The Daily COVID-19 Literature Surveillance Summary

December 21, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Epidemiology

- What was the SARS-CoV-2-specific neutralizing antibody response in Norwegian healthcare workers after the first wave of COVID-19 pandemic? A multicenter prospective survey study of 607 healthcare workers (HCW) by a researcher at the Influenza Centre at the University of Bergen in Norway found 5% of participants (32/607) were seropositive for SARS-CoV-2 (spike-specific IgG, IgM, and IgA antibodies), including 21 who were positive at baseline and 11 who seroconverted during follow-up. 77% of the infected HCWs, in high-risk departments were young nurses aged 23-31. Results also showed that HCW were 11.6 times more likely to contact COVID-19 patients when compared to low-risk HCW or community members, while HCW with partial PPE were at a 2.5 fold higher risk. Authors highlight the importance of protecting high-risk frontline HCW and suggest prioritization of this group during vaccine distribution.

- COVID-19 did not appear to have drastic effects on the pregnant population. Researchers affiliated with Department of Obstetrics and Gynecology at University of Toronto, Canada conducted a literature review of 8 studies including 10,966 patients in 15 countries on COVID-19 in pregnancy and found that maternal characteristics, symptoms, and outcomes were not significantly different from the general population. They hypothesize pregnancy-induced changes to the ACE-2-Angiotensin axis might counteract changes induced by SARS-CoV-2, leading to less vasoconstriction, fibrosis, and inflammatory/thrombotic processes. Authors suggest pregnant women may not be more affected by SARS-CoV-2 infection than the general public, but urge for further research due to paucity of data on aggressiveness of COVID-19 in pregnancy.

Understanding the Pathology

- Could there be an association of salivary content alteration and early ageusia symptoms in COVID-19 infections? Dental specialists in Saudi Arabia reviewed 36 studies on chemical and inflammatory changes that occur in SARS-CoV-2 infected salivary glands and propose a chemosensory mechanism to explain alterations in taste and smell found commonly seen in COVID-19. In patients reporting aguesia, they found changes in salivary hormones, inorganic compounds, pH, enzymes, and salivary flow rate, which are all involved in normal taste perception. Authors suggest with better understanding and characterization of these changes, we may be able to prevent or treat changes in smell or taste seen among COVID-19 patients.

Transmission & Prevention

- Specific occupations and risk of severe COVID-19 are positively correlated. In this large-scale prospective cohort study, authors from various public health institutes in Glasgow, UK, Limerick, Ireland, and Syracuse, NY, analyzed data from the UK Biobank, involving 120,075 participants aged 40-69 registered with the National Health Service (NHS) in England, Wales or Scotland, and grouped them into occupational groups with concomitant serious COVID-19 infection (having to be hospitalized), in order to asses risk of infection across essential occupations. They found 29.3% of participants were classified as essential workers (9% healthcare, 11.2% social and education, and 9.1% other essential workers), and that 3,111 (2.6%) of the total participants tested positive for SARS-CoV-2. They concluded healthcare workers were at a 7-fold increased risk of developing severe COVID-19 and that social and transport workers had a doubled risk, highlighting the need for better protection and support for workers at higher risk for infection.

Management

- There may be a high prevalence of pulmonary sequelae at 3 months after hospital discharge in mechanically ventilated COVID-19 survivors. In this letter to the editor, Dutch researchers share their clinical data from 48 critically-ill COVID-19 patients who underwent follow-up screening three months after discharge that included pulmonary function testing (PFT), high resolution chest CT (HRCT), and 6-minute walk test (6-MWT). Prominent findings included diminished diffusion capacity, total lung capacity, and reticular fibrosis with ground-glass opacities present on HRCT. They report some evidence of new emphysematous abnormalities on HRCT which may be novel for COVID-19 compared to SARS or MERS. These findings suggest the necessity for intensive respiratory follow-up for patients with COVID-19 who underwent mechanical ventilation to screen for pulmonary sequelae.

R&D: Diagnosis & Treatments

- There is some data suggesting usage of smartwatch tracking data to detect COVID-19 cases early. An article reviews a study conducted by researchers at Scripps Research Translational Institute who compared the smartwatch data between 333 participants, 54 of which ended up reporting positive for COVID-19, and found that symptom tracking plus smartwatch biometric data collecting yielded more predictive results of COVID-19 positive test probability than symptom tracking alone. This study was conducted earlier this year and used a smartphone/smartwatch app called DETECT.

- Delayed specific IgM antibody responses observed among COVID-19 patients with severe progression. Virologists and immunologists from China and Canada analyzed the diagnostic accuracy of RT-qPCR testing compared to IgM-based antibody testing for COVID-19. They found IgM-based gold immunochromatographic assay (GICA) detected 82.2% (n=37/45) of RT-qPCR confirmed COVID-19 cases and 32.0% (n=8/25) of clinically suspected patients who falsely tested negative by RT-qPCR (Figure 1). Interestingly, 50% (n=4/8) of patients who were IgM-negative and RT-qPCR-positive developed severe disease (Figure 2). Researchers concluded that IgM-based antibody testing may have a complementary role to RT-PCR in diagnosing active infection by reducing false negatives, and delayed IgM antibody response may be predictive of more severe disease progression.

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EPIDEMIOLOGY

SARS-COV-2-SPECIFIC NEUTRALIZING ANTIBODY RESPONSES IN NORWEGIAN HEALTHCARE WORKERS AFTER THE FIRST WAVE OF COVID-19 PANDEMIC: A PROSPECTIVE COHORT STUDY

Trieu MC, Bansal A, Madsen A, Zhou F, Sævik M, Vahokoski J, Brokstad KA, Krammer F, Tøndel C, Mohn KGI, Blomberg B, Langeland N, Cox RJ.. J Infect Dis. 2020 Nov 28:jiaa737. doi: 10.1093/infdis/jiaa737. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A multicenter prospective survey study of healthcare workers (HCW) by a researcher at the Influenza Centre at the University of Bergen in Norway found 5% of participants (32/607) were seropositive for SARS-CoV-2 (spike-specific IgG, IgM, and IgA antibodies; Figures 2,4), including 21 who were positive at baseline and 11 who seroconverted during follow-up. 77% of the infected HCWs, in high-risk departments were young nurses aged 23-31 (Figure 1). Results also showed that HCW were 11.6 times more likely to contact COVID-19 patients when compared to low-risk HCW or community members, while HCW with partial PPE were at a 2.5 fold higher risk. Authors highlight the importance of protecting high-risk frontline HCW and suggest prioritization of this group during vaccine distribution.

ABSTRACT

BACKGROUND: During the coronavirus disease 2019 (COVID-19) pandemic, many countries experienced infection in healthcare workers (HCW) due to overburdened healthcare systems. However, whether infected HCW acquire protective immunity against SARS-CoV-2 is unclear. Here, we characterized SARS-CoV-2-specific antibody responses in Norwegian HCW in a prospective cohort study. METHODS: We enrolled 607 HCW pre- and post-the first COVID-19-pandemic wave. Exposure history, COVID-19-like symptoms and serum samples were collected. SARS-CoV-2-specific antibodies were characterized by spike-protein IgG/IgM/IgA enzyme-linked immunosorbent and live-virus neutralization assays. RESULTS: Spike-specific IgG, IgM, and IgA antibodies increased after the first pandemic wave in HCW with COVID-19-patient exposure, but not in HCW without patient exposure. Thirty-two HCW (5.3%) had spike-specific antibodies (11 seroconverted with >=4-fold increase, 21 were seropositive at baseline). Neutralizing antibodies were found in 11 HCW that seroconverted, of whom 4 (36.4%) were asymptomatic. Ninety-seven HCW were tested by reverse-transcriptase-polymerase chain reaction (RT-PCR) during follow-up, 8 were positive (7 seroconverted and 1 had undetectable antibodies). CONCLUSIONS: We found increases in SARS-CoV-2-neutralizing antibodies in infected HCW, especially after COVID-19-patient exposure. Our data show a low number of SARS-CoV-2-seropositive HCW in a low prevalence setting, however, the proportion of seropositivity was higher than RT-PCR positivity, highlighting the importance of antibody testing.

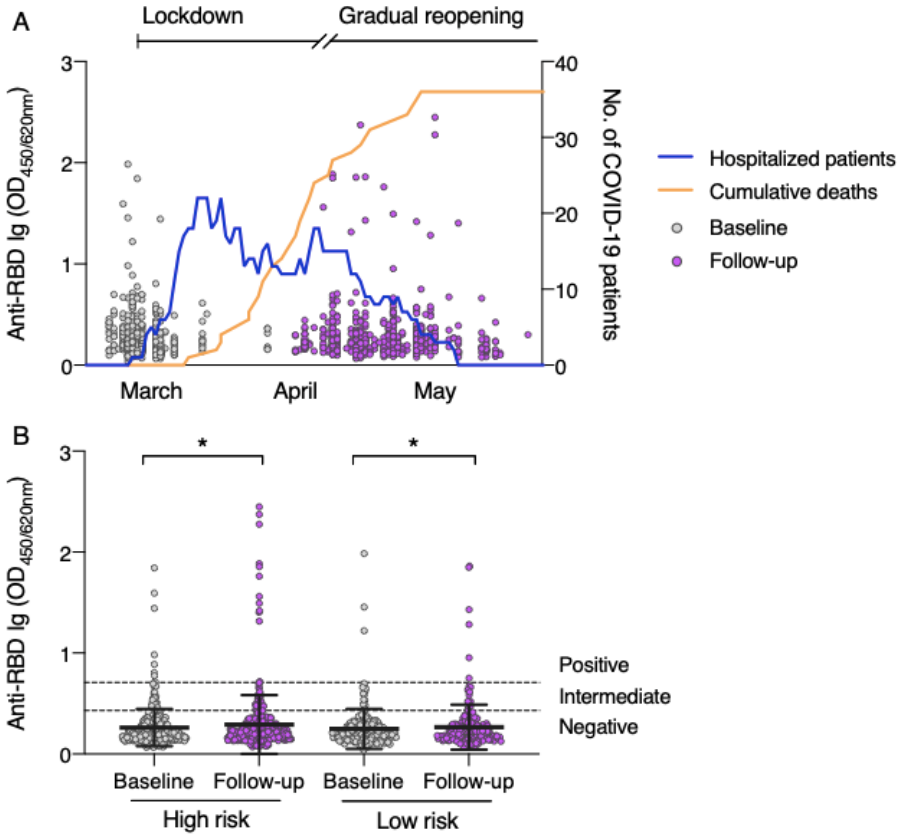

Figure 1: Screening for SARS-CoV-2 receptor-binding domain (RBD)-specific antibodies in healthcare workers (HCW) before and after COVID-19 patient admissions. (a) HCW (n=607) were recruited between March 6th and April 9th, and followed up after 6-10 weeks. Each circle represents one HCW (grey baseline and purple follow-up) and their anti-RBD antibodies measured in the screening ELISA as optical density (OD) at 450/620nm (left y-axis). The numbers of hospitalized COVID-19 patients (blue line) and cumulative deaths (orange line) in Bergen, Norway are plotted on the right y-axis. Lockdown was initiated in Norway on March 12th, 2020, and a gradual reopening starting on April 20th, 2020. (b) HCW were grouped into high risk (testing facility, COVID-19-designated wards and intensive care unit wards) and low risk (no known exposure to COVID-19 patients) of occupational exposure to SARS-CoV-2 according to their working department and information in their case report forms. Dotted lines are cutoffs for negative screening results (OD <0.430) and positive screening results (OD ≥ 0.708) (see Supplementary Figure 1 for further information). Horizontal lines represent mean with standard deviation. OD values were log-transformed and compared between time points in mixed-effects models with adjustment for subject variation, age, sex, and other relevant demographic factors. *p<0.05.

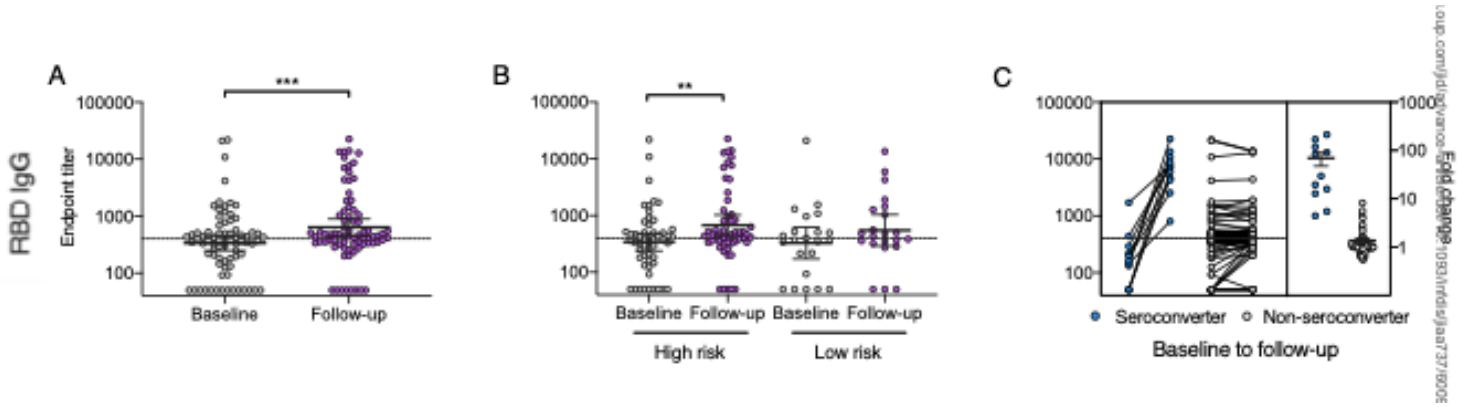

Figure 2: SARS-CoV-2 receptor-binding domain (RBD)-specific IgG antibodies in healthcare workers (HCW) before and after COVID-19 patient admissions. The RBD-specific IgG levels were measured for HCW with positive or intermediate RBD screening results (n=76) were titrated for endpoint titres (A) by enzyme-linked immunosorbent assay (ELISA). RBD- specific IgG endpoint titers (B) in high-risk and low-risk HCW groups. HCWs were divided into seroconverters (blue circle) who were seropositive and had ≥4-fold increase in IgG titers at follow-up and non-seroconverters (grey circle) who were either seronegative or had <4-fold increase in IgG titers at follow-up (C). The fold changes are plotted on the right y-axis with horizontal lines representing the mean with standard error of the mean. Dotted lines represent cutoffs for positive results, calculated as 3 standard deviations above the mean of the pre-pandemic negative sera (RBD IgG endpoint titer ≥400). Individuals with undetectable antibodies were assigned an endpoint titer of 50 for plotting and calculation purposes. Endpoint titers were log transformed and compared between time points in mixed-effects models with adjustment for subject variation, age, sex, and other relevant demographic factors. **p<0.01. ***p<0.001.

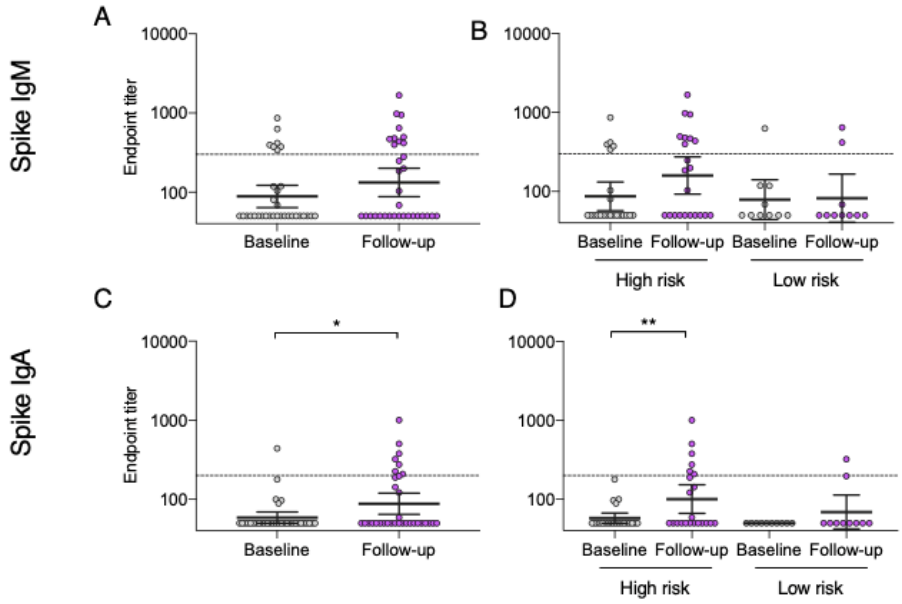

Figure 4: SARS-CoV-2 spike-specific IgM and IgA antibodies in healthcare workers (HCW) before and after COVID-19 patient admissions. HCW with positive spike IgG results (n=32) were further analyzed in spike IgM and IgA enzyme-linked immunosorbent assay (ELISA). Spike-specific IgM and IgA endpoint titers (A,C) were calculated and each circle represents one HCW (grey baseline and purple follow-up). Horizontal lines represent geometric mean with 95% confidence interval. The spike-specific IgM and IgA endpoint titers in HCW in high-risk and low-risk groups (B, D). Dotted lines represent cutoffs for positive results, calculated as 3 standard deviations above the mean of the pre-pandemic negative sera (IgM endpoint titer ≥300, IgA endpoint tire ≥200). Individuals with undetectable antibodies were assigned an endpoint titer of 50 for plotting and calculation purposes. Endpoint titers were logtransformed
and compared between time points in mixed-effects models with adjustment for subject variation, age, sex, and other relevant demographic factors. *p<0.05. **p<0.01.

LOW RATE OF COVID-19 SEROCONVERSION IN HEALTH-CARE WORKERS AT A DEPARTMENT OF INFECTIOUS DISEASES IN SWEDEN DURING THE LATER PHASE OF THE FIRST WAVE; A PROSPECTIVE LONGITUDINAL SEROEPIDEMIOLOGICAL STUDY

Rashid-Abdi M, Krifors A, Sälléber A, Eriksson J, Månsson E.. Infect Dis (Lond). 2020 Nov 24:1-7. doi: 10.1080/23744235.2020.1849787. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A prospective cohort study by infectious disease specialists examined 131 individuals working at Department of Infectious Disease, Hospital of Västmanland in Sweden from May 4 to August 17, 2020 for anti-SARS-CoV-2 IgG antibodies (Abbott's SARS-CoV-2 IgG immunoassay) as well as symptoms consistent with COVID-19 (Table 2). At the start of the study, 15% (n=18) of participants had IgG antibodies against SARS-CoV-2 compared with 19% (n=25) at the end (Figure 2); a single asymptomatic infection was discovered, while two individuals with PCR-confirmed COVID-19 did not develop IgG antibodies. This study demonstrates the possibility of limiting COVID-19 transmission in a high-risk workplace via social distancing and proper protective measures, though asymptomatic individuals could pose a threat to such policies.

ABSTRACT

Background: Health-care workers are at risk of contracting and transmitting SARS-CoV-2. The aim of this study was to investigate the prevalence of SARS-CoV-2 IgG antibodies and the rate of seroconversion in an environment with high exposure to SARS-CoV-2. Methods: 131 health-care workers at the Department of Infectious Diseases in Vasteras, Sweden, were included in the study. Abbott's SARS-COV-2 IgG immunoassay was used with a signal cut-off ratio of >=1.4. Every third week from the beginning of May, blood samples were drawn, and the participants completed a questionnaire regarding symptoms consistent with COVID-19 and the result of any SARS-CoV-2 PCR performed since the last sampling occasion. Participants with IgG antibodies against SARS-CoV-2 were re-sampled only on the sixth and last occasion. Results: At the start of the study, 18 (15%) participants had SARS-CoV-2 IgG antibodies. At the end, 25 (19%) of 131 participants were seropositive. One case of asymptomatic infection was detected, and two cases with PCR-confirmed COVID-19 did not develop IgG antibodies. Conclusion: The low rate of seroconversion during the study suggests that it is possible to prevent transmission of SARS-COV-2 in a high-exposure environment. Compliance with adequate infection control guidelines is the likely explanation of our findings.

FIGURES

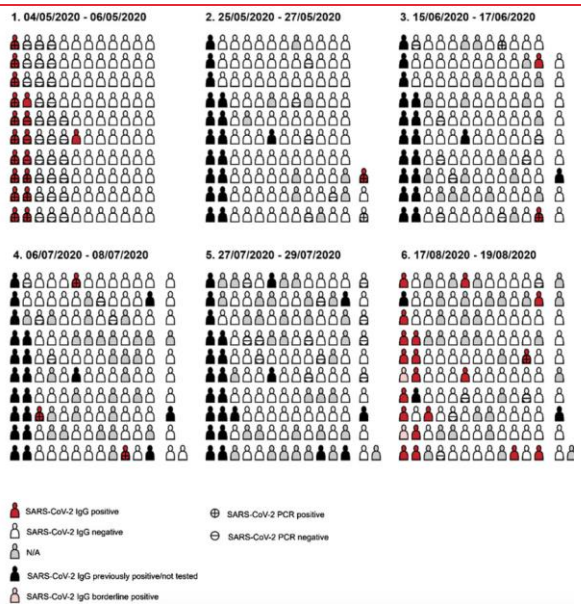

Figure 2. SARS-CoV-2 IgG cohort

	All ($n = 131$)	SARS-CoV-2 RNA/IgG positive[a] ($n = 27$)	SARS-CoV-2 negative ($n = 104$)	p-value
Fever > 38°	29 (22%)	15 (56%)	14 (13%)	<.001
Chills	25 (19%)	11 (41%)	14 (13%)	
Fatigue	97 (74%)	18 (67%)	79 (76%)	
Myalgia	42 (32%)	15 (56%)	27 (26%)	.003
Cough	54 (41%)	12 (44%)	42 (40%)	
Sneeze	85 (65%)	15 (56%)	70 (67%)	
Sore throat	66 (50%)	13 (48%)	53 (51%)	
Rhinorrhea	71 (54%)	14 (52%)	57 (49%)	
Nasal congestation	64 (49%)	17 (63%)	47 (45%)	
Dyspnoea	11 (8%)	5 (19%)	6 (6%)	.033
Shortness of breath	30 (23%)	10 (37%)	20 (19%)	
Chest pain	16 (12%)	5 (19%)	11 (11%)	
Other respiratory symptoms	15 (11%)	5 (19%)	10 (10%)	
Headache	90 (69%)	17 (63%)	73 (70%)	
Nausea/vomiting	34 (26%)	9 (33%)	25 (24%)	
Abdominal pain	26 (20%)	6 (22%)	20 (19%)	
Diarrhea	31 (24%)	6 (22%)	25 (24%)	
Loss of appetite	24 (18%)	12 (44%)	12 (12%)	<.001
Sick leave	78 (60%)	23 (85%)	55 (53%)	.002
Hospitalization	3 (2%)	1 (4%)	2 (2%)	

[a]SARS CoV-2 RNA or SARS-CoV-2 IgG positive at any point during the study.

Table 2. Symptoms

METABOLIC SYNDROME AND COVID-19

Yanai H.. Cardiol Res. 2020 Dec;11(6):360-365. doi: 10.14740/cr1181. Epub 2020 Nov 2.
Level of Evidence: 5 - Review / Literature Review

BLUF

This review conducted by an endocrinologist in Japan analyzed 37 articles for a possible link between metabolic syndrome and susceptibility/severity of SARS-CoV-2 infection. Findings suggest increased expression of inflammatory cytokines, endothelial dysfunction, and increased vWF seen in insulin resistance related to metabolic syndrome may cause a cytokine storm leading to thrombus formation, thus increasing the severity of infection (Figure 2), while obesity showed increased expression of the ACE2 receptor through which SARS-CoV-2 entry occurs. The author suggests metabolic syndrome and its components may be associated with increased COVID-19 susceptibility and severity (Figure 1), which will require special attention by providers caring for this patient population.

ABSTRACT

Recent studies showed that comorbidities such as diabetes, hypertension and obesity contribute to severe and worse outcomes of coronavirus disease 2019 (COVID-19), suggesting that metabolic syndrome and its components are associated with severity of COVID-19. Here, I systematically reviewed a possible association of metabolic syndrome with the susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severity of COVID-19 by literature search. A population-based study and UK Biobank studies showed that patients with metabolic syndrome is highly susceptible to SARS-CoV-2 infection. Recent meta-analyses showed that metabolic syndrome is significantly associated with the development of severe COVID-19. Angiotensin-converting enzyme (ACE) 2 is the cellular entry receptor of SARS-CoV-2. Enhanced ACE2 expression, pre-existing endothelial dysfunction and procoagulant state induced by adipocytokines dysregulation in metabolic syndrome may play a crucial role for the development of severe COVID-19.

FIGURES

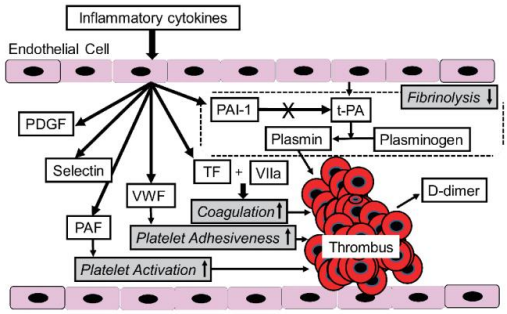

Figure 2. A mechanism for inflammatory cytokines-induced thrombosis formation. AGT: angiotensinogen; CI: confidence interval; FFA: free fatty acids; IL: interleukin; PAF: platelet-activating factor; PAI-1: plasminogen activator inhibitor-1; TF: tissue factor; t-PA: tissue-type plasminogen activator; PDGF: platelet-derived growth factor; VWF: von Willebrand factor.

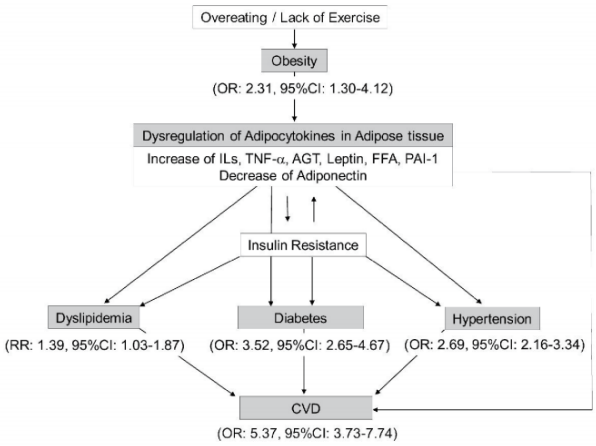

Figure 1. A significant association between metabolic syndrome and severity of COVID-19. OR (odds ratio) and RR (relative risk) indicate the risk for the development of severe COVID-19. AGT: angiotensinogen; CI: confidence interval; CVD: cardiovascular disease; FFA: free fatty acids; IL: interleukin; PAI-1: plasminogen activator inhibitor-1; TNF-α: tumor necrosis factor-alpha; COVID-19: coronavirus disease 2019.

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

PHENOTYPICAL AND FUNCTIONAL ALTERATION OF UNCONVENTIONAL T CELLS IN SEVERE COVID-19 PATIENTS

Jouan Y, Guillon A, Gonzalez L, Perez Y, Boisseau C, Ehrmann S, Ferreira M, Daix T, Jeannet R, François B, Dequin PF, Si-Tahar M, Baranek T, Paget C.. J Exp Med. 2020 Dec 7;217(12):e20200872. doi: 10.1084/jem.20200872.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

Investigators from various institutions in France analyzed 30 patients admitted to Bretonneau Hospital ICU (Tours, France) with severe COVID-19 from March 18 to April 17, 2020, accessing the frequency and functions of patients' unconventional T (uT) cells, against control groups of 20 healthy volunteers and 17 critically ill non-COVID-19 patients (admitted with cardiac arrest, stroke, neuromuscular disease, or hemorrhage from March 14, 2018 to July 7, 2019). The results revealed a change in various phenotypes of uT cells in patients with severe COVID-19 (Figure 2A), with a decrease in MAIT and iNKT cells, suggesting status of certain uT cell phenotypes at admission may be a helpful diagnostic predictor of disease severity.

ABSTRACT

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, gammadeltaT, 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.

FIGURES

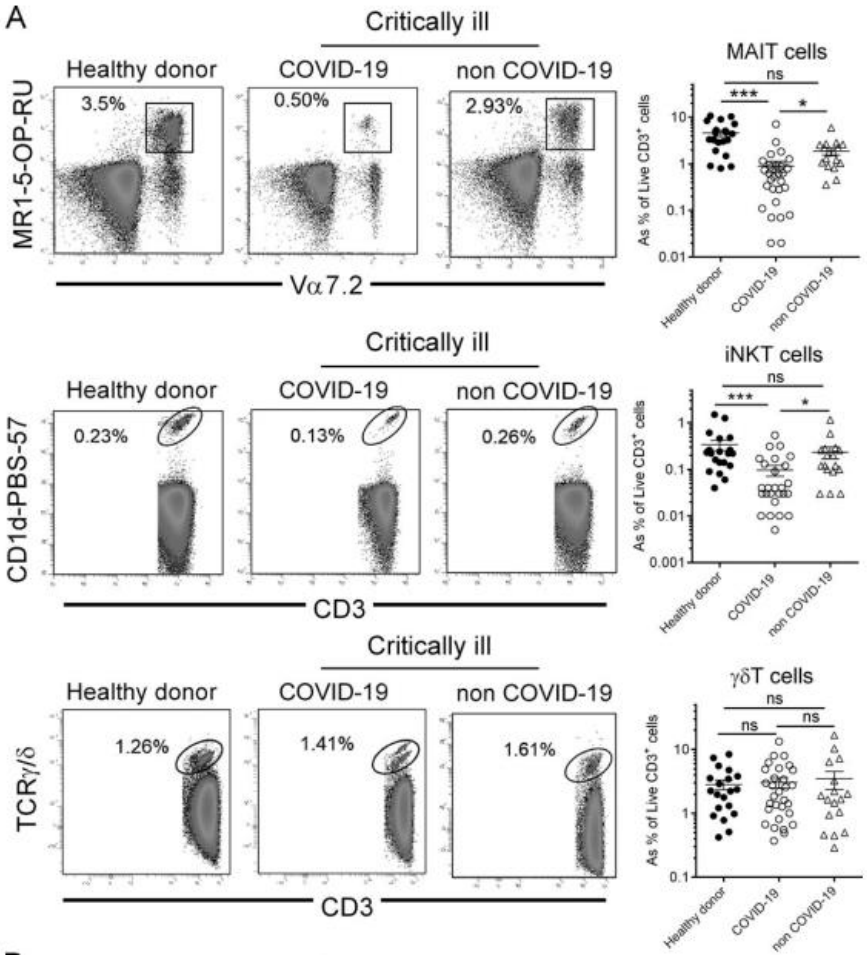

Figure 2. Relative proportion of uT cells in PBMCs and ETA of COVID-19 patients. Flow cytometry analyses of uT cells in the blood of healthy donors (n = 20) and COVID-19 (n = 30) and non–COVID-19 (n = 17) patients. Representative dot plots of MAIT, iNKT, and γδT cells of the three groups are shown in the left panel as percentage of CD3+ live cells. Individuals and means ± SEM are shown in the right panel. Of note, iNKT cells could not be detected in four COVID-19 patients and one non–COVID-19 patient. Kruskal–Wallis test followed by a Dunn's multiple comparisons test.

PREGNANT PERSONS

COVID-19 DURING PREGNANCY: AN OVERVIEW OF MATERNAL CHARACTERISTICS, CLINICAL SYMPTOMS, MATERNAL AND NEONATAL OUTCOMES OF 10,996 CASES DESCRIBED IN 15 COUNTRIES

Figueiro-Filho EA, Yudin M, Farine D.. J Perinat Med. 2020 Nov 26;48(9):900-911. doi: 10.1515/jpm-2020-0364.
Level of Evidence: 5 - Review / Literature Review

BLUF

Researchers affiliated with Department of Obstetrics and Gynecology at University of Toronto, Canada conducted a literature review (8 studies including 10,966 patients in 15 countries) on COVID-19 in pregnancy and found that maternal characteristics, symptoms, and outcomes were not significantly different from the general population (Tables 3,4,6). They hypothesize pregnancy-induced changes to the ACE-2-Angiotensin axis might counteract changes induced by SARS-CoV-2, leading to less vasoconstriction, fibrosis, and inflammatory/thrombotic processes. Authors suggest pregnant women may not be more affected by SARS-CoV-2 infection than the general public, but urge for further research due to paucity of data on aggressiveness of COVID-19 in pregnancy.

ABSTRACT

The objective of this review was to identify the most significant studies reporting on COVID-19 during pregnancy and to provide an overview of SARS-CoV-2 infection in pregnant women and perinatal outcomes. Eligibility criteria included all reports, reviews; case series with more than 100 individuals and that reported at least three of the following: maternal characteristics, maternal COVID-19 clinical presentation, pregnancy outcomes, maternal outcomes and/or neonatal/perinatal outcomes. We included eight studies that met the inclusion criteria, representing 10,966 cases distributed in 15 countries around the world until July 20, 2020. The results of our review demonstrate that the maternal characteristics, clinical symptoms, maternal and neonatal outcomes almost 11,000 cases of COVID-19 and pregnancy described in 15 different countries are not worse or different from the general population. We suggest that pregnant women are not more affected by the respiratory complications of COVID-19, when compared to the outcomes described in the general population. We also suggest that the important gestational shift Th1-Th2 immune response, known as a potential contributor to the severity in cases of viral infections during pregnancy, are counter-regulated by the enhanced-pregnancy-induced ACE2-Ang-(1-7) axis. Moreover, the relatively small number of reported cases during pregnancy does not allow us to affirm that COVID-19 is more aggressive during pregnancy. Conversely, we also suggest, that down-regulation of ACE2 receptors induced by SARS-CoV-2 cell entry might have been detrimental in subjects with pre-existing ACE2 deficiency associated with pregnancy. This association might explain the worse perinatal outcomes described in the literature.

FIGURES

	Zaigham & Andersson 2020 (n=108)	Khoury et al. 2020 (n=241)	Kayem et al. 2020 (n=617)	Elshafeey et al. 2020 (n=385)	Juan et al. 2020 (n=324)	Matar et al. 2020 (n=136)	Ellington et al. 2020 (n=8,207)	Takemoto et al. 2020 (n=978)	Total (n=2,789; 10,996)
Maternal Characteristics									
Age , years	30.4± 3.6	32 (18–47)	INA	21–42	20–49	21.7 (25–41)	INA	30.5±7.2	NA
Age>35 years	INA	INA	194/617 (31.4%)	INA	INA	INA	1,817/8,207 (22.1%)	INA	2,011/8,824 (22.8%)
15–24 years	INA	INA	INA	INA	INA	INA	1921/8,207 (23.4%)	INA	1921/8,207 (23.4%)
25–34 years	INA	INA	INA	INA	INA	INA	4,469/8,207 (54.4%)	INA	4,469/8,207 (54.4%)
35–44 years	INA	INA	INA	INA	INA	INA	1,817/8,207 (22.1%)	INA	1,817/8,207 (22.1%)
BMI	INA	30.5 (21–56)	INA	INA	INA	INA	INA		30.5 (21–56)
>30	INA	98/178 (55.0%)	139/617 (22.5%)	INA	INA	INA	INA	89/978 (9.1%)	326/1,773 (18.4%)
30–39.9	INA	84/178 (47.2%)	INA	INA	INA	INA	INA	INA	84/178 (47.2%)
>40	INA	14/178 (7.9%)	INA	INA	INA	INA	INA	INA	14/178 (7.9%)
Race-Ethnicity									
Asian, non-Hispanic	INA	INA	INA	INA	INA	INA	254/8,207 (3.1%)	INA	254/8,207 (3.1%)
Black, non-Hispanic	INA	24/221 (10.9%)	INA	INA	INA	INA	1,459/8,207 (22.1%)	INA	1,483/8,428 (17.5%)
White, non-Hispanic	INA	67/221 (30.3%)	INA	INA	INA	INA	1,520/8,207 (23.0%)	235/978 (24.0%)	1,822/9,406 (19.4%)
Hispanic or Latino	INA	33/221 (14.9%)	INA	INA	INA	INA	3,048/8,207 (46.2%)	INA	3,081/8,428 (36.5%)
Multiple or other race	INA	INA	INA	INA	INA	INA	321/8,207 (3.9%)	743/978 (76.0%)	1,064/9,185 (11.6%)
Comorbidities									
Known underlying medical condition	INA	INA	INA	INA	INA	27/136 (19.8%)	1,878/8,207 (22.9%)	INA	1,905/8,343 (22.8%)
Asthma	INA	INA	37/617 (6%)	INA	INA	INA	INA	23/978 (2.4%)	60/1,595 (3.76%)
Chronic respiratory diseases	INA	INA	6/617 (1%)	INA	INA	INA	409/1,878 (21.8%)	INA	415/2,495 (16.6%)
DM 1/2	INA	INA	14/617 (2.3%)	INA	INA	INA	288/1,878 (15.3%)	89/978 (9.1%)	391/3,473 (11.3%)
History of preeclampsia	INA	INA	27/617 (4.4%)	INA	INA	INA	INA	INA	27/617 (4.4%)
Cardiovascular disease	INA	INA	INA	INA	INA	INA	262/1,878 (14.0%)	54/978 (5.5%)	316/2,856 (11.1%)
Chronic hypertension/ hypertensive disorders in P	INA	INA	18/617 (2.9%)	INA	11/178 (6.2%)	INA	INA	INA	29/795 (3.64%)
Preeclampsia	INA	INA	21/617 (3.4%)	INA	3/178 (1.7%)	INA	INA	INA	24/795 (3.01%)
GDM	INA	INA	71/617 (11.5%)	INA	18/220 (8.2%)	INA	INA	INA	89/837 (10.6%)
Hypothyroidism	INA	INA	INA	INA	2/234 (0.9%)	INA	INA	INA	2/234 (0.9%)
Chronic renal disease	INA	INA	INA	INA	INA	INA	12/1,878 (0.6%)	INA	12/1,878 (0.6%)
Chronic liver disease	INA	INA	INA	INA	INA	INA	8/1,878 (0.4%)	INA	8/1,878 (0.4%)
Immuno compromised condition	INA	INA	INA	INA	INA	INA	66/1,878 (3.5%)	INA	66/1,878 (3.5%)
Neurological/ Neurodevelopmental/ intellectual D	INA	INA	INA	INA	INA	INA	17/1,878 (0.9%)	INA	17/1,878 (0.9%)
Placenta previa/acreta	INA	INA	INA	INA	1/38 (2.6%)	INA	INA	INA	1/38 (2.6%)
Smoking in pregnancy	INA	INA	16/617 (2.6%)	INA	INA	INA	INA	INA	16/617 (2.6%)

NA, not applicable; INA, information not available; DM, diabetes mellitus; GDM, gestational diabetes.

Table 3. Maternal characteristics of 10,966 pregnant women with COVID-19 described in 15 countries until July 20 2020.

	Zaigham & Anderson 2020 (n=108)	Khonry et al. 2020 (n=241)	Kavem et al. 2020 (n=617)	Elshafeev et al. 2020 (n=385)	Juan et al. 2020 (n=324)	Matar et al. 2020 (n=136)	Ellington et al. 2020 (n=8.207)	Takemoto et al. 2020 (n=978)	Total (n=2,789; 10.996)
Maternal COVID-19 clinical presentation									
Asymptomatic	INA	102/241 (42.3%)	120/617 (19.5%)	29/385 (7.5%)	INA	INA	156/5,355 (2.9%)	INA	407/6,598 (6.2%)
Symptomatic	INA	139/241 (57.7%)	497/617 (80.5%)	356/385 (92.5%)	INA	INA	5,199/5,355 (97.1%)	978/978 (100%)	7,169/7,576 (94.6%)
Mild	INA	64/241 (26.5%)	489/617 (79.2%)	368/385 (95.6%)	INA	INA	INA	INA	921/1,243 (74.1%)
Severe	INA	63/241 (26.1%)	93/617 (15.1%)	14/385 (3.6%)	INA	INA	INA	INA	170/1,243 03.7%)
Critical	INA	12/241 (5.0%)	35/617 (5.7%)	3/385 (0.8%)	INA	INA	INA	INA	50/1,243 (4.0%)
Maternal COVID-19 symptoms									
Fever	63/92 (68%)	46/139 (33.0%)	285/617 (46.2%)	259/385 (67.3%)	138/295 (46.8%)	69 136 (51%)	1,190/3,474 (343%)	INA	2,050/5,138 (39.99%)
Cough	37/108 (34%)	54/139 (38.8%)	384/617 (62.2%)	253/385 (65.7%)	101/295 (34.2%)	39 136 (29%)	1,799/3,474 (51.8%)	INA	2,667/5,154 (51.75%)
Loss of taste/smell	INA	INA	172/617 (27.9%)	INA	INA	INA	587.3,474 (16.9%)	INA	759/4,091 (18–49)
Malaise	14/108 (13%)	INA	INA	INA	0 (0%)	INA	INA	INA	14/108 (13%)
Dyspnea	13/108 (12%)	19/139 (13.6%)	165/617 (26.7%)	28/385 (7.3%)	39/295 (13.2%)	7/136 (5.1%)	1,045/3,474 (30.1%)	INA	1,303/5,154 (25.3%)
Myalgia	11 108 (7%)	INA	INA	24/385 (6.2%)	27/295 (92%)	10/136 (7.35%)	1,323/3,474 (38.1%)	INA	1,861/4,290 (43.4%)
Sore throat	8/108 (7%)	INA	INA	27/385 (7.0%)	10/295 (3.4%)	5/136 (3.7%)	942/3,474 (27.1%)	INA	984/4,290 (22.94%)
Headache	INA	INA	INA	INA	INA	INA	1,409/3,474 (40.6%)	INA	1,409/3,474 (40.6%)
Nausea/Vomitting	INA	INA	INA	INA	INA	INA	682/3,474 (19.6%)	INA	682/3,474 (19.6%)
Diarrhea	7/108 (6%)	INA	54617 (8.8%)	28/385 (7.3%)	11/295 (3 7%)	7/136 (5.1%)	497/3,474 (14.39%)	INA	597/5,154 (11.6%)
Fatigue	INA	INA	INA	27/385 (7.0%)	28/295 (9.5%)	INA	INA	INA	55/680 (8.1%)
Chills	INA	INA	INA	21/385 (5.5%)	INA	INA	989/3,474 (28.59%)	INA	989/3,474 (28.59%)
Runny nose	INA	INA	INA	INA	INA	INA	326/3,474 (9.4%)	INA	326/3,474 (9.4%)
Other	INA	INA	INA	<5%	INA	INA	1,190/3,474 (343%)	INA	1,190/3,474 (34.3%)
Symptoms during Post-Partum	INA	INA	INA	19 385 (4.9%)	INA	INA	INA	224 978 (22.9%)	243/1,363 (4.9%)
Radiological and laboratory findings									
Patchy shadowing ground glass opacity	INA	INA	INA	102/125 (81.6%)	183/190 (96.3%)	111/136 (81.6%)	INA	INA	396/451 (87.8%)
No Radiological findings	INA	INA	INA	4/125 (3.2%)	7/190 (3.7%)	INA	INA	INA	11/315 (3 .49%)
Leukocytes (reduced)	INA	INA	INA	INA	146/182 (80.2%)	INA	INA	INA	146/182 (802%)
Lymphocyte (reduced)	INA	INA	INA	54/385 (14.0%)	85/197 (45.7%)	INA	INA	INA	139/582 (23.8%)
CRP (elevated)	INA	INA	INA	72/385 (18.7%)	90/197 (45.7%)	INA	INA	INA	162/592 (27.49.)
AST, ALT (elevated)	INA	INA	INA	43/385 (11.2%)	5/42 (11.9%)	INA	INA	INA	48/427 (11.2%)
Platelet (reduced)	INA	INA	INA	4/385 (1.0%)	INA	INA	INA	INA	4/385 (1.0%)
D-dimer (elevated)	INA	INA	INA	86/385 (22.3%)	INA	INA	INA	INA	86/385 (22.3%)

NA, not applicable; INA, information not available; CRP, C-reactive protein; AST, aspartate aminostransferase; ALT, alanine aminotransferase.

Table 4. Maternal clinical presentation, symptoms, radiological and laboratory findings of 10,966 pregnant women with COVID-19 described in 15 countries until July 20 2020

	Zaigham & Andersson 2020 (n= 108)	Khoury et al. 2020 (n=241)	Kayem et al. 2020 (n=617)	Elshafeey et al. 2020 (n=385)	Juan et al. 2020 (n=324)	Matar et al. 2020 (n=126)	Ellington et al. 2020 (n=8,207)	Takemoto et al. 2020 (n=978)	Total (n=1,811; 10,018)
Neonatal outcomes									
Live Birth, g	86/87 (99%)	245/247 (99.2%)	174/181 (96.1%)	251/256 (98%)	INA	91/94 (96.8%)	INA	INA	847/865 (98%)
Birth weight	INA	3,135 g (640–4,700 g)	INA	1,520–4,050g	INA	3,127 g (1,500–3,400 g)	INA	INA	NA
Low birth weight (<2,500 g)	INA	INA	INA	20/256 (7.8%)	8/103 (7.8%)	INA	INA	INA	28/259 (11%)
Gestational age at delivery, weeks	INA	39 (247–41.6)	INA	30–41	28–41	36.2 (30–40)	INA	INA	NA
Apgar 5 min	INA	9 (0–9)	INA	INA	7 (7–10)	9 (0–9)	INA	INA	NA
Twins	INA	6/241 (2.5%)	INA	4/252 (1.6%)	INA	INA	INA	INA	10/493 (2.0%)
Term	INA	198/241 (82.5%)	126/181 (69.6%)	217/256 (84.7%)	INA	63/94 (67.0%)	INA	INA	604/772 (78.2%)
Preterm birth < 37 weeks	INA	34/233 (14.6%)	55/181 (30.3%)	39/256 (15.2%)	INA	31/94 (33.0%)	INA	INA	159/764 (21%)
Preterm birth < 34 weeks	INA	10/233 (4.3%)	26/181 (14.3%)	20/256 (7.8%)	INA	INA	INA	INA	56/670 (8.35%)
Fetal loss 14–21 weeks	INA	INA	5/181 (2.8%)	INA	INA	INA	INA	INA	5/181 (2.8%)
Preterm birth 22–31 weeks	INA	INA	21/181 (11.6%)	INA	INA	INA	INA	INA	21/181 (11.6%)
Preterm birth 32–36 weeks	INA	INA	29/181 (16%)	INA	INA	INA	INA	INA	29/181 (16%)
Overall preterm birth 22–36 weeks	INA	INA	50/181 (27.6%)	INA	INA	INA	INA	INA	50/181 (27.6%)
Male	INA	119/247 (48.2%)	INA	INA	INA	INA	INA	INA	119/247 (48.2%)
Female	INA	128/247 (51.8%)	INA	INA	INA	INA	INA	INA	128/247 (51.8%)
Resuscitation at Delivery	INA	70/233 (30%)	INA	INA	INA	INA	INA	INA	70/233 (30%)
Newborn complications							**INA**	**INA**	
Respiratory distress syndrome	INA	14/241 (5.8%)	INA	12/256 (4.7%)	2/79 (2.5%)	INA	INA	INA	28/576 (4.86%)
Complications prematurity/ preterm birth	INA	21/241 (8.7%)	INA	6/256 (2.4%)	INA	INA	INA	INA	27/497 (5.43%)
Sepsis	INA	1/241 (0.4%)	INA	INA	INA	INA	INA	INA	1/241 (0.4%)
Congenital anomaly	INA	8/241 (3.3%)	INA	INA	INA	INA	INA	INA	8/241 (3.3%)
None	INA	191/241 (79.3%)	INA	INA	INA	INA	INA	INA	191/241 (79.3%)
Other	INA	14/241 (5.8%)	INA	INA	INA	INA	INA	INA	14/241 (5.8%)
Admission neonatal intensive care unit	INA	61/237 (25.7%)	37/190 (19.5%)	8/256 (3.1%)	49/173 (28.3%)	28/136 (20.6%)	INA	INA	183/992 (18.45%)
Neonatal hospitalization							**INA**	**INA**	
<2 days	INA	153/245 (62.4%)	INA	INA	INA	INA	INA	INA	153/245 (62.4%)
3–7 days	INA	65/245 (26.5%)	INA	INA	INA	INA	INA	INA	65/245 (26.5%)
>7 days	INA	29/245 (11.8%)	INA	INA	INA	INA	INA	INA	29/245 (11.8%)
Neonatal death	1/87 (1%)	0/247 (0%)	1/190 (0.5%)	3/256 (1.2%)	1/221 (0.5%)	3/136 (2.2%)	INA	INA	9/1,137 (0.8%)
Fetal demise/stillbirth	1/87 (1%)	2/247 (0.8%)	7/181 (3.9%)	2/256 (0.8%)	4/223 (1.79%)	3/136 (2.2%)	INA	INA	19/1,130 (1.7%)
SARS-COV-2-positive	1/75 (1%)	6/236 (2.5%)	2/190 (1.1%)	6/256 (2.4%)	1/223 (0.5%)	2/136 (1.47%)	INA	INA	18/1,116 (1.6%)
SARS-COV-2-negative	74/75 (99%)	230/236 (97.5%)	188/190 (98.9%)	250/256 (97.6%)	222/223 (99.5%)	134/136 (98.5%)	INA	INA	1,098/1,116 (98.4%)

NA, not applicable; INA, information not available.

Table 6. Neonatal outcomes of 10,966 pregnant women with COVID-19 described in 15 countries until July 20 2020

PEDIATRICS

EVIDENCE OF THROMBOTIC MICROANGIOPATHY IN CHILDREN WITH SARS-COV-2 ACROSS THE SPECTRUM OF CLINICAL PRESENTATIONS

Diorio C, McNerney KO, Lambert M, Paessler M, Anderson EM, Henrickson SE, Chase J, Liebling EJ, Burudpakdee C, Lee JH, Balamuth FB, Blatz AM, Chiotos K, Fitzgerald JC, Giglia TM, Gollomp K, Odom John AR, Jasen C, Leng T, Petrosa W, Vella LA, Witmer C, Sullivan KE, Laskin BL, Hensley SE, Bassiri H, Behrens EM, Teachey DT.. Blood Adv. 2020 Dec 8;4(23):6051-6063. doi: 10.1182/bloodadvances.2020003471.

Level of Evidence: 3 - Local non-random sample

BLUF

Pediatric hematologists from the Children's Hospital of Philadelphia conducted a single center prospective controlled cohort study of 50 hospitalized children with evidence of SARS-CoV-2 infection (positive by SARS-CoV-2 RT-PCR or serology, or met clinical criteria for multisystem inflammatory syndrome) compared to 26 healthy controls. They found elevated plasma levels of sC5b9 (soluble membrane attack complex) in patients with SARS-CoV-2 infection ($p<0.001$), with no difference in sC5b9 level when stratified by disease severity (Table 2). Of the 19 patients with complete medical records, 17 (89%) met diagnostic criteria for complement-mediated thrombotic microangiopathy (TMA)(Table 3). Authors suggest these findings are consistent with previous research indicating sC5b9 plays a role in TMA, and recommend further research to determine whether TMA screening in children with SARS-CoV-2 is warranted given universally high sC5b9 levels.

ABSTRACT

Most children with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have mild or minimal disease, with a small proportion developing severe disease or multisystem inflammatory syndrome in children (MIS-C). Complement-mediated thrombotic microangiopathy (TMA) has been associated with SARS-CoV-2 infection in adults but has not been studied in the pediatric population. We hypothesized that complement activation plays an important role in SARS-CoV-2 infection in children and sought to understand if TMA was present in these patients. We enrolled 50 hospitalized pediatric patients with acute SARS-CoV-2 infection (n = 21, minimal coronavirus disease 2019 [COVID-19]; n = 11, severe COVID-19) or MIS-C (n = 18). As a biomarker of complement activation and TMA, soluble C5b9 (sC5b9, normal 247 ng/mL) was measured in plasma, and elevations were found in patients with minimal disease (median, 392 ng/mL; interquartile range [IQR], 244-622 ng/mL), severe disease (median, 646 ng/mL; IQR, 203-728 ng/mL), and MIS-C (median, 630 ng/mL; IQR, 359-932 ng/mL) compared with 26 healthy control subjects (median, 57 ng/mL; IQR, 9-163 ng/mL; P < .001). Higher sC5b9 levels were associated with higher serum creatinine (P = .01) but not age. Of the 19 patients for whom complete clinical criteria were

available, 17 (89%) met criteria for TMA. A high proportion of tested children with SARS-CoV-2 infection had evidence of complement activation and met clinical and diagnostic criteria for TMA. Future studies are needed to determine if hospitalized children with SARS-CoV-2 should be screened for TMA, if TMA-directed management is helpful, and if there are any short- or long-term clinical consequences of complement activation and endothelial damage in children with COVID-19 or MIS-C.

FIGURES

Table 2.

Median, IQR, and number of patients of the most extreme laboratory values during the admission for patients included in the sample

Value (reference range)	Minimal COVID-19		Severe COVID-19		MIS-C	
	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n
Coagulation						
D-dimer, highest (0.27-0.60 µg/mL FEU)	—		2.53 (0.6-20.5)	11	4.93 (3.42-5.75)	17
PT, highest (11.6-13.8 s)	—		16 (13.2-31)	11	15.4 (14.4-17.4)	18
PTT, highest (22-36 s)	—		52.4 (37.5-78.8)	11	31.8 (28.4-36.6)	17
Fibrinogen (172-471 mg/dL)						
Lowest	—		297 (239-332)	10	297 (237-370)	17
Highest	—		488 (305-890)	10	572 (484-721)	17
Chemistry						
AST, highest (10-30 U/L)	59 (40-72)	17	123 (54-627)	11	88 (63-104)	18
Creatinine, highest (0.3-0.8 mg/dL)	0.4 (0.3-0.8)	19	0.7 (0.3-2.3)	11	0.6 (0.5-1.3)	18
GFR, minimum (mL/min)	193 (108-221)	18	111 (40-243)	11	136 (65-182)	18
BUN, highest (7-18 mg/dL)	12 (7-23)	19	23 (13-34)	11	21.5 (16-39)	18
Hematology						
Platelets (150-400 K/µL)						
Lowest	220 (127-295)	21	128 (78-165)	11	141 (121-194)	18
Highest	414 (165-363)	21	311 (223-347)	11	414 (275-483)	18
Hemoglobin, lowest (12-16 g/dL)	9.2 (7.4-11.9)	21	8.9 (6.7-11.1)	11	8.9 (7.9-10)	18
Inflammatory and cardiac						
Ferritin, highest (10.0-82.0 ng/ml)	—		419 (164-2747)	10	806 (665-1162)	17
CRP, highest (0-0.9 mg/dL)	13.9 (3.1-18.3)	11	30.3 (7-34.9)	11	23.7 (19-34.6)	18
ESR, highest (0-20 mm/h)	—		–		59 (43-82)	17
BNP, highest (≤100 pg/mL)	—		307 (46-542)	8	997 (510-1242)	17
Troponin, highest (<0.3 ng/ml)	—		0.13 (0.02-1.79)	9	0.39 (0.07-1.34)	17
IL-8	10 (5-16.6)	15	32.7 (12.3-124)	11	37.3 (20.4-56.7)	17
Interferon-γ	14 (4-150)	15	54 (12-100)	11	191 (41-481)	17
sC5b9 (≤257 ng/mL)	392 (244-622)	21	646 (203-728)	11	630 (359-932)	18

Results were not reported if >50% of data were missing.

AST, aspartate transaminase; BNP, B-type natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEU, fibrinogen equivalent units; PT, prothrombin time; PTT, partial thromboplastin time.

Table 3. Criteria for TMA in patients with MIS-C, minimal COVID-19, and severe COVID-19

ID	Age, y	Other conditions	Elevated LDH	Schistocytes	Low platelets	Anemia	HTN	Protein in urine	Elevated sC5b9	Met criteria for TMA?	No. of criterion
Minimal COVID-19											
13	4	Sickle cell disease	✓	✓	✓	✓	✓			Yes	5
38	17	Obesity, asthma	✓		✓		✓	✓	✓	Yes	5
Summary: fraction (%)			2/2 (100)	1/2 (50)	2/2 (100)	1/2 (50)	2/2 (100)	1/2 (50)	1/2 (50)	2/2 (100)	
Severe COVID-19											
10	10	Panhypopituitarism	✓	✓	✓	✓		✓	✓	Yes	6
33	15	Obesity, PCOS	✓	✓		✓	✓		✓	Yes	5
37	15	Obesity	✓	✓		✓	✓	✓	✓	Yes	6
4	18	Obesity, hypertension, diabetes mellitus	✓	✓	✓	✓	✓	✓	✓	Yes	7
Summary: fraction (%)			4/4 (100)	4/4 (100)	2/4 (67)	4/4 (100)	3/4 (75)	3/4 (75)	4/4 (100)	4/4 (100)	
MIS-C											
19	5	Previously healthy		✓	✓	✓	✓	✓	✓	Yes	6
22	6	Previously healthy	✓	✓		✓	✓	✓	✓	Yes	6
18	6	Previously healthy	✓	✓	✓	✓	✓	✓	✓	Yes	7
24	7	Previously healthy	✓	✓	✓	✓	✓		✓	Yes	6
29	8	Asthma	✓	✓			✓	✓	✓	Yes	5
44	8	Previously healthy	✓	✓		✓	✓		✓	Yes	5
55	8	Precocious puberty	✓		✓	✓	✓	✓	✓	Yes	6
28	9	Previously healthy		✓	✓	✓	✓		✓	Yes	5
50	9	Previously healthy	✓	✓	✓	✓	✓	✓	✓	Yes	7
48	11	Previously healthy	✓	✓		✓		✓	✓	Yes	5
26	13	Previously healthy		✓	✓	✓	✓	✓		Yes	5
27	14	Previously healthy		✓	✓	✓			✓	No	4
51	17	Asthma		✓		✓		✓	✓	No	4
Summary: fraction (%)			8/13(61)	12/13 (92)	8/13(61)	12/13 (92)	10/13 (76)	9/13 (69)	12/13 (92)	11/13 (85)	

Criteria for TMA as defined by Gloude et al.[27] Meeting at least 5 of the 7 criteria are required to meet definition. Protein in urine defined as random urine protein measurement ≥30 mg/dL or urine protein/creatinine ratio ≥2 mg/mg. Hypertension defined as >99th percentile for age, height, and sex. Check marks indicate that the criterion was met; blank spaces indicate that the criterion was not met.

B-ALL, B-cell acute lymphoblastic leukemia; HTN, hypertension; PCOS, polycystic ovarian syndrome.

UNDERSTANDING THE PATHOLOGY

ASYMPTOMATIC SARS-COV-2 INFECTION: IS IT ALL ABOUT BEING REFRACTILE TO INNATE IMMUNE SENSING OF VIRAL SPARE-PARTS? - CLUES FROM EXOTIC ANIMAL RESERVOIRS

Shankar EM, Che KF, Yong YK, Girija ASS, Velu V, Ansari AW, Larsson M.. Pathog Dis. 2020 Dec 8:ftaa076. doi: 10.1093/femspd/ftaa076. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Physicians and scientists from India, Sweden, Emory University, and UAE aimed to understand the mechanisms that animal species such as bats and pangolins use to achieve viral control and inflammatory regulation against COVID-19, as illustrated in Figures 1 and 2. Understanding these mechanisms could potentially assist in the development of therapeutics against human infection of COVID-19 by avoiding an exaggerated inflammatory response.

SUMMARY

One proposed idea (Figure 1) is that the initial virus (found in bats) undergoes a homologous recombination of nucleotide base pairs before entering humans (through inhalation or consumption), which begins the outbreak. Bats skip over an 'exaggerated inflammation' by 'limiting the expression of NLRP3 (NLR family pyrin domain containing 3) in monocytes' and either completely lose or have a scarce supply of KIR (functional killer cell Ig-like) KLR (killer cell lectin-like) receptor loci on NK cells.

Another proposed idea (Figure 2) is that SARS-CoV-2 can activate the STING pathway (a component of the innate immune system that trigger expression of inflammatory genes) to induce cytokine storm syndrome, NLRP3 inflammasome activation, and produce cytokines IL-1β, and IL-18 to decrease disease severity.

ABSTRACT

A vast proportion of coronavirus disease 2019 (COVID-19) individuals remain asymptomatic and can shed severe acute respiratory syndrome (SARS-CoV) type 2 virus to transmit the infection, which also explains the exponential increase in the number of COVID-19 cases globally. Furthermore, the rate of recovery rates from clinical COVID-19 in certain pockets of the globe is surprisingly high. Based on published reports and available literature, here, we speculated a few immunovirological mechanisms as to why a vast majority of individuals remain asymptomatic similar to exotic animal (bats and pangolins) reservoirs that remain refractile to disease development despite carrying a huge load of diverse insidious viral species, and whether such evolutionary advantage would unveil therapeutic strategies against human COVID-19 infection. Understanding the unique mechanisms that exotic animal species employ to achieve viral control, as well as inflammatory regulation, appears to hold key clues to the development of therapeutic versatility against COVID-19.

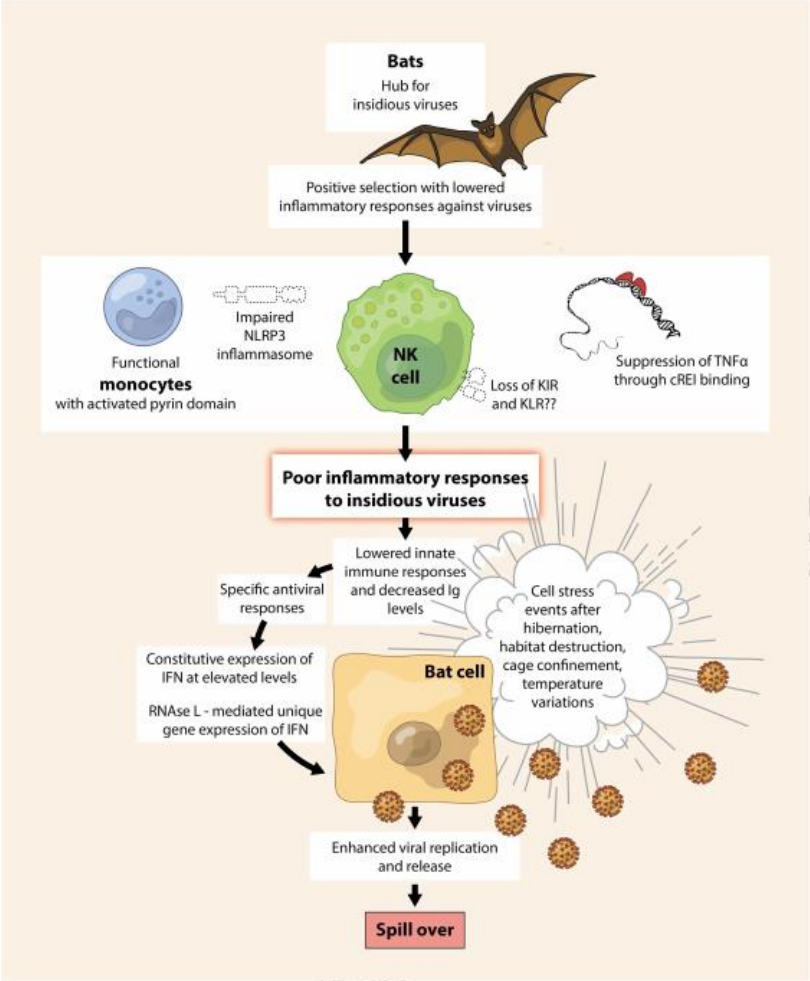

Figure 1. Proposed mechanism of existence of β-coronaviruses (β-CoV) in exotic mammalian animal reservoirs. Exotic bats serve as primary reservoirs of βcoronaviruses (β-CoV) from where the later appears to have 'landed' into pangolins (not shown) where the virus seems to have undergone a homologous recombination of nucleotide base pairs with insidious pangolin-CoV before getting into the human system (upon consumption or inhalation of virus present in body fluids), potentially initiating an outbreak. It also appears that bats bypass exaggerated inflammation by limiting the assembly of the NLR family pyrin domain containing 3 (NLRP3) in monocytes, and besides the paucity of functional killer cell Ig-like (KIR), and killer cell lectin-like (KLR) receptor loci expressed classically by NK cells.

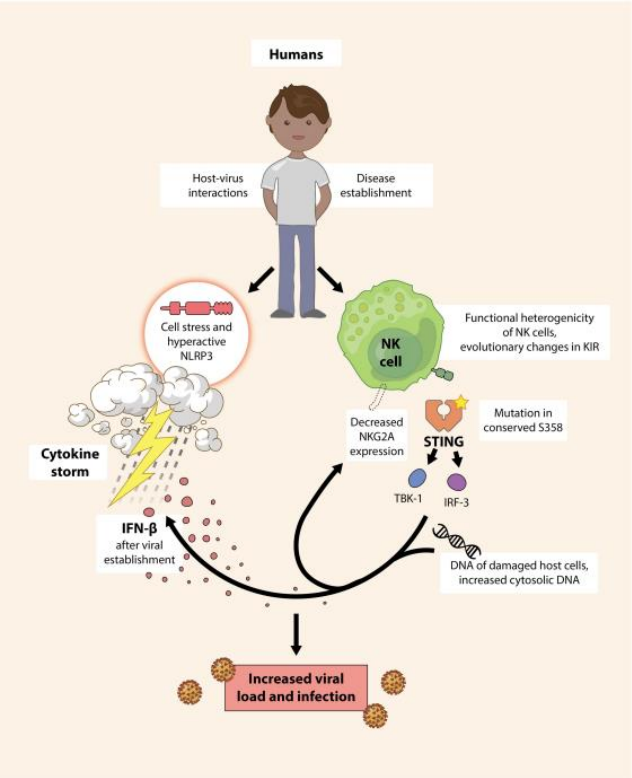

Figure 2. Mechanistic basis of COVID-19 immunopathogenesis in humans. Notwithstanding the proportion of asymptomatic COVID-19 disease warrants an extensive global population screening, some studies have estimated that ~80% of individuals, diagnosed with the SARS-CoV-2 remain sub-clinical. Despite being an RNA virus, SARS-CoV-2 can activate the STING pathway (Fischer et al. 2020) to induce cytokine storm syndrome, also fueled by NLRP3 inflammasome activation and production of IL-1β, and IL-18, besides TNF-α, IFN-γ and IL-6 to deteriorate disease severity. A Chinese study has shown that asymptomatic individuals displayed an extended median duration of 19 days of viral shedding compared to symptomatic patients portraying the role of asymptomatic/subclinical disease status with the exponential upsurge in global COVID-19 cases.

ASSOCIATION OF SALIVARY CONTENT ALTERATION AND EARLY AGEUSIA SYMPTOMS IN COVID-19 INFECTIONS: A SYSTEMIC REVIEW

Abduljabbar T, Alhamdan RS, Al Deeb M, AlAali KA, Vohra F.. Eur J Dent. 2020 Nov 26. doi: 10.1055/s-0040-1716986. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Dental specialists in Saudi Arabia reviewed 36 studies on chemical and inflammatory changes that occur in SARS-CoV-2 infected salivary glands and propose a chemosensory mechanism to explain alterations in taste and smell found commonly seen in COVID-19. In patients reporting aguesia, they found changes in salivary hormones, inorganic compounds, pH, enzymes, and salivary flow rate, which are all involved in normal taste perception. Authors suggest with better understanding and characterization of these changes, we may be able to prevent or treat changes in smell or taste seen among COVID-19 patients.

ABSTRACT

Coronavirus disease (COVID-19) is a major threat to the health and prosperity of human life at present. It has resulted in loss of thousands of lives globally and has brought countries to the brink of economic, social, and health collapse. A major issue of this infection is the ease with which it transmits through salivary droplets and its survival for long durations outside the body. Therefore, its early detection is critical in prevention, diagnostic, and management efforts of COVID-19 patients. Loss of taste and smell is one of the early symptoms reported in these patients and the virus is abundantly found in the salivary secretion of the infected symptomatic and asymptomatic patients. Infection and inflammation of salivary glands are common among viral

infections, particularly in the early stages, which lead to salivary composition changes. Chemosensory sensation of taste is critically dependent on the salivary flow rate and its inorganic constituents, protein levels, specific 3',5'-cyclic adenosine monophosphate and 3',5'-cyclic guanosine monophosphate levels, ghrelins, pH levels, and enzymes. Therefore, the question arises, "Does COVID-19 infection alter the salivary components and composition leading to early transient symptoms of Ageusia and hypogeusia?" This review shows association of the COVID-19 and Ageusia, in addition to the early viral infection of salivary glands and possible changes in salivary flow and content. Therefore, suggesting a potential association between early ageusia in COVID-19 infection and salivary compositional changes.

TRANSMISSION & PREVENTION

WHO SHOULD BE PRIORITISED FOR COVID-19 VACCINES?

Hassan-Smith Z, Hanif W, Khunti K.. Lancet. 2020 Nov 28;396(10264):1732-1733. doi: 10.1016/S0140-6736(20)32224-8. Epub 2020 Oct 27.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

This opinion piece by endocrinologists from Birmingham NHS Foundation Trust proposes a scheme for the distribution of newly developed COVID-19 vaccines based on risk assessment and emphasizing socioeconomic disparities (Figure 1). Level 1 encompasses health care workers and geriatric populations, while Level 2 consists of care-home residents, patients with co-morbidities and those facing occupational hazards such as the transportation force. The last level, Level 3, requires closer examination of each person based on individual risk factors. Authors present this as a clinical predictor to inform on further risk stratification strategies.

FIGURES

Figure 1. Priority groups for COVID-19 vaccinations and preventable therapies.

PREVENTION IN THE COMMUNITY

OCCUPATION AND RISK OF SEVERE COVID-19: PROSPECTIVE COHORT STUDY OF 120 075 UK BIOBANK PARTICIPANTS

Mutambudzi M, Niedwiedz C, Macdonald EB, Leyland A, Mair F, Anderson J, Celis-Morales C, Cleland J, Forbes J, Gill J, Hastie C, Ho F, Jani B, Mackay DF, Nicholl B, O'Donnell C, Sattar N, Welsh P, Pell JP, Katikireddi SV, Demou E.. Occup Environ Med. 2020 Dec 9:oemed-2020-106731. doi: 10.1136/oemed-2020-106731. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

In this large-scale prospective cohort study, authors from various public health institutes in Glasgow, UK, Limerick, Ireland, and Syracuse, NY, analyzed data from the UK Biobank, involving 120,075 participants aged 40-69 registered with the National Health Service (NHS) in England, Wales or Scotland, and grouped them into occupational groups with concomitant serious COVID-19 infection (having to be hospitalized), in order to asses risk of infection across essential occupations. They found 29.3% of participants were classified as essential workers (9% healthcare, 11.2% social and education, and 9.1% other essential workers), and that 3,111 (2.6%) of the total participants tested positive for SARS-CoV-2 between March 16 and July 26, 2020. They concluded healthcare workers were at a 7 fold increased risk of developing severe COVID-19 and that social and transport workers had a doubled risk (Table 3), highlighting the need for better protection and support for workers at higher risk for infection.

ABSTRACT

OBJECTIVES: To investigate severe COVID-19 risk by occupational group. METHODS: Baseline UK Biobank data (2006-10) for England were linked to SARS-CoV-2 test results from Public Health England (16 March to 26 July 2020). Included participants were employed or self-employed at baseline, alive and aged <65 years in 2020. Poisson regression models were adjusted sequentially for baseline demographic, socioeconomic, work-related, health, and lifestyle-related risk factors to assess risk

ratios (RRs) for testing positive in hospital or death due to COVID-19 by three occupational classification schemes (including Standard Occupation Classification (SOC) 2000). RESULTS: Of 120 075 participants, 271 had severe COVID-19. Relative to non-essential workers, healthcare workers (RR 7.43, 95% CI 5.52 to 10.00), social and education workers (RR 1.84, 95% CI 1.21 to 2.82) and other essential workers (RR 1.60, 95% CI 1.05 to 2.45) had a higher risk of severe COVID-19. Using more detailed groupings, medical support staff (RR 8.70, 95% CI 4.87 to 15.55), social care (RR 2.46, 95% CI 1.47 to 4.14) and transport workers (RR 2.20, 95% CI 1.21 to 4.00) had the highest risk within the broader groups. Compared with white non-essential workers, non-white non-essential workers had a higher risk (RR 3.27, 95% CI 1.90 to 5.62) and non-white essential workers had the highest risk (RR 8.34, 95% CI 5.17 to 13.47). Using SOC 2000 major groups, associate professional and technical occupations, personal service occupations and plant and machine operatives had a higher risk, compared with managers and senior officials. CONCLUSIONS: Essential workers have a higher risk of severe COVID-19. These findings underscore the need for national and organisational policies and practices that protect and support workers with an elevated risk of severe COVID-19.

FIGURES

Table 3 Risk ratios for severe COVID-19 by occupational groups (n=120 075)

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Severe COVID-19	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Broad occupational groups of essential workers						
Non-essential workers (reference)	1	1	1	1	1	1
Healthcare workers	7.43*** (5.52 to 10.00)	8.45*** (6.22 to 11.47)	7.57*** (5.50 to 10.41)	8.44*** (6.21 to 11.46)	8.53*** (6.29 to 11.58)	7.69*** (5.58 to 10.60)
Social and education workers	1.84** (1.21 to 2.82)	2.00** (1.30 to 3.08)	1.90** (1.22 to 2.94)	1.99** (1.29 to 3.06)	1.97** (1.28 to 3.03)	1.88** (1.21 to 2.91)
Other essential workers	1.60* (1.05 to 2.45)	1.30 (0.85 to 1.98)	1.17 (0.76 to 1.80)	1.30 (0.85 to 1.98)	1.27 (0.83 to 1.94)	1.15 (0.75 to 1.77)
Detailed occupational groups of essential workers						
Non-essential workers (reference)	1	1	1	1	1	1
Healthcare professionals	6.19*** (3.68 to 10.43)	8.62*** (4.98 to 14.94)	8.26*** (4.77 to 14.28)	8.70*** (5.02 to 15.06)	9.33*** (5.40 to 16.14)	8.99*** (5.20 to 15.54)
Medical support staff	8.70*** (4.87 to 15.55)	7.43*** (4.17 to 13.25)	6.48*** (3.62 to 11.58)	7.39*** (4.13 to 13.19)	7.33*** (4.13 to 13.02)	6.42*** (3.60 to 11.45)
Health associate professionals	7.53*** (5.44 to 10.43)	8.54*** (6.13 to 11.90)	7.61*** (5.33 to 10.87)	8.52*** (6.11 to 11.88)	8.54*** (6.12 to 11.92)	7.65*** (5.34 to 10.95)
Social care workers	2.46*** (1.47 to 4.14)	2.38** (1.42 to 4.00)	2.19** (1.29 to 3.72)	2.36** (1.40 to 3.97)	2.31** (1.37 to 3.88)	2.13** (1.25 to 3.63)
Education workers	1.36 (0.75 to 2.48)	1.61 (0.88 to 2.96)	1.59 (0.86 to 2.92)	1.61 (0.88 to 2.95)	1.62 (0.88 to 2.96)	1.59 (0.87 to 2.91)
Food workers	1.12 (0.52 to 2.42)	0.93 (0.43 to 1.98)	0.85 (0.40 to 1.83)	0.93 (0.43 to 1.98)	0.92 (0.43 to 1.96)	0.84 (0.39 to 1.80)
Transport workers	2.20** (1.21 to 4.00)	1.66 (0.91 to 3.01)	1.48 (0.81 to 2.70)	1.66 (0.91 to 3.01)	1.58 (0.87 to 2.90)	1.43 (0.78 to 2.63)
Police and protective service workers	1.55 (0.72 to 3.32)	1.36 (0.63 to 2.93)	1.21 (0.56 to 2.64)	1.35 (0.62 to 2.92)	1.32 (0.61 to 2.86)	1.19 (0.55 to 2.58)
SOC 2000 major occupational groups						
Managers and senior officials (reference)	1	1	1	1	1	1
Professional occupations	1.36 (0.85 to 2.18)	1.47 (0.91 to 2.36)	1.49 (0.92 to 2.41)	1.47 (0.91 to 2.36)	1.51 (0.94 to 2.43)	1.53 (0.95 to 2.48)
Associate professional and technical occupations	3.19*** (2.10 to 4.85)	3.11*** (2.05 to 4.72)	2.73*** (1.77 to 4.23)	3.10*** (2.04 to 4.71)	3.15*** (2.08 to 4.79)	2.78*** (1.79 to 4.29)
Administrative and secretarial occupations	1.24 (0.73 to 2.12)	1.14 (0.67 to 1.95)	1.22 (0.71 to 2.11)	1.14 (0.67 to 1.94)	1.17 (0.68 to 2.00)	1.24 (0.72 to 2.15)
Skilled trades occupations	0.82 (0.39 to 1.74)	0.67 (0.31 to 1.44)	0.49 (0.22 to 1.06)	0.68 (0.32 to 1.45)	0.69 (0.32 to 1.49)	0.50 (0.23 to 1.09)
Personal service occupations	2.73*** (1.56 to 4.76)	2.31** (1.32 to 4.03)	1.75 (0.99 to 3.10)	2.29** (1.32 to 4.00)	2.33** (1.34 to 4.06)	1.77 (1.00 to 3.13)
Sales and customer service occupations	1.36 (0.59 to 3.17)	1.09 (0.46 to 2.57)	0.91 (0.38 to 2.18)	1.08 (0.46 to 2.55)	1.08 (0.46 to 2.56)	0.90 (0.38 to 2.16)
Process, plant and machine operatives	2.39** (1.31 to 4.36)	1.82 (0.99 to 3.34)	1.25 (0.66 to 2.36)	1.81 (0.99 to 3.33)	1.81 (0.99 to 3.34)	1.26 (0.67 to 2.37)
Elementary occupations	1.76 (0.92 to 3.34)	1.29 (0.65 to 2.53)	0.87 (0.43 to 1.75)	1.28 (0.65 to 2.52)	1.31 (0.67 to 2.59)	0.89 (0.44 to 1.79)
Observations	120075	120075	120075	120075	120075	120075

Coefficients for the covariates not shown.
Model 1: Adjusted for age group, sex, ethnicity, country of birth.
Model 2: Model 1+socioeconomic deprivation quartile, education level.
Model 3: Model 2+shift work, manual work, job tenure, working hours.
Model 4: Model 2+number of chronic conditions, long-standing illness/disability.
Model 5: Model 2+BMI category, smoking status, alcohol consumption.
Model 6: All above covariates.
*p<0.05, **p<0.01, ***p<0.001.
BMI, body mass index; SOC, Standard Occupation Classification.

Table 3. Risk ratios for severe COVID-19 by occupational groups (n=120 075).

THE POTENTIAL TRANSMISSION OF SARS-COV-2 FROM PATIENTS WITH NEGATIVE RT-PCR SWAB TESTS TO OTHERS: TWO RELATED CLUSTERS OF COVID-19 OUTBREAK

Cao G, Tang S, Yang D, Shi W, Wang X, Wang H, Li C, Wei J, Ma L.. Jpn J Infect Dis. 2020 Nov 24;73(6):399-403. doi: 10.7883/yoken.JJID.2020.165. Epub 2020 May 29.
Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

A retrospective case-series conducted by pediatric surgeons and critical care specialists at Tongji Medical College in China found 2/6 patients COVID-19 patients were infected nosocomially and 2/6 who were family members of a healthcare worker. All six developed clinically and CT significant pulmonary COVID-19 and developed IgG and IgM antibodies during recovery despite having initially negative RT-PCR nasopharyngeal swab results (Table 1). Authors suggest using serologic anti-SARS-CoV-2 IgG and IgM testing for early detection since false-negative swab results can significantly increase risk of transmission.

ABSTRACT

In December 2019, a cluster of cases of acute respiratory illness, novel coronavirusinfected pneumonia, occurred in Wuhan, Hubei Province, China. The false-negative nasopharyngeal swabs of SARS-CoV-2 caused the delayed diagnosis of COVID-19 which hindered the prevention and control of the pandemic. The transmission risk of SARS-CoV-2 in negative nasopharyngeal swabs cases were little addressed previously. This study evaluated two clusters of COVID-19 in six patients. Four of six (66.7%) showed negative RNA of SARS-CoV-2 by nasopharyngeal swabs. All epidemiological, clinical and laboratory information was collected. The first cluster was a nosocomial infection of four health care providers at early January. One of them made sequential familial cluster of infection. All patients received either selfquarantined at home or were admitted to hospital for isolated treatment. All recovered and had anti-SARS-CoV-2 IgG and/or IgM positive (100%) for serological detection of SARS-CoV-2 at recovery stage. Our study provides a cautionary warning that negative results of nasopharyngeal swabs of suspected SARS-CoV-2 infection can increase the risk of nosocomial infection among health care providers. Serologic detection for anti-SARS-CoV-2 IgG and/or IgM is an important test in the assistant diagnosis of COVID-19.

FIGURES

Table 1. Summary of clinical and laboratory examination results of the hospital cluster infected with SARS-CoV-2

Case	Position	Sex/ Age	Onset Time	Main Onset Symptoms	Influenza A/B RSV[1)]	CRP (mg/L)	WBC/ LYM ($\times 10^9$/L)	First Swab Time/ Results[2)]	Way of Treatment	Anti-SARS-CoV-2-IgG[3)]	Anti-SARS-CoV-2-IgM[3)]	Time interval[4)]
1	Nurse	F/46	Jan.1	fever, sore throat and dry cough	negative	0.05	5.86/1.06	d18/ (-)	Home care	19.79	11.04	41d
2	Surgeon	M/33	Jan.8	fever,fatigue, muscle soreness	negative	1.09	2.87/1.09	d11/ (-)	Home care	2.79	0.99	41d
3	Nurse	F/54	Jan.8	fatigue, diarrhea	negative	0.76	5.04/1.25	d11/ (+)	Isolated treatment	31.76	1.17	41d
	-Husband	M/59	Jan.10	fever, fatigue, dry cough	negative	-	4.83/0.96	d22/ (-)	Isolated treatment	90.71	0.83	30d
	-Daughter	F/29	Jan.13	fatigue, cough	negative	-	3.40/1.25	d19/ (-)	Isolated treatment	81.38	0.69	30d
4	Nurse	F/31	Jan.18	fever,fatigue, dry cough	negative	0.59	2.97/1.14	d9/ (+)	Isolated treatment	116.90	1.24	30d

Table 1. Summary of clinical and laboratory examination results of the hospital cluster infected with SARS-CoV-2.

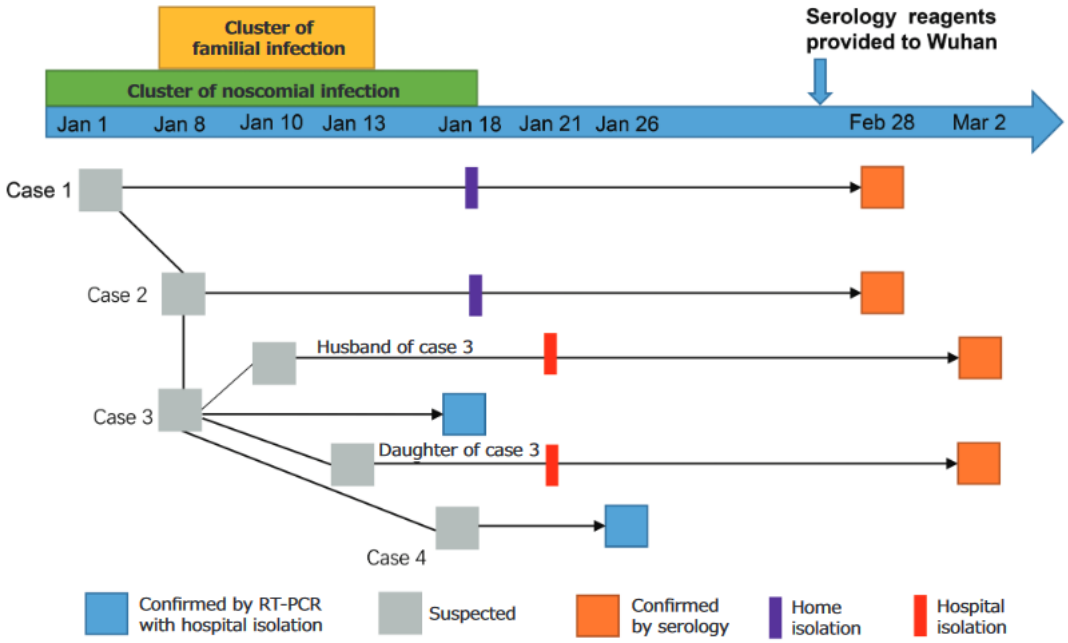

Fig. 1. (Color online) The timeline of illness onset and diagnositic information of nosocomial and following familial cluster cases.

CRITICAL CARE

HIGH PREVALENCE OF PULMONARY SEQUELAE AT 3 MONTHS AFTER HOSPITAL DISCHARGE IN MECHANICALLY VENTILATED COVID-19 SURVIVORS

van Gassel RJJ, Bels JLM, Raafs A, van Bussel BCT, van de Poll MCG, Simons SO, van der Meer LWL, Gietema HA, Posthuma R, van Santen S.. Am J Respir Crit Care Med. 2020 Dec 16. doi: 10.1164/rccm.202010-3823LE. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

In this letter to the editor, Dutch researchers share their clinical data from 48 critically-ill COVID-19 patients who underwent follow-up screening three months after discharge that included pulmonary function testing (PFT), high resolution chest CT (HRCT), and 6-minute walk test (6-MWT). Prominent findings included diminished diffusion capacity, total lung capacity, and reticular fibrosis with ground-glass opacities present on HRCT (See Figure 1). They report some evidence of new emphysematous abnormalities on HRCT (See Table 1) which may be novel for COVID-19 compared to SARS or MERS. These findings suggest the necessity for intensive respiratory follow-up for patients with COVID-19 who underwent mechanical ventilation to screen for pulmonary sequelae.

Baseline characteristics on admission	N = 48
Age (years)	63.00 [55.00 - 68.00]
Sex (Male)	33 (68.8%)
BMI (kg/m²)	27.68 [25.18 - 30.47]
Origin of admission	
Emergency department	11 (22.9%)
Hospital ward	27 (56.2%)
Transfer from another ICU	10 (20.8%)
pre-ICU length of stay (days)	3.00 [1.00 - 5.00]
APACHE II score	15.0 [13.0 - 17.3]
Pre-existing lung disease	3 (6.2%)
Asthma	3 (6.2%)
COPD	0 (0.0%)
Smoking status	
Current smoker	0 (0%)
Former smoker	23 (48%)
Charlson comorbidity index	
0	6 (12.5%)
1 – 2	24 (50.0%)
3 – 4	15 (31.2%)
5 or more	3 (6.2%)
Leucocyte count ($10E^3$/L)	9.25 [7.88 - 10.75]
C-reactive protein (mg/L)	191 [99 - 264]
D-dimer (µg/L)	1343 [726 - 5097]
PaO_2/FiO_2 ratio (mmHg)	116 [92, 156]
Proned during ICU admission	22 (45.8%)
Pinsp (cm H_2O)	26 [24 - 28]
PEEP (cm H_2O)	14 [12 - 14]
VT/kg bodyweight (ml/kg)	5.46 [4.98 - 6.02]
Dynamic compliance (ml/cm H_2O)	37.25 [29.80 - 48.85]
Received steroids during admission[a]	12 (25.0%)
IMV duration (days)	18.5 [9.0 - 28.5]
Days in ICU	20.5 [10.8 - 33.3]
Days in Hospital	32.0 [21.0 - 40.0]
Hospital discharge location	
Home	7 (14.9%)
Nursing home	1 (2.1%)
Rehabilitation centre	39 (83.0%)
Days in rehabilitation centre[b]	14.0 [7.0 - 27.3]
ECMO during admission?	3 (6.2%)

Pulmonary function test (PFT)		N = 43	
	Absolute value	% of predicted	Below LLN, N (%)
FEV1 (L)	2.9 [2.6 - 3.5]	95.0 [77.0 - 104.5]	11 (25.6%)
FEV1/VC (%)	79.9 [76.1 - 86.6]	-	0 (0.0%)
FVC (L)	3.6 [3.1 - 4.2]	87.0 [70.0 - 106.0]	16 (37.2%)
RV (L)	2.0 [1.6 - 2.2]	88.0 [70.0 - 103.0]	9 (20.9%)
TLC (L)	5.6 [4.6 - 6.7]	84.0 [71.5 - 102.5]	23 (53.5%)
DLCOc (L)[c]	5.4 [4.6 – 6.3]	61.0 [50.0 – 69.0]	36 (87.8%)
6-MWT (meters)[d]	480.0 [386.0 - 536.0]	81.5 [69.5 - 99.5]	-

MRC Dyspnea score	
Grade 0-1 (None/Mild)	27 (62.8%)
Grade 2-3 (Moderate)	14 (32.5%)
Grade 4-5 (Severe)	2 (4.7%)
HRCT results	N = 46
Fibrosis	42 (91.3%)
Ground glass	41 (89.1%)
Atelectasis	15 (32.6%)
Dominant pattern	
Reticular	31 (67.4%)
Ground glass	13 (28.3%)
No abnormalities	2 (4.3%)
Decreased attenuation	25 (54.3%)
Due to small-airways disease	21 (45.7%)
Due to new emphysema	12 (25.0%)
CT Severity Score (CTSS)	11.0 [5.0 - 15.0]

Table 1. Baseline characteristics, pulmonary function tests (PFT) and high-resolution chest tomography (HRCT) results at three months follow-up. Data are presented as median [IQR] or numbers (percentage), unless indicated otherwise. For laboratory results and ventilator settings, the worst value for the first 24 hours of admission was recorded. Pinsp = inspiratory pressure in bilevel pressure controlled ventilation (BIPAP). IMV = Invasive mechanical ventilation, LLN = lower limit of normal, FEV1 = forced expiratory volume in 1 second, VC = vital capacity, FVC = forced vital capacity, RV = residual volume, TLC = total lung capacity, DLCOc = diffusing capacity for carbon monoxide adjusted for hemoglobin, 6-MWT = 6-minute walk test, MRC Dyspnea = Medical Research Council Dyspnea questionnaire. a Defined as receiving steroid treatment for at least 2 days or more. b 3 patients were still admitted to a rehabilitation centre at the moment of follow-up. c DLCOc failed in 2 patients. d Two patients were on supplemental oxygen while performing the 6-MWT.

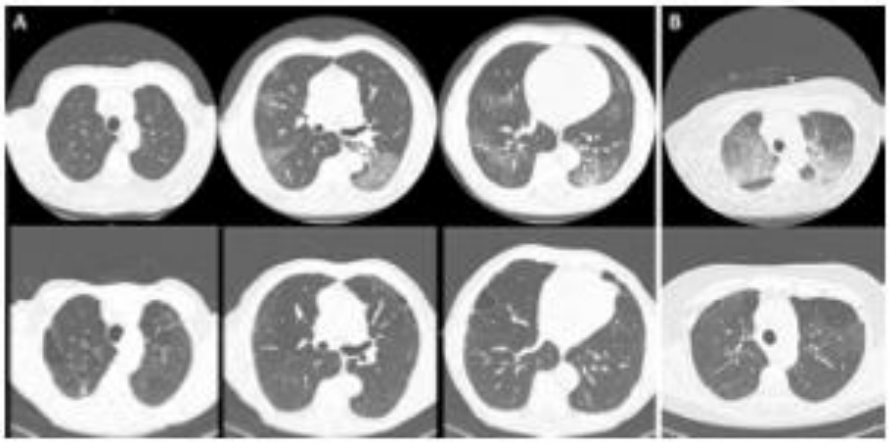

Figure 1.
Representative HRCT images of two of the survivors. Panel A: HRCT performed at admission (upper row) and at 3-month follow-up (lower row). Chest CT at admission shows typical bilateral subpleural ground glass opacities. No signs of previous emphysema were detected. However, follow-up HRCT shows obvious emphysematous destruction. Panel B: CT image at presentation at emergency department with evident ground areas with reticulation (crazy paving). Follow-up reveals diffuse areas of persistent ground glass without reticulation, as well as areas with low density in previously normal areas, possibly due to hypoperfusion.

USING SMARTWATCH DATA TO DETECT COVID-19 CASES EARLY

Abbasi J.. JAMA. 2020 Dec 8;324(22):2247. doi: 10.1001/jama.2020.23696.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

This article reviews a study conducted by researchers at Scripps Research Translational Institute who compared the smartwatch data between 333 participants, 54 of which ended up reporting positive for COVID-19, and found that symptom tracking plus smartwatch biometric data collecting yielded more predictive results of COVID-19 positive test probability than symptom tracking alone. This study was conducted earlier this year and used a smartphone/smartwatch app called DETECT.

DELAYED SPECIFIC IGM ANTIBODY RESPONSES OBSERVED AMONG COVID-19 PATIENTS WITH SEVERE PROGRESSION

Shen L, Wang C, Zhao J, Tang X, Shen Y, Lu M, Ding Z, Huang C, Zhang J, Li S, Lan J, Wong G, Zhu Y.. Emerg Microbes Infect. 2020 Dec;9(1):1096-1101. doi: 10.1080/22221751.2020.1766382.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

Virologists and immunologists from China and Canada analyzed the diagnostic accuracy of RT-qPCR testing compared to IgM-based antibody testing for COVID-19. They found IgM-based gold immunochromatographic assay (GICA) detected 82.2% (n=37/45) of RT-qPCR confirmed COVID-19 cases and 32.0% (n=8/25) of clinically suspected patients who falsely tested negative by RT-qPCR (Figure 1). Interestingly, 50% (n=4/8) of patients who were IgM-negative and RT-qPCR-positive developed severe disease (Figure 2). Researchers concluded that IgM-based antibody testing may have a complementary role to RT-PCR in diagnosing active infection by reducing false negatives, and delayed IgM antibody response may be predictive of more severe disease progression.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly worldwide since it was confirmed as the causative agent of COVID-19. Molecular diagnosis of the disease is typically performed via nucleic acid-based detection of the virus from swabs, sputum or bronchoalveolar lavage fluid (BALF). However, the positive rate from the commonly used specimens (swabs or sputum) was less than 75%. Immunological assays for SARS-CoV-2 are needed to accurately diagnose COVID-19. Sera were collected from patients or healthy people in a local hospital in Xiangyang, Hubei Province, China. The SARS-CoV-2 specific IgM antibodies were then detected using a SARS-CoV-2 IgM colloidal gold immunochromatographic assay (GICA). Results were analysed in combination with sera collection date and clinical information. The GICA was found to be positive with the detected 82.2% (37/45) of RT-qPCR confirmed COVID-19 cases, as well as 32.0% (8/25) of clinically confirmed, RT-qPCR negative patients (4-14 days after symptom onset). Investigation of IgM-negative, RT-qPCR-positive COVID-19 patients showed that half of them developed severe disease. The GICA was found to be a useful test to complement existing PCR-based assays for confirmation of COVID-19, and a delayed specific IgM antibody response was observed among COVID-19 patients with severe progression.

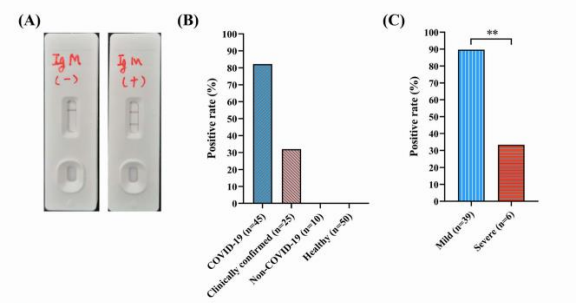

Figure 1. Use of the GICA for the detection of SARS-CoV-2 specific IgM in human sera. (A) Sample negative or positive IgM test. (B) Positive IgM antibody rates between COVID-19 patients, clinically confirmed but RT-qPCR negative patients, non-COVID-19 respir- atory illness and healthy people. (C) Comparison of IgM detection rates in RT-qPCR confirmed, mild vs. severe, COVID-19 patients. **P< 0.01.

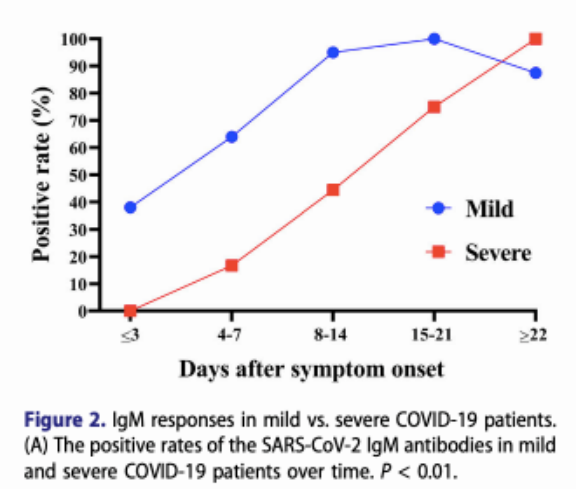

Figure 2. IgM responses in mild vs. severe COVID-19 patients. (A) The positive rates of the SARS-CoV-2 IgM antibodies in mild and severe COVID-19 patients over time. $P < 0.01$.

Figure 2. IgM responses in mild vs. severe COVID-19 patients. (A) The positive rates of the SARS-CoV-2 IgM antibodies in mild and severe COVID-19 patients over time. P< 0.01

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CONTRIBUTORS

Ankita Dharmendran
Ellen Reidy
Jonathan Baker
Renate Meckl
Sarala Kal
Sokena Zaidi
Tyler Gallagher
Veronica Graham

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