19 polymerase chain reaction (PCR)-negative conversion occurred within 3 weeks. Peripheral blood samples were collected to compare the differences in the phenotype and functions of major populations of immune cells between the two groups of patients. The result shows that the proportions of CD3 + CD8 + CD38 + HLA-DR + CD27 - effector T killer cells generally declined, whereas that of CD3 + CD4 + CD8 + double-positive T cells (DPTs) increased in the persistently PCR-positive patients. In summary, considering the imbalance between effector T killer cells/CD3+CD4+CD8+ DPTs was a possible key factor for PCR-negative conversion in patients with COVID-19.	
2020	Usefulness and Safety of Remote Continuous Glucose Monitoring for a Severe COVID-19 Patient with Diabetes.	Diabetes is associated with mortality and severity of coronavirus disease (COVID-19). Protecting against infection in health care workers at high risk of COVID-19 is critical. This report investigates the usefulness and safety of remote continuous glucose monitoring (CGM) in a patient with diabetes and severe interstitial pneumonia caused by the coronavirus disease. The Dexcom G4 Platinum CGM system ® was used to monitor blood glucose (BG) levels from outside the patient's isolation room. Continuous insulin infusion rates and boluses were determined based on the patient's BG levels. Real-time CGM made it possible to track BG trends and prevent dramatic variations in BG, although the rate of insulin infusion changed dynamic. Furthermore, the need for health care workers to enter the isolation room was minimized because the Dexcom G4 Platinum CGM system can evaluate from a distance of up to 6.0 m.	
2020	Clinical analysis of risk factors for severe COVID-19 patients with type 2 diabetes.	To describe characteristics of COVID-19 patients with type 2 diabetes and to analyze risk factors for severity. Demographics, comorbidities, symptoms, laboratory findings, treatments and outcomes of COVID-19 patients with diabetes were collected and analyzed. Seventy-fourCOVID-19 patients with diabetes were included. Twenty-seven patients (36.5%) were severe and 10 patients (13.5%) died. Higher levels of blood glucose, serum amyloid A (SAA), C reactive protein and interleukin 6 were associated with severe patients compared to non-severe ones (P<0.05). Levels of albumin, cholesterol, high density lipoprotein, small and dense low density lipoprotein and CD4 + T lymphocyte counts in severe patients were lower than those in non-severe patients (P<0.05). Logistic regression analysis identified decreased CD4 + T lymphocyte counts (odds ratio [OR]=0.988, 95%Confidence interval [95%CI] 0.979-0.997) and increased SAA levels (OR=1.029, 95%CI 1.002-1.058) as risk factors for severity of COVID-19 with diabetes (P<0.05). Type 2 diabetic patients were more susceptible to COVID-19 than overall population, which might be associated with hyperglycemia and dyslipidemia. Aggressive treatment should be suggested, especially when these patients had low CD4 + T lymphocyte counts and high SAA levels.	

2020	A novel indicator predicts 2019 novel coronavirus infection in subjects with diabetes.	Diabetes mellitus (DM) is associated with significant morbidity and mortality. The disease severity in 2019 novel coronavirus (Covid 19) infection has varied from mild self-limiting flu-like illness to fulminant pneumonia, respiratory failure and death. Since DM and Covid 19 infection are closely associated with inflammatory status, mean platelet volume (MPV) was suggested to be useful in predicting Covid infection onset. This study aimed to evaluate the diagnostic role of MPV in Covid patients with diabetes. A total of 640 subjects (160 Covid patients with type 2 diabetes, 160 healthy controls, 160 patients with non-spesific infections and 160 Covid patients without type 2 diabetes) enrolled in the study. MPV was significantly higher (11.21 ± 0.61 fL) as compared to the results from the last routine visits of the the same individuals with diabetes (10.59 ± 0.96 fL) ($p = 0.000$). MPV could be used as a simple and cost-effective tool to predict the Covid infection in subjects with diabetes in primary care.	
2020	Characteristics of laboratory indexes in COVID-19 patients with non-severe symptoms in Hefei City, China: diagnostic value in organ injuries.	This study compared the laboratory indexes in 40 non-severe COVID-19 patients with those in 57 healthy controls. In the peripheral blood system of non-severe symptom COVID-19 patients, lymphocytes, eosinophils, basophils, total procollagen type 1 amino-terminal propeptide, osteocalcin N-terminal, thyroid-stimulating hormone, growth hormone, and insulin-like growth factor-binding protein 3 significantly decreased, and total protein, albumin, alanine transaminase, alkaline phosphatase, γ-glutamyl transferase, activated partial thromboplastin time, prothrombin time, fibrinogen, D-dimer, fibrinogen degradation products, human epididymal protein 4, serum ferritin, and C-reactive protein were elevated. SARS-CoV-2 infection can affect hematopoiesis, hemostasis, coagulation, fibrinolysis, bone metabolism, thyroid, parathyroid glands, the liver, and the reproductive system.	

2020	Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting.	To investigate the incidence of bacterial and fungal coinfection of hospitalized patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in this retrospective observational study across two London hospitals during the first UK wave of coronavirus disease 2019 (COVID-19). A retrospective case series of hospitalized patients with confirmed SARS-CoV-2 by PCR was analysed across two acute NHS hospitals (20 February-20 April 2020; each isolate reviewed independently in parallel). This was contrasted to a control group of influenza-positive patients admitted during the 2019-2020 flu season. Patient demographics, microbiology and clinical outcomes were analysed. A total of 836 patients with confirmed SARS-CoV-2 were included; 27 (3.2%) of 836 had early confirmed bacterial isolates identified (0-5 days after admission), rising to 51 (6.1%) of 836 throughout admission. Blood cultures, respiratory samples, pneumococcal or Legionella urinary antigens and respiratory viral PCR panels were obtained from 643 (77%), 110 (13%), 249 (30%), 246 (29%) and 250 (30%) COVID-19 patients, respectively. A positive blood culture was identified in 60 patients (7.1%), of which 39 were classified as contaminants. Bacteraemia resulting from respiratory infection was confirmed in two cases (one each community-acquired Klebsiella pneumoniae and ventilator-associated Enterobacter cloacae). Line-related bacteraemia was identified in six patients (three Candida, two Enterococcus spp. and one Pseudomonas aeruginosa). All other community-acquired bacteraemias (n = 16) were attributed to nonrespiratory infection. Zero concomitant pneumococcal, Legionella or influenza infection was detected. A low yield of positive respiratory cultures was identified; Staphylococcus aureus was the most common respiratory pathogen isolated in community-acquired coinfection (4/24; 16.7%), with pseudomonas and yeast identified in late-onset infection. Invasive fungal infections (n = 3) were attributed to line-related infections. Comparable rates of positive coinfection were identified in the control group of confirmed influenza infection; clinically relevant bacteraemias (2/141; 1.4%), respiratory cultures (10/38; 26.3%) and pneumococcal-positive antigens (1/19; 5.3%) were low. We found a low frequency of bacterial coinfection in early COVID-19 hospital presentation, and no evidence of concomitant fungal infection, at least in the early phase of COVID-19.	

2020	SARS-CoV, MERS-CoV and SARS-CoV-2 infections in pregnancy and fetal development.	Recently, in China, in 2019, a new type of disease has arisen caused by a new strain of coronavirus, the SARS-CoV-2 virus, considered extremely worrying due to its high infectivity power and the easy ability to spread geographically. For patients in general, the clinical features resulting from respiratory syndromes can trigger an asymptomatic condition. However, 25 % of patients infected by SARS-CoV-2 can progress to severity. Pregnant women are an unknown field in this complex process, and although they have symptoms similar to non-pregnant women, some points should be considered, such as complications during pregnancy and postpartum. Thus, the aim of this study was to understand the consequences of pregnancy and fetal development, caused by infections by the SARS-CoV, MERS-CoV and SARS-CoV-2 viruses. Among the aforementioned infections, MERS-CoV seems to be the most dangerous for newborns, inducing high blood pressure, pre-eclampsia, pneumonia, acute renal failure, and multiple organ failure in mother. This also causes a higher occurrence of emergency cesarean deliveries and premature births, in addition, some deaths of mothers and fetuses were recorded. Meanwhile, SARS-CoV and SARS-CoV-2 appear to have less severe symptoms. Furthermore, although a study found the ACE2 receptor, used by SARS-CoV-2, widely distributed in specific cell types of the maternal-fetal interface, there is no evidence of vertical transmission for any of the coronaviruses. Thus, the limited reported obstetric cases alert to the need for advanced life support for pregnant women infected with coronaviruses and to the need for further investigation for application in clinical practice.	
2020	Covid-19 and cardiovascular risk: Susceptibility to infection to SARS-CoV-2, severity and prognosis of Covid-19 and blockade of the renin-angiotensin-aldosterone system. An evidence-based viewpoint.	The presence of cardiovascular co-morbidities and the known effects of coronaviruses on the cardiovascular system have called attention to the potential implications for patients with cardiovascular risk factors. This evidence-based viewpoint will address two questions: (a) are individuals with underlying cardiovascular risk factors (e.g. high blood pressure or diabetes) or overt disease (e.g. coronary heart disease, heart failure, kidney disease) more likely to develop severe Covid-19 and to die than those without underlying conditions? (b) does the regular use of angiotensin-converting enzyme inhibitors (ACE-i) or angiotensin-receptor blockers (ARB) make patients more likely to get infected and to die of Covid-19? With a necessary cautionary note that the evidence around the links between Covid-19 and cardiovascular disease is accruing at a fast pace, to date we can conclude that: (a) the greater susceptibility of individuals with underlying cardiovascular conditions to develop more severe Covid-19 with higher mortality rate is likely to be confounded, in part, by age and the type of co-morbidities. Patients with heart failure or chronic kidney disease might show an excess risk; (b) neither ACE-i nor ARB are associated with greater risk of SARS-Cov2 infection, or severity or risk of death in patients with Covid-19. Patients on these drugs should not stop them, unless under strict medical supervision and with the addition of a suitable replacement medicine.	
2020	Sedentariness and physical activity in type 2 diabetes during the COVID-19 pandemic.	NA	

2020	CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF PATIENTS DIAGNOSED WITH COVID-19 IN A TERTIARY CARE CENTER IN MEXICO CITY: A PROSPECTIVE COHORT STUDY.	Regional information regarding the characteristics of patients with coronavirus disease (COVID)-19 is needed for a better understanding of the pandemic. The objective of the study to describe the clinical features of COVID-19 patients diagnosed in a tertiary-care center in Mexico City and to assess differences according to the treatment setting (ambulatory vs. hospital) and to the need of intensive care (IC). We conducted a prospective cohort, including consecutive patients with COVID-19 from February 26, 2020 to April 11, 2020. We identified 309 patients (140 inpatients and 169 outpatients). The median age was 43 years (interquartile range, 33-54), 59.2% men, and 18.6% healthcare workers (12.3% from our center). The median body mass index (BMI) was 29.00 kg/m 2 and 39.6% had obesity. Compared to outpatients, inpatients were older, had comorbidities, cough, and dyspnea more frequently. Twenty-nine (20.7%) inpatients required treatment in the IC unit (ICU). History of diabetes (type 1 or 2) and abdominal pain were more common in ICU patients compared to non-ICU patients. ICU patients had higher BMIs, higher respiratory rates, and lower room-air capillary oxygen saturations. ICU patients showed a more severe inflammatory response as assessed by white blood cell count, neutrophil and platelet count, C-reactive protein, ferritin, procalcitonin, and albumin levels. By the end of the study period, 65 inpatients had been discharged because of improvement, 70 continued hospitalized, and five had died. Patients with comorbidities, either middle-age obese or elderly complaining of fever, cough, or dyspnea, were more likely to be admitted. At admission, patients with diabetes, high BMI, and clinical or laboratory findings consistent with a severe inflammatory state were more likely to require IC.	

2020	Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters.	The third fatal coronavirus is the novel coronavirus (SARS-CoV-2) that causes novel coronavirus pneumonia (COVID-19) which first broke out in December 2019. Patients will develop rapidly if there is no any intervention, so the risk identification of severe patients is critical. The aim of this study was to investigate the characteristics and rules of hematology changes in patients with COVID-19, and to explore the possibility differentiating moderate and severe patients using conventional hematology parameters or combined parameters. The clinical data of 45 moderate and severe type patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Jingzhou Central Hospital from January 23 to February 13, 2020 were collected. The epidemiological indexes, clinical symptoms, and laboratory test results of the patients were retrospectively analyzed. Those parameters with significant differences between moderate and severe cases were analyzed, and the combination parameters with the best diagnostic performance were selected using the linear discriminant analysis (LDA) method. Of the 45 patients with the novel 2019 corona virus (COVID-19) (35 moderate and 10 severe cases), 23 were male and 22 were female, with ages ranging from 16 to 62 years. The most common clinical symptoms were fever (89%) and dry cough (60%). As the disease progressed, white blood cell count (WBC), neutrophil count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red blood cell distribution width-coefficient of variation (RDW-CV), and red cell volume distribution width-standard deviation (RDW-SD) parameters in the severe group were significantly higher than those in the moderate group ($P<0.05$); meanwhile, lymphocyte count (Lym#), eosinophil count (Eos#), high fluorescent cell percentage (HFC%), red blood cell count (RBC), hemoglobin (HGB), and hematocrit (HCT) parameters in the severe group were significantly lower than those in the moderate group ($P<0.05$). For NLR parameter, it's area under the curve (AUC), cutoff, sensitivity and specificity were 0.890, 13.39, 83.3% and 82.4% respectively; meanwhile, for PLR parameter, it's AUC, cutoff, sensitivity and specificity were 0.842, 267.03, 83.3% and 74.0% respectively. The combined parameters of NLR and RDW-SD had the best diagnostic efficiency (AUC =0.938), and when the cutoff value was 1.046, the sensitivity and the specificity were 90.0% and 84.7% respectively, followed by the combined parameter NLR&RDW-CV (AUC =0.923). When the cut-off value was 0.62, the sensitivity and the specificity for distinguishing severe type from moderate cases of COVID-19 were 90.0% and 82.4% respectively. The combined NLR and RDW-SD parameter is the best hematology index. It may help clinicians to predict the severity of COVID-19 patients and can be used as a useful indicator to help prevent and control the epidemic.	

2020	Cardiovascular manifestations in severe and critical patients with COVID-19.	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could cause virulent infection leading to Corona Virus Disease 2019 (COVID-19)-related pneumonia as well as multiple organ injuries. COVID-19 infection may result in cardiovascular manifestations leading to worse clinical outcome. Fifty four severe and critical patients with confirmed COVID-19 were enrolled. Risk factors predicting the severity of COVID-19 were analyzed. Of the 54 patients (56.1 ± 13.5 years old, 66.7% male) with COVID-19, 39 were diagnosed as severe and 15 as critical cases. The occurrence of diabetes, the level of D-dimer, inflammatory and cardiac markers in critical cases were significantly higher. Troponin I (TnI) elevation occurred in 42.6% of all the severe and critical patients. Three patients experienced hypotension at admission and were all diagnosed as critical cases consequently. Hypotension was found in one severe case and seven critical cases during hospitalization. Sinus tachycardia is the most common type of arrythmia and was observed in 23 severe patients and all the critical patients. Atrioventricular block and ventricular tachycardia were observed in critical patients at end stage while bradycardia and atrial fibrillation were less common. Mild pericardial effusion was observed in one severe case and five critical cases. Three critical cases suffered new onset of heart failure. Hypotension during treatment, severe myocardial injury and pericardial effusion were independent risk factors predicting the critical status of COVID-19 infection. This study has systemically observed the impact of COVID-19 on cardiovascular system, including myocardial injury, blood pressure, arrythmia and cardiac function in severe and critical cases. Monitoring of vital signs and cardiac function of COVID-19 patients and applying potential interventions especially for those with hypotension during treatment, severe myocardial injury or pericardial effusion, is of vital importance.	
2020	Dissecting the interaction between COVID-19 and diabetes mellitus.	Coronavirus disease 2019 (COVID-19) is a global pandemic that is caused by a novel coronavirus, severe acute respiratory syndrome coronavirus-2. Data from several countries have shown higher morbidity and mortality among individuals with chronic metabolic diseases, such as diabetes mellitus. In this review, we explore the contributing factors for poorer prognosis in these individuals. As a significant proportion of patients with COVID-19 also have diabetes mellitus, this adds another layer of complexity to their management. We explore potential interactions between antidiabetic medications and renin-angiotensin-aldosterone system inhibitors with COVID-19. Suggested recommendations for the use of antidiabetic medications for COVID-19 patients with diabetes mellitus are provided. We also review pertinent clinical considerations in the management of diabetic ketoacidosis in COVID-19 patients. In addition, we aim to increase clinicians' awareness of the metabolic effects of promising drug therapies for COVID-19. Finally, we highlight the importance of timely vaccinations for patients with diabetes mellitus.	
2020	The renin-angiotensin system: An integrated view of lung disease and coagulopathy in COVID-19 and therapeutic implications.	The renin-angiotensin system (RAS) has long been appreciated as a major regulator of blood pressure, but has more recently been recognized as a mechanism for modulating inflammation as well. While there has been concern in COVID-19 patients over the use of drugs that target this system, the RAS has not been explored fully as a druggable target. The abbreviated description of the RAS suggests that its dysregulation may be at the center of COVID-19.	

2020	Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Infection (MIS-C): A Multi-institutional Study from New York City.	To assess clinical characteristics and outcomes of severe acute respiratory syndrome coronavirus 2-associated multisystem inflammatory syndrome in children (MIS-C). Children with MIS-C admitted to pediatric intensive care units in New York City between April 23 and May 23, 2020, were included. Demographic and clinical data were collected. Of 33 children with MIS-C, the median age was 10 years; 61% were male; 45% were Hispanic/Latino; and 39% were black. Comorbidities were present in 45%. Fever (93%) and vomiting (69%) were the most common presenting symptoms. Depressed left ventricular ejection fraction was found in 63% of patients with median ejection fraction of 46.6% (IQR, 39.5-52.8). C-reactive protein, procalcitonin, d-dimer, and pro-B-type natriuretic peptide levels were elevated in all patients. For treatment, intravenous immunoglobulin was used in 18 (54%), corticosteroids in 17 (51%), tocilizumab in 12 (36%), remdesivir in 7 (21%), vasopressors in 17 (51%), mechanical ventilation in 5 (15%), extracorporeal membrane oxygenation in 1 (3%), and intra-aortic balloon pump in 1 (3%). The left ventricular ejection fraction normalized in 95% of those with a depressed ejection fraction. All patients were discharged home with median duration of pediatric intensive care unit stay of 4.7 days (IQR, 4-8 days) and a hospital stay of 7.8 days (IQR, 6.0-10.1 days). One patient (3%) died after withdrawal of care secondary to stroke while on extracorporeal membrane oxygenation. Critically ill children with coronavirus disease-2019-associated MIS-C have a spectrum of severity broader than described previously but still require careful supportive intensive care. Rapid, complete clinical and myocardial recovery was almost universal.	
2020	Expression of SARS-CoV-2 receptor ACE2 and coincident host response signature varies by asthma inflammatory phenotype.	More than 300 million people carry a diagnosis of asthma, with data to suggest that they are at a higher risk for infection or adverse outcomes from severe acute respiratory syndrome coronavirus 2. Asthma is remarkably heterogeneous, and it is currently unclear how patient-intrinsic factors may relate to coronavirus disease 2019. We sought to identify and characterize subsets of patients with asthma at increased risk for severe acute respiratory syndrome coronavirus 2 infection. Participants from 2 large asthma cohorts were stratified using clinically relevant parameters to identify factors related to angiotensin-converting enzyme-2 (ACE2) expression within bronchial epithelium. ACE-2-correlated gene signatures were used to interrogate publicly available databases to identify upstream signaling events and novel therapeutic targets. Stratifying by type 2 inflammatory biomarkers, we identified subjects who demonstrated low peripheral blood eosinophils accompanied by increased expression of the severe acute respiratory syndrome coronavirus 2 receptor ACE2 in bronchial epithelium. Genes highly correlated with ACE2 overlapped with type 1 and 2 IFN signatures, normally induced by viral infections. T-cell recruitment and activation within bronchoalveolar lavage cells of ACE2-high subjects was reciprocally increased. These patients demonstrated characteristics corresponding to risk factors for severe coronavirus disease 2019, including male sex, history of hypertension, low peripheral blood, and elevated bronchoalveolar lavage lymphocytes. ACE2 expression is linked to upregulation of viral response genes in a subset of type 2-low patients with asthma with characteristics resembling known risk factors for severe coronavirus disease 2019. Therapies targeting the IFN family and T-cell-activating factors may therefore be of benefit in a subset of patients.	

2020	Impact of diabetes mellitus on clinical outcomes in patients affected by Covid-19.	A possible association could exist between type 2 diabetes mellitus (T2DM) and Coronavirus-19 (Covid-19) infection. Indeed, patients with T2DM show high prevalence, severity of disease and mortality during Covid-19 infection. However, the rates of severe disease are significantly higher in patients with diabetes compared with non-diabetes (34.6% vs. 14.2%; $p < 0.001$). Similarly, T2DM patients have higher rates of need for Intensive Care Unit (ICU, 37.0% vs. 26.7%; $p = 0.028$). Thus, about the pneumonia of Covid-19, we might speculate that the complicated alveolar-capillary network of lungs could be targeted by T2DM micro-vascular damage. Therefore, T2DM patients frequently report respiratory symptoms and are at increased risk of several pulmonary diseases. In addition, pro-inflammatory pathways as that involving interleukin 6 (IL-6), could be a severity predictor of lung diseases. Therefore, it looks intuitive to speculate that this condition could explain the growing trend of cases, hospitalization and mortality for patients with T2DM during Covid-19 infection. To date, an ongoing experimental therapy with monoclonal antibody against the IL-6 receptor in Italy seems to have beneficial effects on severe lung disease and prognosis in patients with Covid-19 infection. Therefore, should patients with T2DM be treated with more attention to glycemic control and monoclonal antibody against the IL-6 receptor during the Covid-19 infection?	
2020	Intracerebral haemorrhage and COVID-19: Clinical characteristics from a case series.	NA	
2020	Rationale and design of the PRAETORIAN-COVID trial: A double-blind, placebo-controlled randomized clinical trial with valsartan for PRevention of Acute rEspiraTORy dIstress syndrome in hospitAlized patieNts with SARS-COV-2 Infection Disease.	There is much debate on the use of angiotensin receptor blockers (ARBs) in severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)-infected patients. Although it has been suggested that ARBs might lead to a higher susceptibility and severity of SARS-CoV-2 infection, experimental data suggest that ARBs may reduce acute lung injury via blocking angiotensin-II-mediated pulmonary permeability, inflammation, and fibrosis. However, despite these hypotheses, specific studies on ARBs in SARS-CoV-2 patients are lacking. METHODS: The PRAETORIAN-COVID trial is a multicenter, double-blind, placebo-controlled 1:1 randomized clinical trial in adult hospitalized SARS-CoV-2-infected patients ($n = 651$). The primary aim is to investigate the effect of the ARB valsartan compared to placebo on the composite end point of admission to an intensive care unit, mechanical ventilation, or death within 14 days of randomization. The active-treatment arm will receive valsartan in a dosage titrated to blood pressure up to a maximum of 160 mg bid, and the placebo arm will receive matching placebo. Treatment duration will be 14 days, or until the occurrence of the primary end point or until hospital discharge, if either of these occurs within 14 days. The trial is registered at clinicaltrials.gov (NCT04335786, 2020). SUMMARY: The PRAETORIAN-COVID trial is a double-blind, placebo-controlled 1:1 randomized trial to assess the effect of valsartan compared to placebo on the occurrence of ICU admission, mechanical ventilation, and death in hospitalized SARS-CoV-2-infected patients. The results of this study might impact the treatment of SARS-CoV-2 patients globally.	

2020	Targeted Immunosuppression Distinguishes COVID-19 from Influenza in Moderate and Severe Disease.	Coronavirus disease 2019 (COVID-19) is characterized by a high incidence of acute respiratory failure. The underlying immunopathology of that failure and how it compares to other causes of severe respiratory distress, such as influenza virus infection, are not fully understood. Here we addressed this by developing a prospective observational cohort of COVID-19 and influenza subjects with varying degrees of disease severity and assessing the quality and magnitude of their immune responses at the cellular and protein level. Additionally, we performed single-cell RNA transcriptional profiling of peripheral blood mononuclear cells from select subjects. The cohort consists of 79 COVID-19 subjects, 26 influenza subjects, and 15 control subjects, including 35 COVID-19 and 7 influenza subjects with acute respiratory failure. While COVID-19 subjects exhibited largely equivalent or greater activated lymphocyte counts compared to influenza subjects, they had fewer monocytes and lower surface HLA-class II expression on monocytes compared to influenza subjects and controls. At least two distinct immune profiles were observed by cytokine levels in severe COVID-19 patients: 3 of 71 patients were characterized by extreme inflammation, with greater than or equal to ~50% of the 35 cytokines measured greater than 2 standard deviations from the mean level of other severe patients (both influenza and COVID-19); the other immune profile, which characterized 68 of 71 subjects, had a mixed inflammatory signature, where 28 of 35 cytokines in COVID-19 patients had lower mean cytokine levels, though not all were statistically significant. Only 2 cytokines were higher in COVID-19 subjects compared to influenza subjects (IL-6 and IL-8). Influenza and COVID-19 patients could be distinguished statistically based on cytokine module expression, particularly after controlling for the significant effects of age on cytokine expression, but again with lower levels of most cytokines in COVID-19 subjects. Further, high circulating levels of IL-1RA and IL-6 were associated with increased odds of intubation in the combined influenza and COVID-19 cohort [OR = 3.93 and 4.30, respectively] as well as among only COVID-19 patients. Single cell transcriptional profiling of COVID-19 and influenza subjects with respiratory failure identified profound suppression in type I and type II interferon signaling in COVID-19 patients across multiple clusters. In contrast, COVID-19 cell clusters were enriched for alterations in metabolic, stress, and apoptotic pathways. These alterations were consistent with an increased glucocorticoid response in COVID-19 patients compared to influenza. When considered across the spectrum of innate and adaptive immune profiles, the immune pathologies underlying severe influenza and COVID-19 are substantially distinct. The majority of COVID-19 patients with acute respiratory failure do not have a cytokine storm phenotype but instead exhibit profound type I and type II IFN immunosuppression when compared to patients with acute influenza. Upregulation of a small number of inflammatory mediators, including IL-6, predicts acute respiratory failure in both COVID-19 and influenza patients.	

2020	Acute complicated type B aortic dissection during the New York City COVID-19 surge.	The impact of the coronavirus disease 2019 (COVID-19) pandemic in New York City (NYC) is dramatic. COVID-19 cases surged, hospitals expanded to meet capacity, and NYC remains the global epicenter of this pandemic. During this unprecedented time, a young woman with known Marfan syndrome presented with an acute complicated type B aortic dissection to our Aortic Center. Using the provisional extension to induce a complete attachment technique, we treated this patient and quickly discharged her the next day to decrease the risk of COVID-19 infection. Her progress was monitored using frequent phone calls and one office visit at two weeks.	
2020	The effects of blood group types on the risk of COVID-19 infection and its clinical outcome	COVID-19 (Coronavirus disease of 2019) is an infectious disease outbreak later on declared as a pandemic, caused by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2). It spreads very rapidly and can result in severe acute respiratory failure. The clinical studies have shown that advanced age and chronic diseases increase the risk of infection. However, influence of the blood groups on COVID-19 infection and its outcome remains to be confirmed. The aim of this study is to investigate whether there exists a relationship between the blood groups of the patients and risk of SARS-CoV-2 infection and the clinical outcomes in COVID-19 patients 186 patients with PCR confirmed diagnosis of COVID-19 were included in this study. Age, sex, blood groups, comorbidities, need for intubation and intensive care unit follow up and mortalities of the patients were analyzed retrospectively. 1881 healthy individuals, who presented to the Hacettepe University Blood Bank served as the controls. The most frequently detected blood group was blood group A (57%) amongst the COVID-19 patients. This was followed by blood group O (24.8%). The blood group types did not affect the clinical outcomes. The blood group A was statistically significantly more frequent among those infected with COVID-19 compared to controls (57% vs. 38%, $P < 0.001$; OR: 2.1). On the other hand, the frequency of blood group O was significantly lower in the COVID-19 patients, compared to the control group (24.8% vs. 37.2%, P: 0.001; OR: 1.8). The results of the present study suggest that while the blood group A might have a role in increased susceptibility to the COVID-19 infection, the blood group O might be somewhat protective. However, once infected, blood group type does not seem to influence clinical outcome.	

2020	[Clinical features and high resolution CT imaging evolution of coronavirus disease 2019].	Objective: To investigate the clinical manifestations of the clinical characteristics of 141 patients with coronavirus disease 2019 (COVID-19) and the imaging evolution characteristics of High Resolution CT (HRCT) in the chest. Methods: From January 20, 2020 to February 8, 141 COVID-19 patients in Renmin Hospital of Wuhan University, 77 males and 64 females, with a median age of 49 (9,87) , were retrospectively analyzed. The clinical features, laboratory examination indexes and HRCT evolution findings of 141 COVID-19 patients were analyzed. Results: Laboratory examinations of 141 COVID-19 patients showed a decrease in white blood cell count and lymphocyte ratio. Among the 141 patients with COVID-19, fever (>37.5 ℃) was the most common clinical manifestation in 139 cases (98.58%) , and occasionally non-respiratory symptoms such as diarrhea in 4 cases (2.84%) . 141 patients with COVID-19 had abnormal HRCT. 52 (36.88%) chest HRCT images showed ground-glass opacity (GGO) , mainly under pleural; 23 (16.31%) GGO with focal consolidation; 27 (19.15%) small flaky shadows; 20 cases (14.18%) large flaky consolidation shadows; 48 cases (34.04%) bronchovascular bundle thickening and vascular penetrating signs; 5 cases (3.55%) had air bronchial signs; 7 cases (4.96%) of small nodule shadows; 5 cases (3.55%) of fibrosis, grid shadows or strand shadows.135 cases (95.74%) were positive for the first time nucleic acid test, 6 cases (4.26%) were negative, and 71 cases (50.35%) of common type, 47 cases (33.33%) of severe type and 23 cases (16.31%) of critical type were found during the same period. The average time from onset of each type to the first CT examination was: (2.51±1.32) , (5.02±2.01) , and (5.91±1.76) days; 19 (19/47, 40.43%) of which were severe for the first time CT classification worsened at the second examination and lessened at the third examination. 141 cases (100%) were positive for the second nucleic acid test, and the HRCT results for the same period were 44 cases (31.21%) of common type, 53 cases (37.59%) of severe type, and 44 cases (31.21%) of critical type; the average interval time was (3.32±1.61) , (3.93±1.84) , (4.15±1.57) days;the third nucleic acid test were positive among 113 cases and 28 cases were negative, HRCT results of the same period were 79 cases (56.03%) of common type, 46 cases (32.62%) of severe type, and 16 cases (11.35%) of critical type;the average interval from the first CT examination were: (5.59±1.83) , (7.32±1.37) , (7.55±1.78) days. The differences in CT typing at different time were statistically significant ($P< 0.05$) . Conclusion: The clinical features of COVID-19 and HRCT images are diverse, extensive GGO and infiltrates in both lungs are typical. Viral nucleic acid tests usually occur earlier or at the same time as the CT examination positive, and there are false negatives in nucleic acid tests. In some epidemiological backgrounds, CT imaging manifestations and evolutionary characteristics are of great significance for early warning of lung injury, assessment of disease severity, and assistance in clinical typing and post-treatment follow-up.	

2020	Serum KL-6 concentrations as a novel biomarker of severe COVID-19.	Severe acute respiratory syndrome coronavirus 2-induced direct cytopathic effects against type I and II pneumocytes mediate lung damage. Krebs von den Lungen-6 (KL-6) is mainly produced by damaged or regenerating alveolar type II pneumocytes. This preliminary study analyzed serum concentrations of KL-6 in patients with coronavirus disease (COVID-19) to verify its potential as a prognostic biomarker of severity. Twenty-two patients (median age [interquartile range] 63 [59-68] years, 16 males) with COVID-19 were enrolled prospectively. Patients were divided into mild-moderate and severe groups, according to respiratory impairment and clinical management. KL-6 serum concentrations and lymphocyte subset were obtained. Peripheral natural killer (NK) cells/μL were significantly higher in nonsevere patients than in the severe group (P = .0449) and the best cut-off value was 119 cells/μL. KL-6 serum concentrations were significantly higher in severe patients than the nonsevere group (P = .0118). Receiver operating characteristic analysis distinguished severe and nonsevere patients according to KL-6 serum levels and the best cut-off value was 406.5 U/mL. NK cell analysis and assay of KL-6 in serum can help identify severe COVID-19 patients. Increased KL-6 serum concentrations were observed in patients with severe pulmonary involvement, revealing a prognostic value and supporting the potential usefulness of KL-6 measurement to evaluate COVID-19 patients' prognosis.	
2020	Association of viral load with serum biomakers among COVID-19 cases.	Since SARS-CoV-2 spreads rapidly around the world, data have been needed on the natural fluctuation of viral load and clinical indicators associated with it. We measured and compared viral loads of SARS-CoV-2 from pharyngeal swab, IgM anti-SARS-CoV-2, CRP and SAA from serum of 114 COVID-19 patients on admission. Positive rates of IgM anti-SARS-CoV-2, CRP and SAA were 80.7%, 36% and 75.4% respectively. Among IgM-positive patients, viral loads showed different trends among cases with different severity, While viral loads of IgM-negative patients tended to increase along with the time after onset. As the worsening of severity, the positive rates of CRP and SAA also showed trends of increase. Different CRP/SAA type showed associations with viral loads in patients in different severity and different time after onset. Combination of the IgM and CRP/SAA with time after onset and severity may give suggestions on the viral load and condition judgment of COVID-19 patients.	

2020	Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial.	A vaccine to protect against COVID-19 is urgently needed. We aimed to assess the safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing the spike glycoprotein of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain. We did a dose-escalation, single-centre, open-label, non-randomised, phase 1 trial of an Ad5 vectored COVID-19 vaccine in Wuhan, China. Healthy adults aged between 18 and 60 years were sequentially enrolled and allocated to one of three dose groups (5 × 10 10 , 1 × 10 11 , and 1·5 × 10 11 viral particles) to receive an intramuscular injection of vaccine. The primary outcome was adverse events in the 7 days post-vaccination. Safety was assessed over 28 days post-vaccination. Specific antibodies were measured with ELISA, and the neutralising antibody responses induced by vaccination were detected with SARS-CoV-2 virus neutralisation and pseudovirus neutralisation tests. T-cell responses were assessed by enzyme-linked immunospot and flow-cytometry assays. This study is registered with ClinicalTrials.gov, NCT04313127. Between March 16 and March 27, 2020, we screened 195 individuals for eligibility. Of them, 108 participants (51% male, 49% female; mean age 36·3 years) were recruited and received the low dose (n=36), middle dose (n=36), or high dose (n=36) of the vaccine. All enrolled participants were included in the analysis. At least one adverse reaction within the first 7 days after the vaccination was reported in 30 (83%) participants in the low dose group, 30 (83%) participants in the middle dose group, and 27 (75%) participants in the high dose group. The most common injection site adverse reaction was pain, which was reported in 58 (54%) vaccine recipients, and the most commonly reported systematic adverse reactions were fever (50 [46%]), fatigue (47 [44%]), headache (42 [39%]), and muscle pain (18 [17%]. Most adverse reactions that were reported in all dose groups were mild or moderate in severity. No serious adverse event was noted within 28 days post-vaccination. ELISA antibodies and neutralising antibodies increased significantly at day 14, and peaked 28 days post-vaccination. Specific T-cell response peaked at day 14 post-vaccination. The Ad5 vectored COVID-19 vaccine is tolerable and immunogenic at 28 days post-vaccination. Humoral responses against SARS-CoV-2 peaked at day 28 post-vaccination in healthy adults, and rapid specific T-cell responses were noted from day 14 post-vaccination. Our findings suggest that the Ad5 vectored COVID-19 vaccine warrants further investigation. National Key R&D Program of China, National Science and Technology Major Project, and CanSino Biologics.	

2020	Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis.	Metformin was proposed to be a candidate for host-directed therapy for COVID-19. However, its efficacy remains to be validated. In this study, we compared the outcome of metformin users and nonusers in hospitalized COVID-19 patients with diabetes. Hospitalized diabetic patients with confirmed COVID-19 in the Tongji Hospital of Wuhan, China, from January 27, 2020 to March 24, 2020, were grouped into metformin and no-metformin groups according to the diabetic medications used. The demographics, characteristics, laboratory parameters, treatments, and clinical outcome in these patients were retrospectively assessed. A total of 283 patients (104 in the metformin and 179 in the no-metformin group) were included in this study. There were no significant differences between the two groups in gender, age, underlying diseases, clinical severity, and oxygen-support category at admission. The fasting blood glucose level of the metformin group was higher than that of the no-metformin group at admission and was under effective control in both groups after admission. Other laboratory parameters at admission and treatments after admission were not different between the two groups. The length of hospital stay did not differ between the two groups (21.0 days for metformin versus 19.5 days for no metformin, $P = 0.74$). However, in-hospital mortality was significantly lower in the metformin group (3/104 (2.9%) versus 22/179 (12.3%), $P = 0.01$). Antidiabetic treatment with metformin was associated with decreased mortality compared with diabetics not receiving metformin. This retrospective analysis suggests that metformin may offer benefits in patients with COVID-19 and that further study is indicated.	
2020	Implications of the lack of a unified research project framework: an investigation into the registration of clinical trials of COVID-19.	Objective: The aim of this study was to provide recommendations for improving the design of subsequent studies through analysis of the registered coronavirus disease 2019 (COVID-19) clinical trials. Methods: A retrospective analysis of 189 trial retrievals achieved on 20 February 2020. Results: A total of 189 trials are included in the study. There were 69.3% interventional studies, 21.7% observational studies, 5.3% diagnostic tests and 3.7% other studies. The following statistics are provided only for the interventional studies. Severity of disease: 5.3% light and common type, 17.6% severe and critically ill and 59.6% with no restricted classification. Medication use: 51.1% Western medicine, 32.1% Chinese medicine, 10.7% blood related product and 6.1% non-drug therapy. The median and inner quantile range of the sample sizes included in these studies: 104 (IQR: 60, 200). Primary outcome type most used: 45.8% with clinical characteristics and 21.4% with virological. Study design characteristics: 71% of all studies were randomized, 5% of all studies were blinded, 18% of all studies were multicenter and 76% of all studies were single center. Conclusion: Although many COVID-19 studies include randomization in their design, the lack of additional double-blind and placebo-controlled elements in their designs result in a less robust evaluation of intervention safety and efficacy. Furthermore, similar or repeated research and small sample studies that have less promise in gains of new information have possibly led to a shortage of recruitable patients and become a barrier to the completion of large multicenter clinical trial studies.	
2020	Correlation analysis of the severity and clinical prognosis of 32 cases of patients with COVID-19.	NA	

2020	The underlying changes and predicting role of peripheral blood inflammatory cells in severe COVID-19 patients: A sentinel?	The underlying changes of peripheral blood inflammatory cells (PBICs) in COVID-19 patients are little known. Moreover, the risk factors for the underlying changes of PBICs and their predicting role in severe COVID-19 patients remain uncertain. This retrospective study including two cohorts: the main cohort enrolling 45 patients of severe type serving as study group, and the secondary cohort enrolling 12 patients of no-severe type serving as control group. The PBICs analysis was based on blood routine and lymphocyte subsets. The inflammatory cell levels were compared among patients according to clinical classifications, disease-associated phases, as well as one-month outcomes. Compared with patients of non-severe type, the patients of severe type suffered from significantly decreased counts of lymphocytes, eosinophils, basophils, but increased counts of neutrophils. These PBICs alterations got improved in recovery phase, but persisted or got worse in aggravated phase. Compared with patients in discharged group, the patients in un-discharged/died group suffered from decreased counts of total T lymphocytes, CD4 + T lymphocytes, CD8 + T lymphocytes, as well as NK cells at 2 weeks after treatment. Clinical classification-critically severe was the independently risk factor for lymphopenia (OR = 7.701, 95%CI:1.265-46.893, P = 0.027), eosinopenia (OR = 5.595, 95%CI:1.008-31.054, P = 0.049), and worse one-month outcome (OR = 8.984; 95%CI:1.021-79.061, P = 0.048). Lymphopenia and eosinopenia may serve as predictors of disease severity and disease progression in COVID-19 patients, and enhancing the cellular immunity may contribute to COVID-19 treatment. Thus, PBICs might become a sentinel of COVID-19, and it deserves attention during COVID-19 treatment.	

2020	Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review.	Convalescent plasma and hyperimmune immunoglobulin may reduce mortality in patients with respiratory virus diseases, and are currently being investigated in trials as a potential therapy for coronavirus disease 2019 (COVID-19). A thorough understanding of the current body of evidence regarding the benefits and risks is required. OBJECTIVES: To assess whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19. The protocol was pre-published with the Center for Open Science and can be accessed here: osf.io/dwf53 We searched the World Health Organization (WHO) COVID-19 Global Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, Centers for Disease Control and Prevention COVID-19 Research Article Database and trials registries to identify ongoing studies and results of completed studies on 23 April 2020 for case-series, cohort, prospectively planned, and randomised controlled trials (RCTs). We followed standard Cochrane methodology and performed all steps regarding study selection in duplicate by two independent review authors (in contrast to the recommendations of the Cochrane Rapid Reviews Methods Group). We included studies evaluating convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, irrespective of disease severity, age, gender or ethnicity. We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)) and studies evaluating standard immunoglobulins. We followed recommendations of the Cochrane Rapid Reviews Methods Group regarding data extraction and assessment. To assess bias in included studies, we used the assessment criteria tool for observational studies, provided by Cochrane Childhood Cancer. We rated the certainty of evidence using the GRADE approach for the following outcomes: all-cause mortality at hospital discharge, improvement of clinical symptoms (7, 15, and 30 days after transfusion), grade 3 and 4 adverse events, and serious adverse events. MAIN RESULTS: We included eight studies (seven case-series, one prospectively planned, single-arm intervention study) with 32 participants, and identified a further 48 ongoing studies evaluating convalescent plasma (47 studies) or hyperimmune immunoglobulin (one study), of which 22 are randomised. Overall risk of bias of the eight included studies was high, due to: study design; small number of participants; poor reporting within studies; and varied type of participants with different severities of disease, comorbidities, and types of previous or concurrent treatments, including antivirals, antifungals or antibiotics, corticosteroids, hydroxychloroquine and respiratory support. We rated all outcomes as very low certainty, and we were unable to summarise numerical data in any meaningful way. As we identified case-series studies only, we reported results narratively. Effectiveness of convalescent plasma for people with COVID-19 The following reported outcomes could all be related to the underlying natural history of the disease or other concomitant treatment, rather than convalescent plasma. All-cause mortality at hospital discharge All studies reported mortality. All participants were alive at the end of the reporting period, but not all participants had been discharged from hospital by the end of the study (15 participants discharged, 6 still hospitalised, 11 unclear). Follow-up ranged from 3 days to 37 days post-transfusion. We do not know whether convalescent plasma therapy affects mortality (very low-certainty evidence). Improvement of clinical symptoms (assessed by respiratory support) Six studies, including 28 participants, reported the	

		level of respiratory support required; most participants required respiratory support at baseline. All studies reported improvement in clinical symptoms in at least some participants. We do not know whether convalescent plasma improves clinical symptoms (very low-certainty evidence). Time to discharge from hospital Six studies reported time to discharge from hospital for at least some participants, which ranged from four to 35 days after convalescent plasma therapy. Admission on the intensive care unit (ICU) Six studies included patients who were critically ill. At final follow-up the majority of these patients were no longer on the ICU or no longer required mechanical ventilation. Length of stay on the ICU Only one study (1 participant) reported length of stay on the ICU. The individual was discharged from the ICU 11 days after plasma transfusion. Safety of convalescent plasma for people with COVID-19 Grade 3 or 4 adverse events The studies did not report the grade of adverse events after convalescent plasma transfusion. Two studies reported data relating to participants who had experienced adverse events, that were presumably grade 3 or 4. One case study reported a participant who had moderate fever (38.9 °C). Another study (3 participants) reported a case of severe anaphylactic shock. Four studies reported the absence of moderate or severe adverse events (19 participants). We are very uncertain whether or not convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence). Serious adverse events One study (3 participants) reported one serious adverse event. As described above, this individual had severe anaphylactic shock after receiving convalescent plasma. Six studies reported that no serious adverse events occurred. We are very uncertain whether or not convalescent plasma therapy affects the risk of serious adverse events (very low-certainty evidence). AUTHORS' CONCLUSIONS: We identified eight studies (seven case-series and one prospectively planned single-arm intervention study) with a total of 32 participants (range 1 to 10). Most studies assessed the risks of the intervention; reporting two adverse events (potentially grade 3 or 4), one of which was a serious adverse event. We are very uncertain whether convalescent plasma is effective for people admitted to hospital with COVID-19 as studies reported results inconsistently, making it difficult to compare results and to draw conclusions. We identified very low-certainty evidence on the effectiveness and safety of convalescent plasma therapy for people with COVID-19; all studies were at high risk of bias and reporting quality was low. No RCTs or controlled non-randomised studies evaluating benefits and harms of convalescent plasma have been completed. There are 47 ongoing studies evaluating convalescent plasma, of which 22 are RCTs, and one trial evaluating hyperimmune immunoglobulin. We will update this review as a living systematic review, based on monthly searches in the above mentioned databases and registries. These updates are likely to show different results to those reported here.	

2020	Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19.	As a zoonotic disease that has already spread globally to several million human beings and possibly to domestic and wild animals, eradication of coronavirus disease 2019 (COVID-19) appears practically impossible. There is a pressing need to improve our understanding of the immunology of this disease to contain the pandemic by developing vaccines and medicines for the prevention and treatment of patients. In this review, we aim to improve our understanding on the immune response and immunopathological changes in patients linked to deteriorating clinical conditions such as cytokine storm, acute respiratory distress syndrome, autopsy findings and changes in acute-phase reactants, and serum biochemistry in COVID-19. Similar to many other viral infections, asymptomatic disease is present in a significant but currently unknown fraction of the affected individuals. In the majority of the patients, a 1-week, self-limiting viral respiratory disease typically occurs, which ends with the development of neutralizing antiviral T cell and antibody immunity. The IgM-, IgA-, and IgG-type virus-specific antibodies levels are important measurements to predict population immunity against this disease and whether cross-reactivity with other coronaviruses is taking place. High viral load during the first infection and repeated exposure to virus especially in healthcare workers can be an important factor for severity of disease. It should be noted that many aspects of severe patients are unique to COVID-19 and are rarely observed in other respiratory viral infections, such as severe lymphopenia and eosinopenia, extensive pneumonia and lung tissue damage, a cytokine storm leading to acute respiratory distress syndrome, and multiorgan failure. Lymphopenia causes a defect in antiviral and immune regulatory immunity. At the same time, a cytokine storm starts with extensive activation of cytokine-secreting cells with innate and adaptive immune mechanisms both of which contribute to a poor prognosis. Elevated levels of acute-phase reactants and lymphopenia are early predictors of high disease severity. Prevention of development to severe disease, cytokine storm, acute respiratory distress syndrome, and novel approaches to prevent their development will be main routes for future research areas. As we learn to live amidst the virus, understanding the immunology of the disease can assist in containing the pandemic and in developing vaccines and medicines to prevent and treat individual patients.	

2020	Renin-angiotensin-aldosterone system and COVID-19 infection.	With the multiplication of COVID-19 severe acute respiratory syndrome cases due to SARS-COV2, some concerns about angiotensin-converting enzyme 1 (ACE1) inhibitors (ACEi) and angiotensin II type 1 receptor blockers (ARB) have emerged. Since the ACE2 (angiotensin-converting enzyme 2) enzyme is the receptor that allows SARS COV2 entry into cells, the fear was that pre-existing treatment with ACEi or ARB might increase the risk of developing severe or fatal severe acute respiratory syndrome in case of COVID-19 infection. The present article discusses these concerns. ACE2 is a membrane-bound enzyme (carboxypeptidase) that contributes to the inactivation of angiotensin II and therefore physiologically counters angiotensin II effects. ACEis do not inhibit ACE2. Although ARBs have been shown to up-regulate ACE2 tissue expression in experimental animals, evidence was not always consistent in human studies. Moreover, to date there is no evidence that ACEi or ARB administration facilitates SARS-COV2 cell entry by increasing ACE2 tissue expression in either animal or human studies. Finally, some studies support the hypothesis that elevated ACE2 membrane expression and tissue activity by administration of ARB and/or infusion of soluble ACE2 could confer protective properties against inflammatory tissue damage in COVID-19 infection. In summary, based on the currently available evidence and as advocated by many medical societies, ACEi or ARB should not be discontinued because of concerns with COVID-19 infection, except when the hemodynamic situation is precarious and case-by-case adjustment is required.	
2020	ABO blood group predisposes to COVID-19 severity and cardiovascular diseases.	NA	
2020	Retrospective analysis of laboratory testing in 54 patients with severe- or critical-type 2019 novel coronavirus pneumonia.	Timely analysis of the laboratory characteristics associated with 2019 novel coronavirus pneumonia (COVID-19) can assist with clinical diagnosis and prognosis. This study is a collection of clinical data from 54 hospitalized adult patients diagnosed with COVID-19 in the Zhongfa Xincheng district of China at Tongji Hospital of Huazhong University of Science and Technology from January 28, 2020 to February 11, 2020. The average age of the patients was 61.8 ± 14.5 years, and the predominant age group was 50-79. The proportion of critical-type patients with comorbidities was higher than that of severe-type patients. Lymphocyte counts were significantly reduced in routine bloodwork for all patients, but significantly lower in critical-type patients than that in severe-type patients. Prolongation of prothrombin times (PT) and elevation of fibrinogen degradation products (FDPs) and D-dimers (D-Ds) were detected in coagulation function tests, and more significant changes were observed in critical-type patients compared to severe-type patients. Serum ferritin levels were sensitive to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection but could not be used for disease assessment. In addition, levels of two inflammatory factors, soluble interleukin-2 receptor (sIL-2R) and interleukin-6 (IL-6) were significantly increased in all patients, but higher in critical-type patients than in severe-type patients. Moreover, kidney injury was the second-most common organ affected by COVID-19 followed by heart and liver. Kidney and heart injury were more severe in critical-type patients than in severe-type patients. All of the 31 severe-type patients recovered. Of the critical-type patients, six died and 17 recovered. The length of hospital stay for critical-type patients was significantly longer for severe-type patients. In summary, increased lymphocyte counts, prolonged PT, secondary increases in fibrinolytic activity and increases	

		in sIL-2R and IL-6 are typical features of COVID-19 and are associated with disease severity.	
2020	[Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19].	Objective: To evaluate the cardiovascular damage of patients with COVID-19, and determine the correlation of serum N-terminal pro B-type natriuretic peptide (NT-proBNP） and cardiac troponin-I (cTnI） with the severity of COVID-19, and the impact of concomitant cardiovascular disease on severity of COVID-19 was also evaluated. Methods: A cross-sectional study was designed on 150 consecutive patients with COVID-19 in the fever clinic of Tongji Hospital in Wuhan from January 19 to February 13 in 2020, including 126 mild cases and 24 cases in critical care. Both univariate and multivariate logistic regression were used to analyze the correlation of past medical history including hypertension, diabetes and coronary heart disease (CHD）, as well as the levels of serum NT-proBNP and cTnI to the disease severity of COVID-19 patients. Results: Age, hypersensitive C-reactive protein(hs-CRP) and serum creatinine levels of the patients were higher in critical care cases than in mild cases(all P <0.05). Prevalence of male, elevated NT-proBNP and cTnI, hypertension and coronary heart disease were significantly higher in critical cases care patients than in the mild cases(all P <0.05). Univariate logistic regression analysis showed that age, male, elevated NT-proBNP, elevated cTnI, elevated hs-CRP, elevated serum creatinine, hypertension, and CHD were significantly correlated with critical disease status(all P <0.05). Multivariate logistic regression analysis showed that elevated cTnI(OR =26.909, 95% CI 4.086-177.226, P =0.001) and CHD (OR =16.609 , 95% CI 2.288-120.577, P =0.005) were the independent risk factors of critical disease status. Conclusions: COVID-19 can significantly affect the heart function and lead to myocardial injury. The past medical history of CHD and increased level of cTnI are 2 independent determinants of clinical disease status in patients with COVID-19.	

2020	[Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV].	Objective: To explore the clinical characteristics and prognosis of the new coronavirus 2019-nCoV patients combined with cardiovascular disease （CVD). Methods: A retrospective analysis was performed on 112 COVID-19 patients with CVD admitted to the western district of Union Hospital in Wuhan, from January 20, 2020 to February 15, 2020. They were divided into critical group (ICU, n =16) and general group (n =96) according to the severity of the disease and patients were followed up to the clinical endpoint. The observation indicators included total blood count, C-reactive protein (CRP), arterial blood gas analysis, myocardial injury markers, coagulation function, liver and kidney function, electrolyte, procalcitonin (PCT), B-type natriuretic peptide (BNP), blood lipid, pulmonary CT and pathogen detection. Results: Compared with the general group, the lymphocyte count (0.74 (0.34, 0.94)×10 9 /L vs. 0.99 (0.71, 1.29)×10 9 /L, P =0.03) was extremely lower in the critical group, CRP (106.98 (81.57, 135.76) mg/L vs. 34.34 (9.55,76.54) mg/L, P <0.001) and PCT (0.20 (0.15,0.48) μg/L vs. 0.11 (0.06,0.20) μg/L, P <0.001) were significantly higher in the critical group. The BMI of the critical group was significantly higher than that of the general group (25.5 (23.0, 27.5) kg/m 2 vs. 22.0 (20.0, 24.0) kg/m 2 , P =0.003). Patients were further divided into non-survivor group (17, 15.18%) group and survivor group (95, 84.82%). Among the non-survivors, there were 88.24% (15/17) patients with BMI> 25.0 kg/m 2 , which was significantly higher than that of survivors (18.95% (18/95), P <0.001). Compared with the survived patients, oxygenation index (130 (102, 415) vs. 434 (410, 444), P <0.001) was significantly lower and lactic acid (1.70 (1.30, 3.00) mmol/L vs. 1.20 (1.10, 1.60) mmol/L, P <0.001) was significantly higher in the non-survivors. There was no significant difference in the proportion of ACEI/ARB medication between the critical group and the general group or between non-survivors and survivors （all P >0.05). Conclusion: COVID-19 patients combined with CVD are associated with a higher risk of mortality. Critical patients are characterized with lower lymphocyte counts. Higher BMI are more often seen in critical patients and non-survivor. ACEI/ARB use does not affect the morbidity and mortality of COVID-19 combined with CVD. Aggravating causes of death include fulminant inflammation, lactic acid accumulation and thrombotic events.	