

The Daily COVID-19 Literature Surveillance Summary

July 20, 2020



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COVID-19 Daily Literature Surveillance

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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	Non-randomized controlled cohort/follow-up study**	Case-series, case-control or historically controlled studies**	Mechanism-based reasoning
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

Climate

- Results of pooled data from the [Medical Expenditure Panel Survey \(MEPS\) between 2014-2017](#) (100,064 person-year observations on adults ≥18 years) suggest differences in exposure via employment between races and ethnicities may lead to COVID-19 risk disparities in minority groups. However, other risk factors (age >65, obesity, tobacco use and comorbidities) also play an important role in severity of illness.

Epidemiology

- A systematic review (n=69 studies) and quantitative review (n=61 studies) of case-control, cohort, and cross-sectional studies demonstrate epidemiological evidence for an association of male gender, older age, and comorbidities with [COVID-19 disease severity and prognosis](#), suggesting awareness of these associates can aid in prevention and individualized treatment but urge further studies exploring COVID-19-related factors.

Understanding the Pathology

- A structural analysis of the SARS-CoV-2 virus performed by the Gene Center at the University of Munich in Germany found [the Nsp1 protein shuts down host protein translation](#) by binding to the 40S ribosomal subunit, resulting in immune suppression, suggesting that the Nsp1 protein of SARS-CoV-2 could be the starting point for a structure-based drug design incorporating this Nsp1-ribosome interaction, allowing the host immune system to combat the virus.

Transmission & Prevention

- An evaluation of the effect of [the South Korean response system responsible for early detection of COVID-19](#) in the Gyeongsangnam-do Province reveals that out of 17,400 tested residents and 111 positive cases (25 asymptomatic), only two individuals required mechanical ventilation and there were no reported deaths (January 24 - April 15, 2020). The authors believe that this response system's rapid quarantine protocol for positive cases, in addition to all their possible contacts, is responsible for these encouraging outcomes, giving a potential example for other countries to follow while combating the COVID-19 pandemic.

Management

- A [systematic review of 204 kidney transplant recipients](#) (74% men) with COVID-19 through 12 case series conducted in multiple countries from January 1 to June 4, 2020 found a higher mortality rate of 21.2% compared with a 5.8% mortality rate in the general population. Mortality was strongly correlated to advanced age, ICU admission, and intubation and a majority of the patients were treated with immunosuppression and hydroxychloroquine, 34% were admitted to the ICU, and 19.7% were administered mechanical ventilation.
- A retrospective cohort study of 326 COVID-19 patients at Shanghai Public Health Clinical Center from 20 January to 24 February 2020 found that 20 patients who had [Hepatitis B virus \(HBV\) co-infection](#) (6.1%) had lower pre-albumin levels yet similar liver function tests, hospital stay duration, and discharge rates compared to patients with COVID-19 alone, potentially suggesting that HBV does not exacerbate COVID-19-related liver damage or cause a worse prognosis for this population.

Adjusting Practice During COVID-19

- [Dental guidelines are included for optimized pediatric care and to minimize the risk of COVID-19 transmission](#) during office visits and emergency situations (ie., cellulitis, severe tooth pain, and dental trauma).
- A survey study of 220 participants at five major pediatric dialysis centers in China conducted by Children's Hospital of Fudan University found that among [families with children on long-term kidney replacement therapy \(KRT\)](#) 78% (n=171) reported COVID-19 had influenced treatment, 61% (n=135) described current difficulties, 79% (n=173) worried about difficulties in the next 2, 13% (n=29) had depressive symptoms, and 11% (n=24) endorsed anxiety, suggesting that the COVID-19 outbreak has had a negative impact on both medical accessibility for children on long-term KRT and the mental health of their families.

R&D: Diagnosis & Treatments B working on now

- A longitudinal study found that 21.1% of 217 laboratory confirmed, hospitalized COVID-19 patients had detectable SARS-CoV-2 RNA in [anal swabs](#) and that detectable viral RNA in anal swabs is associated with increased risks of disease severity, ICU admission, and development of gastrointestinal symptoms.
- A study compared the ability of [6 commercial enzyme immunoassays and 8 lateral flow point of care assays](#) to test for antibodies to SARS-CoV-2 in the serum of 28 COVID-19 patients and found that while commercial enzyme

immunoassays and lateral flow point of care tests were both able to detect SARS-CoV-2, Abbott, Affinity, and BioRad enzyme immunoassays had the highest clinical sensitivity and specificity.

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CLIMATE GLOBAL

THE CLIMATE CRISIS AND COVID-19 - A MAJOR THREAT TO THE PANDEMIC RESPONSE

Salas RN, Shultz JM, Solomon CG.. N Engl J Med. 2020 Jul 15. doi: 10.1056/NEJMp2022011. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

In this perspective article from the New England Journal of Medicine, physicians affiliated with Harvard University and the University of Miami emphasize the ongoing need for action on climate change and propose modified responses for climate-related crises in the setting of the COVID-19 pandemic (Box 1). Beyond the pandemic, the dire need for prioritization of the climate crisis will remain, and preparedness for future issues regarding both climate and health will need to be revised in order to improve public safety.

SUMMARY

As the COVID-19 pandemic has presented a global challenge unlike any other in recent times, there continues to be the looming and insidious threat of climate change as well. Since the pandemic has started, there have been tropical storms, record heat waves, wild fires, and the prediction that extreme weather will continue to be above average for the remainder of 2020. Responses to climate-related crises, such as evacuations and mass shelterings, jeopardize SARS-CoV-2 infection control, making these events even more dangerous. There is also an additional strain on the already overwhelmed healthcare systems and exacerbation of limited resources, especially in areas that are economically disadvantaged. The authors of this article urge immediate action to overcome both the COVID-19 and climate crises, including modified climate disaster relief plans to reduce viral transmission, emphasis on scientific evidence when making policy changes, improved infrastructure of fragile health care systems, and prioritization of federal and state funded mitigation plans to better prepare for future crises.

FIGURES

Short-Term Strategies for Managing Climate-Related Extreme Events during the Covid-19 Pandemic.	
Extreme events (e.g., hurricanes, wildfires): evacuation and sheltering	Communicate clearly to the public that the Covid-19 pandemic does not change the imperative to evacuate, given the substantial risks of remaining in place during extreme climate-driven hazards.
	Use existing community pandemic-communication channels to disseminate critical information.
	Increase the number of available shelter sites, with lower occupancy per site, more separated spaces within sites, and more space per shelter resident (e.g., using smaller "noncongregate shelters," hotels).
	Use standard shelter-registration information (name, contact phone number) for all persons entering, to facilitate contact tracing in case Covid-19 is diagnosed in persons who used the shelter.
	Implement shelter protocols for infection control, including daily symptom checks, isolation of symptomatic persons, mandatory wearing of face masks, ample supplies of hand sanitizer, hand-washing stations, and meals provided in disposable containers.
	Adapt guidance for minimizing Covid-19 viral transmission in mass care settings for use with in-home sheltering — because many evacuees shelter with family and friends.
Extreme heat: remaining at home and cooling locations	Provide electricity subsidies and extend moratoriums to prevent electricity and water shutoffs for people with pandemic-related unemployment and economic hardships to allow them to remain in their homes.
	Ensure effective alternatives to minimize heat exposure if designated cooling centers or popular indoor, air-conditioned venues are closed.
	Ensure that cooling centers follow guidelines similar to best-practice guidelines noted above.
	Minimize transmission risks by limiting occupancy and providing or requiring masks and hand sanitizer in air-conditioned venues open to the public, such as malls or movie theaters.
	Use phone text messages, as used for pandemic communication, for heat-health notifications.

Box 1. Short-Term Strategies for Managing Climate-Related Extreme Events during the Covid-19 Pandemic.

AFFECTING THE HEALTHCARE WORKFORCE

ENVIRONMENTAL HEALTH WORKFORCE - ESSENTIAL FOR INTERDISCIPLINARY SOLUTIONS TO THE COVID-19 PANDEMIC

Ryan BJ, Swienton R, Harris C, James JJ.. Disaster Med Public Health Prep. 2020 Jul 14:1-7. doi: 10.1017/dmp.2020.242.
Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

Authors stress the importance of rapidly integrating the environmental health workforce as an interdisciplinary connector to monitor, contain, and develop interventions for the COVID-19 pandemic and future outbreaks (Figure 1). They recommend the environmental health workforce harness evidence and legislative support to respond to pandemics with safe community-based plans with local stakeholders, contact tracing, sample collection, monitoring infection control standards in medical settings, inspecting hygiene and sanitation in public spaces, working with schools and churches, and assessing environmental health risks of interventions.

SUMMARY

The authors recommend that engaged environmental health professionals should be members of the National Environmental Health Association or a state affiliated association, have an accredited environmental health degree, and be a Registered Environmental Health Specialist/Registered Sanitarian to maintain a professional workforce dedicated to the Center for Disease Control and Prevention's 10 Essential Environmental Public Health Services. These services include but are not limited to: addressing community environmental health problems, investigating health hazards, educating the public, building community partnerships and connecting people with resources, developing plans and public health solutions, and enforcing environmental health laws and practices.

ABSTRACT

Interdisciplinary public health solutions are vital for an effective COVID-19 response and recovery. However, there is often a lack of awareness and understanding of the environmental health workforce capabilities. In the United States, this is a foundational function of health departments and is the second largest public health workforce. The primary role is to protect the public from exposures to environmental hazards, disasters and disease outbreaks. More specifically, this includes addressing risks relating to sanitation, drinking water, food safety, vector control and mass gatherings. This profession is also recognized in the Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019. Despite this, the entire profession is often not considered an essential service. Rapid integration into COVID-19 activities can easily occur as most are government employees and experienced working in complex and stressful situations. This role, for example, could include working with leaders, businesses, workplaces and churches to safely reopen, and inspections to inform, educate, and empower employers, employees and the public on safe actions. There is now the legislative support, evidence and a window of opportunity to truly enable interdisciplinary public health solutions by mobilizing the entire environmental health workforce to support COVID-19 response, recovery and resilience activities.

FIGURES

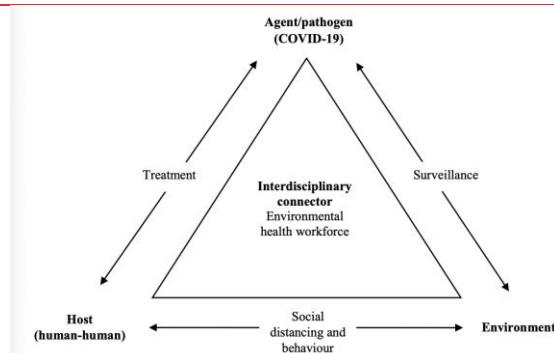


Figure 1: Environmental health role in the epidemiologic triangle for COVID-19

DISPARITIES

COVID-19 AND RACIAL/ETHNIC DISPARITIES IN HEALTH RISK, EMPLOYMENT, AND HOUSEHOLD COMPOSITION

Selden TM, Berdahl TA.. Health Aff (Millwood). 2020 Jul 14:101377hlthaff202000897. doi: 10.1377/hlthaff.2020.00897.
Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Authors in Maryland analyzed pooled data from the Medical Expenditure Panel Survey (MEPS) between 2014-2017 (100,064 person-year observations on adults ≥ 18 years) and found blacks were more likely to work in healthcare than whites (16.3% v. 10.4%), especially women (24.6% v. 17.2%). Additionally, both blacks and Hispanics were less likely to be able to work at home than whites (13.3% and 12.5% v. 22.8%). Conversely, whites were overall at higher risk of severe illness from COVID-19 in comparison to minorities (blacks, Asians, and Hispanics) but the authors attribute this to older average age among white participants. The results suggest differences in exposure via employment between races and ethnicities may lead to COVID-19 risk disparities in minority groups. However, other risk factors (age >65 , obesity, tobacco use and comorbidities) also play an important role in severity of illness.

ABSTRACT

We used data from the Medical Expenditure Panel Survey to explore potential explanations for racial-ethnic disparities in coronavirus disease 2019 (COVID-19) hospitalizations and mortality. Black adults in every age group were more likely than whites to have health risks associated with severe COVID-19 illness. However, whites were older on average than blacks. Thus, when all factors were considered, whites tended to be at higher overall risk compared to blacks, with Asians and Hispanics having much lower overall levels of risk compared to either whites or blacks. We explored additional explanations for COVID-19 disparities, namely differences in job characteristics and how they interact with household composition. Blacks at high risk of severe illness were 1.6 times as likely as whites to live in households containing health-sector workers. Among Hispanic adults at high risk of severe illness, 64.5 percent lived in households with at least one worker who was unable to work at home, versus 56.5 percent among blacks and only 46.6 percent among whites. [Editor's Note: This Fast Track Ahead Of Print article is the accepted version of the peer-reviewed manuscript. The final edited version will appear in an upcoming issue of Health Affairs.]

EPIDEMIOLOGY

DETECTION OF SARS-COV-2 RNA IN COMMERCIAL PASSENGER AIRCRAFT AND CRUISE SHIP WASTEWATER: A SURVEILLANCE TOOL FOR ASSESSING THE PRESENCE OF COVID-19 INFECTED TRAVELERS

Ahmed W, Bertsch PM, Angel N, Bibby K, Bivins A, Dierens L, Edson J, Ehret J, Gyawali P, Hamilton K, Hosegood I, Hugenholtz P, Jiang G, Kitajima M, Sichani HT, Shi J, Shimko KM, Simpson SL, Smith WJM, Symonds EM, Thomas DSC KV, Verhagen R, Zaugg J, Mueller JF.. J Travel Med. 2020 Jul 14:taaa116. doi: 10.1093/jtm/taaa116. Online ahead of print.
Level of Evidence: 4 - Local non-random sample

BLUF

Multidisciplinary researchers conducted a study of 21 wastewater samples from a cruise ship docked in Australia on April 23, 2020, as well as three aircrafts traveling from Los Angeles to Brisbane on April 26, Hong Kong to Brisbane on May 7, and New Delhi to Sydney on May 10, 2020, to detect the presence of SARS-CoV-2. Samples were analyzed with RT-qPCR and/or RT-ddPCR assays after concentrating the viral load within the samples. Wastewater samples from aircraft 1 and the cruise ship were positive for SARS-CoV-2, while those from aircrafts 2 and 3 were negative. The authors state that testing vessel waste water might be an efficient and cost-effective method to monitor viral spread and they recommend further studies to optimize sampling and analysis.

ABSTRACT

BACKGROUND: Wastewater-based epidemiology (WBE) for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be an important source of information for coronavirus disease 2019 (COVID-19) management during and after the pandemic. Currently, governments and transportation industries around the world are developing strategies to minimise SARS-CoV-2 transmission associated with resuming activity. This study investigated the possible use of SARS-CoV-2 RNA wastewater surveillance from airline and cruise ship sanitation systems and its potential use as a COVID-19 public health management tool.

METHODS: Airline and cruise ship wastewater samples ($n = 21$) were tested for SARS-CoV-2 RNA using two virus concentration methods, adsorption-extraction by electronegative membrane ($n = 13$) and ultrafiltration by Amicon ($n = 8$), and five assays using reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) and RT-droplet digital PCR (RT-ddPCR). Representative amplicons from positive samples were sequenced to confirm assay specificity.

RESULTS: SARS-CoV-2 RNA was detected in samples from both aircraft and cruise ship wastewater; however, concentrations were near the assay limit of detection. The analysis of multiple replicate samples and use of multiple RT-qPCR and/or RT-ddPCR assays increased detection sensitivity and minimised false-negative results. Representative amplicons were confirmed for the correct PCR product by sequencing. However, differences in sensitivity were observed among assays and concentration methods.

CONCLUSIONS: The study indicates that surveillance of wastewater from large transport vessels with their own sanitation systems has potential as a complementary data source to prioritize clinical testing and contact tracing among disembarking passengers. Importantly, sampling methods and molecular assays must be further optimized to maximize sensitivity. The potential for false negatives by both wastewater testing and clinical swab testing suggests that the two strategies could be employed together to maximize the probability of detecting SARS-CoV-2 infections amongst passengers.

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

EPIDEMIOLOGICAL, COMORBIDITY FACTORS WITH SEVERITY AND PROGNOSIS OF COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Fang X, Li S, Yu H, Wang P, Zhang Y, Chen Z, Li Y, Cheng L, Li W, Jia H, Ma X.. Aging (Albany NY). 2020 Jul 13;12. doi: 10.18632/aging.103579. Online ahead of print.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A systematic review (n=69 studies) and quantitative review (n=61 studies) of case-control, cohort, and cross-sectional studies demonstrate epidemiological evidence for an association of male gender, older age, and comorbidities epidemiological with COVID-19 disease severity and prognosis (Figure 1 & S11). The authors suggest awareness of these associates can aid in prevention and individualized treatment but urge further studies exploring COVID-19-related factors.

SUMMARY

In particular, comorbidities of hypertension, diabetes, cardiovascular disease, cerebrovascular disease, COPD, respiratory system disease, chronic kidney disease, hepatitis B infection, digestive disease and malignancy were significantly associated with COVID-19 disease severity. The prognostic endpoints of this study included death, ARDS, admission to ICU, invasive ventilation, and cardiac abnormality. Supplementary Table 2 summarizes the quantitative data for the associations of epidemiological and comorbidity factors with prognosis in COVID-19.

ABSTRACT

A systematic review and meta-analysis was conducted in an attempt to systematically collect and evaluate the associations of epidemiological, comorbidity factors with the severity and prognosis of coronavirus disease 2019 (COVID-19). The systematic review and meta-analysis was conducted according to the guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Sixty nine publications met our study criteria, and 61 studies with more than 10,000 COVID-19 cases were eligible for the quantitative synthesis. We found that the males had significantly higher disease severity (RR: 1.20, 95% CI: 1.13-1.27, P <0.001) and more prognostic endpoints. Older age was found to be significantly associated with the disease severity and six prognostic endpoints. Chronic kidney disease contributed mostly for death (RR: 7.10, 95% CI: 3.14-16.02), chronic obstructive pulmonary disease (COPD) for disease severity (RR: 4.20, 95% CI: 2.82-6.25), admission to intensive care unit (ICU) (RR: 5.61, 95% CI: 2.68-11.76), the composite endpoint (RR: 8.52, 95% CI: 4.36-16.65,), invasive ventilation (RR: 6.53, 95% CI: 2.70-15.84), and disease progression (RR: 7.48, 95% CI: 1.60-35.05), cerebrovascular disease for acute respiratory distress syndrome (ARDS) (RR: 3.15, 95% CI: 1.23-8.04), coronary heart disease for cardiac abnormality (RR: 5.37, 95% CI: 1.74-16.54). Our study highlighted that the male gender, older age and comorbidities owned strong epidemiological evidence of associations with the severity and prognosis of COVID-19.

FIGURES

Figure S11 Forest plot of association between comorbidity and disease severity.

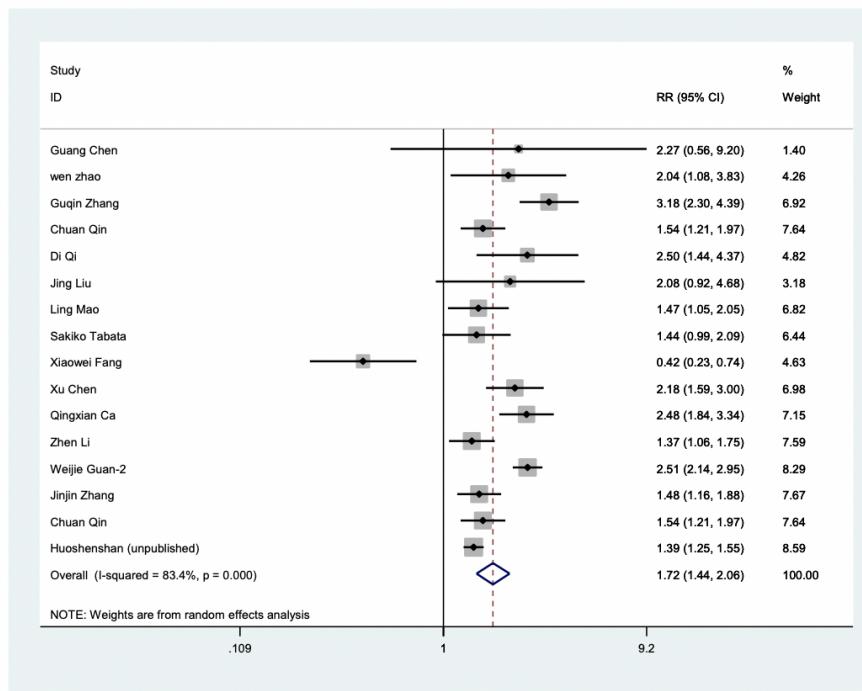
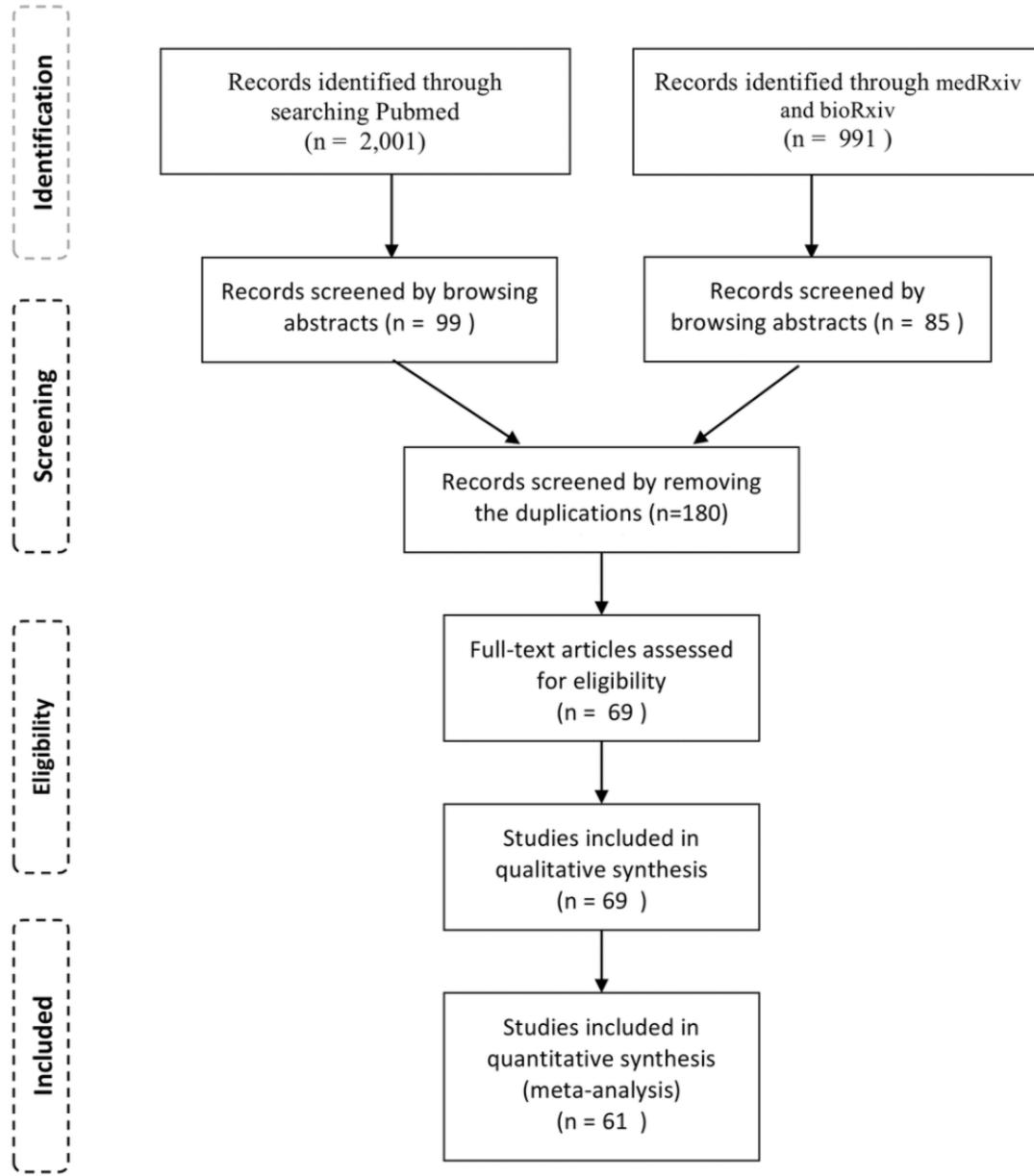


Figure S11: Forest plot of association between comorbidity and disease severity



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097

Figure 1: PRISMA flow diagram

Table 2. Quantitative data synthesis for the associations of the epidemiological, comorbidity factors with prognosis of COVID-19 (P value<0.05).

Variables	No of studies	Total cases	P heterogeneity	I ² (%)	RR (95% CIs)	P value	P Egger
Death							
Sex, male	10	4214	0.443	0.0	1.23 (1.14-1.33)	<0.001	0.276
Comorbidities	8	4499	<0.001	88.7	1.68 (1.32-2.13)	<0.001	0.248
Hypertension	11	4860	<0.001	84.4	1.74 (1.31-2.30)	<0.001	0.418
Diabetes	10	4748	0.001	67.1	1.75 (1.27-2.41)	0.001	0.057
Malignancy	6	3978	0.262	22.8	3.09 (1.59-6.00)	0.001	0.006
Cardiovascular disease	11	4860	<0.001	75.9	2.67 (1.60-4.43)	<0.001	0.654
Coronary heart disease	5	2452	<0.001	87.7	3.16 (1.45-6.91)	0.004	0.435
Cerebrovascular disease	6	3771	0.457	0.0	4.61 (2.51-8.47)	<0.001	0.766
COPD	4	3677	0.279	22.0	5.31 (2.63-10.71)	<0.001	0.107
Respiratory system disease	7	4472	0.185	31.8	3.22 (2.12-4.90)	<0.001	0.761
Chronic kidney disease	5	2219	0.477	0.0	7.10 (3.14-16.02)	<0.001	0.772
Admission to ICU							
Sex, male	5	2224	0.011	69.6	1.29 (1.13-1.47)	<0.001	0.651

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Comorbidities	5	3747	0.038	60.5	1.82 (1.45-2.29)	<0.001	0.646
Hypertension	5	3747	0.601	0.0	2.31 (1.97-2.70)	<0.001	0.312
Diabetes	5	3747	0.084	51.4	1.88 (1.10-3.23)	0.021	0.457
Malignancy	5	3747	0.427	0.0	2.52 (1.38-5.59)	0.003	0.158
Cardiovascular disease	5	3747	0.511	0.0	2.74 (1.92-3.92)	<0.001	0.692
Cerebrovascular disease	3	3508	0.349	4.9	5.12 (2.86-9.17)	<0.001	0.273
COPD	4	3549	0.800	0.0	5.61 (2.68-11.76)	<0.001	0.740
Respiratory system disease	4	3549	0.613	0.0	4.66 (2.59-8.40)	<0.001	0.637
Composite endpoint							
Smoking	2	2879	0.604	0.0	2.67 (1.91-3.73)	<0.001	-
Comorbidities	2	3370	<0.001	95.3	1.96 (1.06-3.60)	0.031	-
Hypertension	2	3370	0.011	84.5	2.20 (1.44-3.36)	<0.001	-
Cardiovascular disease	2	3370	0.927	0.0	3.09 (2.09-4.57)	<0.001	-
Coronary heart disease	2	3370	0.473	0.0	3.36 (2.15-5.25)	<0.001	-
Cerebrovascular disease	2	3370	0.225	32.0	4.10 (2.34-7.18)	<0.001	-
COPD	2	3370	0.185	43.0	8.52 (4.36-16.65)	<0.001	-
Respiratory system disease	2	3370	0.185	43.0	8.52 (4.36-16.65)	<0.001	-
ARDS							
Sex, male	3	2090	0.464	0.0	1.15 (1.01-1.30)	0.033	0.353
Hypertension	3	2090	0.377	0.0	1.90 (1.57-2.30)	<0.001	0.520
Diabetes	3	2090	0.068	62.9	3.07 (1.28-7.36)	0.012	0.066
Cardiovascular disease	3	2090	0.244	29.2	2.26 (1.43-3.58)	<0.001	0.422
Cerebrovascular disease	2	1889	0.152	51.2	3.15 (1.23-8.04)	0.016	-
Respiratory system disease	2	1889	0.303	5.6	2.44 (1.20-4.97)	0.014	-
Invasive ventilation							
Sex, male	2	1825	0.403	0.0	1.35 (1.11-1.64)	0.002	-
Family cluster	2	1825	0.646	0.0	1.58 (1.13-2.14)	0.006	-
Comorbidities	3	3415	0.005	81.2	1.83 (1.19-2.79)	0.006	0.569
Hypertension	3	3415	0.131	50.9	2.35 (1.92-2.89)	<0.001	0.366
Diabetes	3	3415	0.131	50.8	1.85 (1.24-2.76)	0.003	0.021
Cardiovascular disease	3	3415	0.844	0.0	2.90 (1.63-5.15)	<0.001	0.618
Cerebrovascular disease	2	3370	0.602	0.0	3.98 (1.77-8.93)	0.001	-
COPD	2	3370	0.383	0.0	6.53 (2.70-15.84)	<0.001	-
Respiratory system disease	3	3415	0.260	25.7	4.34 (2.04-9.26)	<0.001	0.567
Cardiac abnormality							
Sex, male	4	439	0.211	33.6	1.33 (1.02-1.72)	0.036	0.624
Hypertension	4	439	0.947	0.0	2.97 (1.65-5.34)	<0.001	0.610
Cardiovascular disease	4	439	0.915	0.0	4.90 (1.82-13.21)	0.002	0.177
Coronary heart disease	3	386	0.819	0.0	5.37 (1.74-16.54)	0.003	0.408
Disease progression							
Hypertension	2	219	0.547	0.0	2.90 (1.45-5.81)	0.003	-
Diabetes	2	219	0.746	0.0	3.30 (1.08-10.07)	0.036	-
COPD	2	219	0.848	0.0	7.48 (1.60-35.05)	0.011	-
Respiratory system disease	2	219	0.848	0.0	7.48 (1.60-35.05)	0.011	-

Figure 1: PRISMA flow diagram

CASE REPORT: COVID-19-ASSOCIATED BILATERAL SPONTANEOUS PNEUMOTHORAX-A LITERATURE REVIEW

Alhakeem A, Khan MM, Al Soub H, Yousaf Z.. Am J Trop Med Hyg. 2020 Jul 14. doi: 10.4269/ajtmh.20-0680. Online ahead of print.

Level of Evidence: Other - Case Report

BLUF

This case report describes a 49 year-old male with no known medical history who presented to Hamad Medical Corporation in Doha, Qatar. He was COVID-19 positive via nasopharyngeal swab polymerase chain reaction (PCR) and ultimately developed bilateral pneumothorax (see summary). Based on this and similar cases (Table 1), the authors suggest pneumothorax associated with COVID-19 pneumonia may be underdiagnosed in otherwise healthy individuals and should be considered in differential diagnosis of COVID-19.

SUMMARY

The patient was admitted to a quarantine facility for observation after positive COVID-19 nasopharyngeal swab PCR. On day 5 he developed severe shortness of breath (SOB) and oxygen desaturation to 85% on room air, chest X-ray showed bilateral infiltrates (Figure 1A), and inflammatory markers were elevated (C-reactive protein 133.1 mg/L and ferritin 8,382.0 µg/L). He was admitted to the ICU and treatments included 15 liters of oxygen via non-rebreather mask, azithromycin, hydroxychloroquine, ceftriaxone, lopinavir-ritonavir, tocilizumab and convalescent plasma. On day 10 he was transferred to the medical ward, but his SOB returned on day 12 and chest X-ray showed a right-sided pneumothorax (Figure 1B) and a chest tube was inserted. After initial symptom improvement he again developed SOB on day 17. Chest X-ray showed a left-sided pneumothorax (Figure 1C) and another chest tube was inserted. At this time, high resolution chest CT showed multiple bilateral bullae in the lungs complicated by pneumothorax due to rupture (Figure 1D). Alpha-1-antitrypsin level was normal and tuberculosis workup was negative. The right chest tube was removed on day 23 and the patient continues to receive care with near-complete expansion of the left lung at the time of this report.

ABSTRACT

COVID-19 is a pandemic caused by SARS-CoV-2, primarily affecting the respiratory tract. Pulmonary complications of COVID-19 may include acute respiratory distress syndrome and pulmonary embolism. Pneumothorax has been recently reported in association with COVID-19. We report a case of COVID-19 pneumonia with bilateral spontaneous pneumothorax with no known underlying lung disease or risk factors.

FIGURES

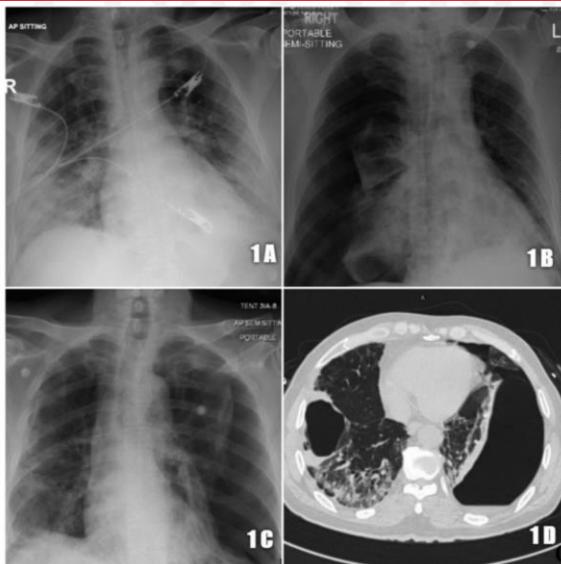


Figure 1. (A) Chest X-ray depicting bilateral lung infiltrates, (B) chest X-ray depicting right pneumothorax with right lung collapse and tracheal deviation to the left, (C) chest X-ray depicting bilateral pneumothorax with left > right and tracheal deviation to the right, and (D) chest CT depicting bilateral bullae, ground-glass appearance, and large left pneumothorax with underlying collapsed lung.

TABLE 1
Literature review of COVID-19-associated pneumothorax

Serial number	Author/published year/country	Number of cases	Age (years)	Gender	Comorbidities	Diagnosis	Treatment/intervention	Outcome
1.	Lyu R, et al., April 2020, Wuhan, China	1	38	Male	Smoker	Left pneumothorax	Conservative	Recovered and discharged
2.	Rohailla S, et al., May 2020, Toronto, Canada	1	26	Male	Nil	Right pneumothorax	Chest tube	Recovered and discharged
3.	Agridag B, et al., May 2020, Istanbul, Turkey	1	82	Female	Nil	Left pneumothorax and subcutaneous emphysema	Chest tube	Recovered and discharged
4.	Aydin S, et al., May 2020, Afyonkarahisar, Turkey	1	24	Male	Nil	Left pneumothorax	Chest tube	Recovered and discharged
5.	Wang W, et al., May 2020, Wuhan, China	1	62	Male	Nil	Right pneumothorax	Conservative	Recovered and discharged
6.	Poggiali E, et al., June 2020, Piacenza, Italy	1	87	Male	Smoker + chronic obstructive pulmonary disease	Left pneumothorax and subcutaneous emphysema	Chest tube	Recurrence and expired
7.	Flower L, et al., May 2020, London, United Kingdom	1	36	Male	Smoker + asthma	Left pneumothorax	Needle decompression + chest tube	Recovered and discharged
8.	Sun R, et al., March 2020, Wuhan, China	1	38	Male	Nil	Left pneumothorax	Conservative	Recovered
9.	Wang J, et al., March 2020, Guangzhou, China	1	36	Male	Nil	Pneumomediastinum	Conservative	Expired
10.	Lei P, et al., April 2020, Guiyang, China	1	64	Male	Nil	Pneumomediastinum	Conservative	Recovered
11.	López V, et al., June 2020, Madrid, Spain	3	84	Female	Hypertension, prosthetic heart valve, chronic kidney disease, and congestive cardiac failure	Right hydro-pneumothorax	Conservative	Expired
			67	Male	Nil	Bilateral pneumothorax + pneumomediastinum	Chest tube	Expired
			73	Male	Epithelioma, obstructive sleep apnea	Pneumomediastinum	Conservative	Expired
12.	Alolfi A, et al., April 2020, Milan, Italy	2	56	Male	Smoker	Left pneumothorax	Chest tube thoracoscopy: bleb resection + pleurodesis	Recovered
			70	Male	Nil	Left pneumothorax	Chest tube thoracoscopy: bleb resection + pleural scratch	Recovered
13.	Kolani S, et al., May 2020, Fez, Morocco	1	23	Female	Nil	Pneumomediastinum	Conservative	Recovered
14.	Mohan V, et al., May 2020, New Jersey	1	49	Male	Hypertension and diabetes mellitus	Pneumomediastinum	Conservative	Recovered
15.	Xiang C, et al., May 2020, Wuhan, China	1	67	Male	CAD/COPD	Pneumothorax + subcutaneous emphysema	Chest tube	Expired

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease.

Table 1. Literature review of COVID-19-associated pneumothorax.

ADVANCED AGE

PRESYMPOMATIC TRANSMISSION OF SARS-COV-2 AMONGST RESIDENTS AND STAFF AT A SKILLED NURSING FACILITY: RESULTS OF REAL-TIME PCR AND SEROLOGIC TESTING

Goldberg SA, Lennerz J, Klompas M, Mark E, Pierce VM, Thompson RW, Pu CT, Ritterhouse LL, Dighe A, Rosenberg ES, Grabowski DC.. Clin Infect Dis. 2020 Jul 15:ciaa991. doi: 10.1093/cid/ciaa991. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

This study conducted at a skilled nursing facility in Massachusetts, United States between April 1-5, 2020 found that despite all participants (n=97; aged 54-102 years) being asymptomatic at the time of SARS-CoV-2 nasopharyngeal polymerase chain reaction testing, 85% (n=83) tested positive. Additionally, 45/56 residents who underwent IgM and IgG serologic testing had

negative results. 37.1% (n=36) of staff members subsequently tested positive on April 6, 2020. The authors recommend large scale SARS-CoV-2 testing for vulnerable populations even if asymptomatic and note serologic testing appears to have limited use in early stages of an outbreak.

ABSTRACT

High rates of asymptomatic infection suggest benefits to routine testing in congregate care settings. SARS-CoV-2 screening was undertaken in a single nursing facility without a known case of COVID-19, demonstrating an 85% prevalence among residents and 37% among staff. Serology was not helpful in identifying infections.

UNDERSTANDING THE PATHOLOGY

THE ROLE OF HOST GENETICS IN THE IMMUNE RESPONSE TO SARS-COV-2 AND COVID-19 SUSCEPTIBILITY AND SEVERITY

Ovsyannikova IG, Haralambieva IH, Crooke SN, Poland GA, Kennedy RB.. Immunol Rev. 2020 Jul 13. doi: 10.1111/imr.12897.
Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

A review conducted by Mayo Clinic Vaccine Research Group in Rochester, MN reported findings on immunologic mechanisms and regions of interest related to the susceptibility and presentation of SARS-CoV-1, MERS-CoV, and SARS-CoV-2. The authors also discuss SARS-CoV-2 genetic variants and current unanswered questions and recommend a research agenda of human host genetics to gain a more comprehensive understanding of the disease (see summary).

SUMMARY

Summary of review findings as follows:

Studies reported the following host genetic factors associated with SARS-CoV-1:

- No association with ACE2 gene polymorphisms (Chiu et al).
- Protective role of CLEC4M tandem repeats (Chan et al).
- Link between SARS and mannose-binding lectin (MBL) deficiency (Ip et al).
- HLA-1 polymorphisms were associated with susceptibility.

Host genetic factors associated with MERS were identified, including: "the virus entry receptor (dipeptidyl peptidase-4 [DPP4]), presumed attachment factors, sialic acids, host proteases (i.e. TMPRSS2, furin, cathepsins), interferons, interferon-stimulated genes, and adaptive immune response factors."

Host genetic factors associated with SARS-CoV-2 (Figure 1):

- ACE2 variant (N720D) proximal to TMPRSS2 cleavage site was potentially associated with COVID-19 susceptibility (Renieri et al).
- Levels of expression of ACE2 was correlated with disease severity (Pinto et al).
- SNP associated with TMPRSS2 may cause increased susceptibility due to increased TMPRSS2 (Russo et al).
- Various HLA loci may predict susceptibility.
- Increased inflammatory factors and IL-6 were associated with increased severity of disease.

Current evidence suggests human genetic variations may affect COVID-19 susceptibility, but the variants and their role remain unknown. The authors acknowledge a need for large scale host genetic studies to determine roles of genes, better understand immunity to SARS-CoV-2 for vaccine development, and gain information regarding disease pathogenesis and treatments.

ABSTRACT

This article provides a review of studies evaluating the role of host (and viral) genetics (including variation in HLA genes) in the immune response to coronaviruses, as well as the clinical outcome of coronavirus-mediated disease. The initial sections focus on seasonal coronaviruses, SARS-CoV, and MERS-CoV. We then examine the state of the knowledge regarding genetic polymorphisms and SARS-CoV-2 and COVID-19. The article concludes by discussing research areas with current knowledge gaps and proposes several avenues for future scientific exploration in order to develop new insights into the immunology of SARS-CoV-2.

FIGURES

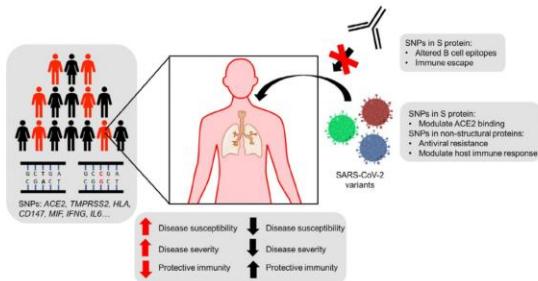


Figure 1. The impact of host genetics and viral variation on SARS-CoV-2 infection and COVID-19 severity. Individuals in the population harbor single nucleotide polymorphisms (SNPs) across a variety of genes (eg, ACE2, TMPRSS2, HLA, CD147, MIF, IFNG, IL6...) that have been implicated in the pathology and immunology of SARS-CoV-2 and other pathogenic coronaviruses. These and other genetic variants may modulate disease susceptibility, increase or decrease disease severity, alter the variety of symptoms developed, and affect the magnitude and/or quality of the immune responses against SARS-CoV-2. In addition to host genetic variation, genetic variants of SARS-CoV-2 (and other pathogenic coronaviruses) can exhibit differences in biological activity. Single amino acid mutations in the spike glycoprotein can modulate ACE2 binding or alter B cell epitopes to promote immune escape or render monoclonal antibodies ineffective, while mutations in non-structural/accessory proteins can promote the development of resistance to antivirals, alter T cell epitopes, disrupt cell mediated immunity, and modulate host cellular interactions with viral particles

IN SILICO

STRUCTURAL BASIS FOR TRANSLATIONAL SHUTDOWN AND IMMUNE EVASION BY THE NSP1 PROTEIN OF SARS-COV-2

Thoms M, Buschauer R, Ameismeier M, Koepke L, Denk T, Hirschenberger M, Kratzat H, Hayn M, Mackens-Kiani T, Cheng J, Straub JH, Stürzel CM, Fröhlich T, Berninghausen O, Becker T, Kirchhoff F, Sparrer KMJ, Beckmann R.. Science. 2020 Jul 17:eabc8665. doi: 10.1126/science.abc8665. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

A structural analysis of the SARS-CoV-2 virus performed by the Gene Center at the University of Munich in Germany found the Nsp1 protein shuts down host protein translation by binding to the 40S ribosomal subunit, resulting in immune suppression (Figure 1). This finding suggests that the Nsp1 protein of SARS-CoV-2 could be the starting point for a structure-based drug design incorporating this Nsp1-ribosome interaction, allowing the host immune system to combat the virus.

ABSTRACT

SARS-CoV-2 is the causative agent of the current COVID-19 pandemic. A major virulence factor of SARS-CoVs is the nonstructural protein 1 (Nsp1) which suppresses host gene expression by ribosome association. Here, we show that Nsp1 from SARS-CoV-2 binds to the 40S ribosomal subunit, resulting in shutdown of mRNA translation both *in vitro* and in cells. Structural analysis by cryo-electron microscopy (cryo-EM) of *in vitro* reconstituted Nsp1-40S and various native Nsp1-40S and -80S complexes revealed that the Nsp1 C terminus binds to and obstructs the mRNA entry tunnel. Thereby, Nsp1 effectively blocks RIG-I-dependent innate immune responses that would otherwise facilitate clearance of the infection. Thus, the structural characterization of the inhibitory mechanism of Nsp1 may aid structure-based drug design against SARS-CoV-2.

FIGURES

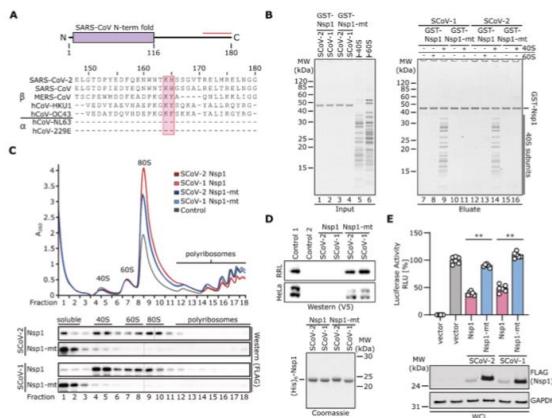


Fig. 1. Nsp1 interacts with 40S ribosomal subunits and inhibits translation. (A) Domain organization of Nsp1 and sequence alignment of the C-terminal segment (red line) of Nsp1 from SARS-CoV-2 with SARS-CoV, MERS-CoV, HCoV-OC43, and HCoV-NL63. The KH motif is marked. (B) In vitro binding assay of GST-TEV (GST) tagged Nsp1 and Nsp1-mt from SCoV-1 and SCoV-2 with human 40S and 60S ribosomal subunits. Coomassie stained SDS-PAGE of inputs and eluates. (C) Polyribosome gradient analysis of HEK293T lysate (Control) and lysate from HEK293T cells transiently transfected with 3xFLAG tagged Nsp1 and Nsp1-mt constructs from SCoV-1 and SCoV-2 and Western blot analysis (anti-FLAG antibody, dashed lines; separate blots). (D) Western blot (top, anti-V5 antibody) and SDS-PAGE analysis (bottom) of cell-free in vitro translation of a capped reporter mRNA with rabbit reticulocytes (RRL) and HeLa S3 lysate. Controls 1 and 2, with and without capped reporter mRNA, respectively. Coomassie stained SDS-PAGE of the applied (His)₆-TEV (His₆) tagged Nsp1 constructs is shown below. (E) Quantification of luciferase in HEK293T cells transfected with indicated 3xFLAG-tagged proteins and in vitro transcribed firefly luciferase mRNA. Bars represent the mean of n=6±SEM RLU, relative light units. Representative immunoblots of whole cell lysates (WCL) stained with anti-FLAG and anti-GAPDH. **, p<0.001. Unpaired student's t test (Welch correction).

IN VITRO

SARS-COV-2-SPECIFIC T CELL IMMUNITY IN CASES OF COVID-19 AND SARS, AND UNINFECTED CONTROLS

Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, Chng MHY, Lin M, Tan N, Linster M, Chia WN, Chen MI, Wang LF, Ooi EE, Kalimuddin S, Tambyah PA, Low JG, Tan YJ, Bertoletti A.. Nature. 2020 Jul 15. doi: 10.1038/s41586-020-2550-z. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A study compared peripheral blood samples of recovered COVID-19 patients (n=36), SARS patients (n=23), and uninfected controls (n=37). All recovered COVID-19 samples possessed T-cell responses to multiple components of the nucleocapsid protein (NP; Figure 2), and the SARS samples displayed lasting memory T-cell response to SARS-NP and cross-reactivity with SARS-CoV-2, whereas unexposed controls showed different immunodominance than the previous infected samples. The authors suggest that "understanding the distribution, frequency, and protective capacity of pre-existing structural or non-structural SARS-CoV-2 cross-reactive T cells could be of great importance to explain some of the differences in infection rates or pathology observed during this pandemic."

ABSTRACT

Memory T cells induced by previous pathogens can shape the susceptibility to, and clinical severity of, subsequent infections 1. Little is known about the presence of pre-existing memory T cells in humans with the potential to recognize SARS-CoV-2. Here, we first studied T cell responses to structural (nucleocapsid protein, NP) and non-structural (NSP-7 and NSP13 of ORF1) regions of SARS-CoV-2 in COVID-19 convalescents (n=36). In all of them we demonstrated the presence of CD4 and CD8 T cells recognizing multiple regions of the NP protein. We then showed that SARS-recovered patients (n=23) still possess long-lasting memory T cells reactive to SARS-NP 17 years after the 2003 outbreak, which displayed robust cross-reactivity to SARS-CoV-2 NP. Surprisingly, we also frequently detected SARS-CoV-2 specific T cells in individuals with no history of SARS, COVID-19 or contact with SARS/COVID-19 patients (n=37). SARS-CoV-2 T cells in uninfected donors exhibited a different pattern of immunodominance, frequently targeting the ORF-1-coded proteins NSP7 and 13 as well as the NP structural protein. Epitope characterization of NSP7-specific T cells showed recognition of protein fragments with low homology to "common cold" human coronaviruses but conserved amongst animal betacoronaviruses. Thus, infection with betacoronaviruses induces multispecific and long-lasting T cell immunity to the structural protein NP. Understanding how pre-existing NP- and ORF-1-

specific T cells present in the general population impact susceptibility and pathogenesis of SARS-CoV-2 infection is of paramount importance for the management of the current COVID-19 pandemic.

FIGURES

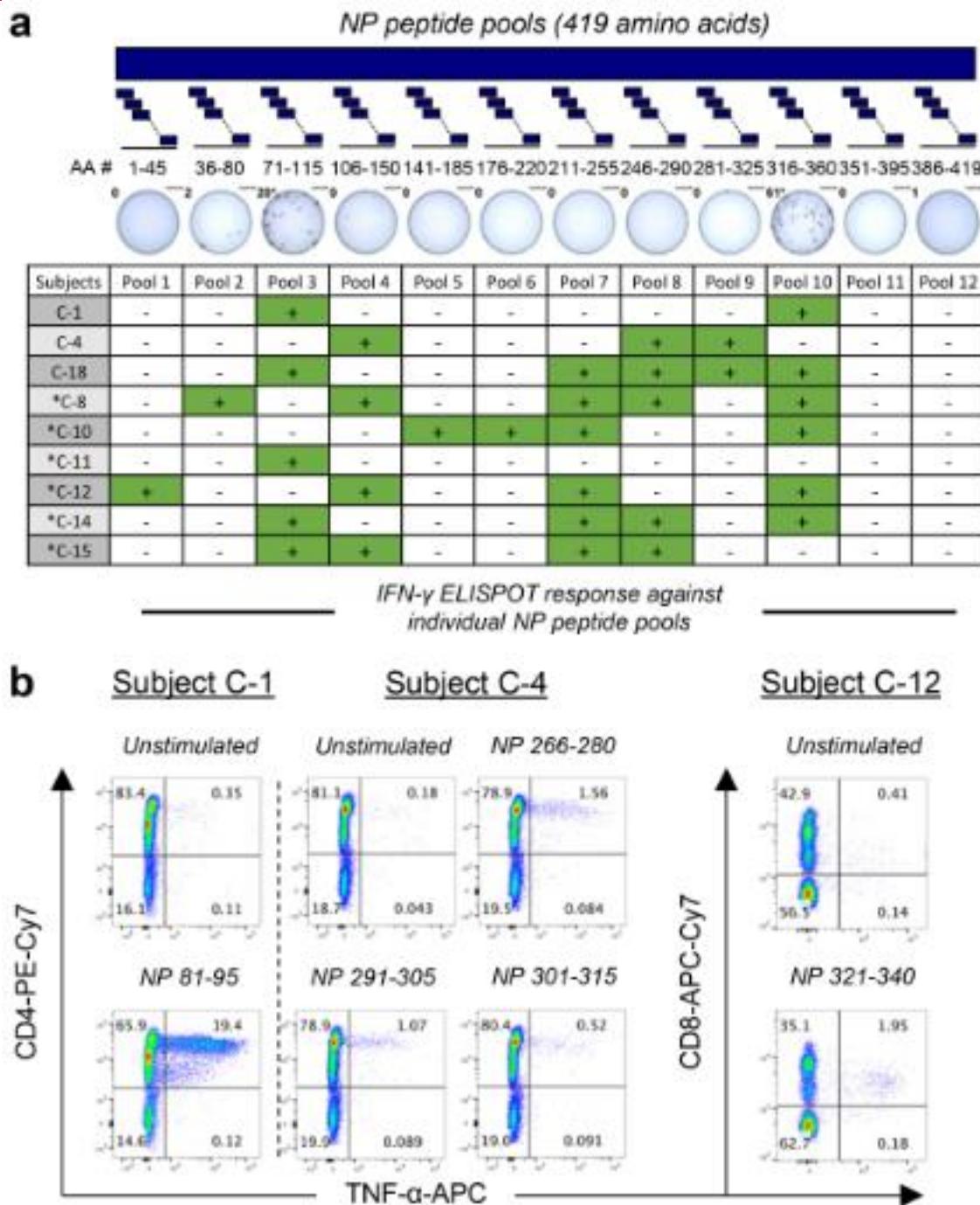


Figure 2. SARS-CoV-2-specific T cells in COVID-19 convalescents are targeting multiple regions of nucleocapsid protein. a, PBMC of 9 COVID-19 recovered individuals were stimulated with 12 different pools of 7-8 NP-peptides. The table shows IFN- γ ELISpot response against the individual NP peptide pools. *denotes responses detected after in vitro expansion. b, Following in vitro cell expansion, a peptide pool matrix strategy was applied. T cells reacting to distinct peptides were identified by IFN- γ ELISpot and confirmed by ICS. Representative dot plots of 3/7 patients are shown.

TRANSMISSION & PREVENTION

DEVELOPMENTS IN TRANSMISSION & PREVENTION

RESPONSE SYSTEM FOR AND EPIDEMIOLOGICAL FEATURES OF COVID-19 IN GYEONGSANGNAM-DO PROVINCE IN SOUTH KOREA

Wi YM, Lim SJ, Kim SH, Lim S, Lee SJ, Ryu BH, Hong SI, Cho OH, Moon K, Hong KW, Kim S, Bae IG.. Clin Infect Dis. 2020 Jul 16:ciaa967. doi: 10.1093/cid/ciaa967. Online ahead of print.

Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

An evaluation of the effect of the Korean response system responsible for early detection of COVID-19 in the Gyeongsangnam-do Province reveals that out of 17,400 tested residents and 111 positive cases (25 asymptomatic), only two individuals required mechanical ventilation and there were no reported deaths (January 24 - April 15, 2020). The authors believe that this response system's rapid quarantine protocol for positive cases, in addition to all their possible contacts, is responsible for these encouraging outcomes, giving a potential example for other countries to follow while combating the COVID-19 pandemic.

SUMMARY

- The Gyeongsangnam-do Province had their first two confirmed cases on February 20.
- The Rapid Response Team was mobilized to study these patients' medical records, interview the patients to determine their recent activities and contacts, and scrutinize their cell phone and credit card data. Any enclosed space that the patient previously occupied was closed for cleaning and opened a day later. Identified contacts were told to self-isolate for 14 days and keep track of their symptoms.
- The province designated Masan Medical Center (MMC) for mild to moderate COVID-19 cases and four university hospitals for severe cases. Patients were released when they had no more symptoms and tested negative twice. The Patient Management Team determined which hospital a patient should be admitted to and when a patient should be released, and they used an instant messenger service to discuss patient information. MMC's policies: healthcare workers donned PPE in a designated place, enter the room through a predetermined route, and leave after a shower; 1 room per patient or 2 patients in a room if the patients could stay at least 6 feet away from each other; portable chest radiography for patients on the day of admission and additional blood tests for those with pneumonia, fever, or co-morbidity; treatment with hydroxychloroquine or lopinavir/ritonavir.
- Average age of patients was 41.3 +/- 19 years. Most common co-morbidities were hypertension (18.9%), diabetes (7.2%), and tumors (3.6%). Average incubation time was 6.5 +/- 4.3 days. Common first symptoms were cough (30%), muscle ache (26.1%), fever (25.2%), loss of taste and smell (15.7% and 14.7%). 25 patients had no symptoms at the time of admission, and 18 of these patients developed symptoms after a mean of 2.6 +/- 1.9 days. 44.1% of the patients developed pneumonia, at an average of 7 days after first symptoms. Low lymphocyte count in 52.2%, low platelet count in 7.5%, and low leukocyte count in 25.4% of patients. Average period of disease detection was 24 +/- 10.8 days after first symptoms.

ABSTRACT

BACKGROUND: The South Korean government has been combating COVID-19 outbreak using public information and extensive viral screening. We described the application of the Korean response system in one province and outlined the epidemiological features of COVID-19 in the cohort. **METHODS:** A Rapid Response Team tracked the patients' activities and identified close contacts. A Patient Management Team made decisions regarding the severity of illness, hospital allocation depending on severity, and time of discharge. A national medical center with 155 beds and 4 university-affiliated hospitals with 48 negative-pressure isolation rooms were dedicated for COVID-19 patients. **RESULTS:** As of April 15, 17 400 residents were tested, of whom 111 were confirmed positive cases. Of the 111 patients, 78 were cured and discharged, 2 recovered after mechanical ventilation, and none died. One healthcare worker at the national center tested positive for SARS-CoV-2. All 412 staff members at the center were tested, but there were no additional infections. Cough (30.0 %) was the most common initial symptom, whereas anosmia and ageusia were the first symptoms in 14.7% and 15.7% of the patients, respectively. Overall, 25 patients (22.5%) reported having no symptoms at admission and 7 (6.3%) remained asymptomatic at discharge. **CONCLUSIONS:** A response system that enabled the early detection of COVID-19 cases, including asymptomatic and pre-symptomatic cases, and timely quarantine of these patients and their contacts, along with efficient allocation of medical resources, was the key to curbing the COVID-19 outbreak in Gyeongsangnam-do Province.

ASSOCIATION BETWEEN RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS AND COVID-19 INFECTION IN SOUTH KOREA

Son M, Seo J, Yang S.. Hypertension. 2020 Jul 13:HYPERTENSIONAHA12015464. doi: 10.1161/HYPERTENSIONAHA.120.15464. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

Investigators from the Republic of Korea conducted a case control study using national health insurance claim data from April 8, 2020 to compare risks and outcomes of 950 COVID-19 patients with hypertension either exposed or unexposed to renin angiotensin-aldosterone system (RAAS) inhibitors (Figure). Multivariable adjusted conditional logistic regression analysis found patients exposed to RAAS inhibitors were no more likely to be diagnosed with COVID-19 (OR: 1.161, 95% CI:[0.958-1.407]; non-significant) or suffer worse outcomes (Table 2) than unexposed patients. These results suggest RAAS inhibitors are not associated with increased COVID-19 risk (supported by a non-significant OR of disease being associated with exposure) and should not be discontinued due to COVID-19 concerns.

ABSTRACT

The severe acute respiratory syndrome coronavirus 2 is known to infect host cells by interacting with ACE2 (angiotensin-converting enzyme 2) expressed in the respiratory epithelium. There have been concerns on whether alterations of ACE2 expression by renin-angiotensin-aldosterone system (RAAS) inhibitors would contribute to the infectivity and severity of coronavirus disease 2019 (COVID-19). We performed a case-control study to investigate the association between RAAS inhibitors and risk and severity of COVID-19 infection in South Korea using the population-based data provided by the Korean National Health Insurance System. Of 16 281 subjects with hypertension, there were 950 (5.8%) confirmed COVID-19 cases. After case-control matching, multivariable-adjusted conditional logistic regression analysis was performed. The adjusted odds ratio and 95% CIs for COVID-19 infection and long-term hospitalization comparing exposure to RAAS inhibitors and nonexposure to RAAS inhibitors was 1.161 (0.958-1.407) and 0.863 (0.533-1.397), respectively. When comparing exposure to RAAS inhibitors and nonexposure to RAAS inhibitors for intensive care unit admission, high-flow oxygen therapy, and death, the adjusted odds ratios (95% CIs) were 1.515 (0.402-5.701), 0.663 (0.272-1.619), and 1.363 (0.513-3.662), respectively. In all analyses, P values were not significant ($P>0.05$). The present study demonstrates the absence of an identifiable association between the exposure to RAAS inhibitors and risk and severity of COVID-19 infection, supporting the current medical guidelines and recommendations that patients should not discontinue RAAS inhibitors out of a concern that they are at increased risk for infection or severe illness of COVID-19.

FIGURES

Table 2. OR and 95% CI for Outcome of COVID-19 According to Exposure to RAAS Inhibitors						
Outcomes	Control Group, %	Case Group, %	Crude OR (95% CI)	PValue	Adjusted OR* (95% CI)	PValue
Infection	1897 (100)	950 (100)	1.000		1.000	
Nonexposure to RAAS inhibitors	486 (25.6)	214 (22.5)	1.161 (0.958-1.407)	0.0702	1.161 (0.958-1.407)	0.1277
Exposure to RAAS inhibitors	1411 (74.4)	736 (77.5)	1.188 (0.865-1.433)	0.8077	0.927 (0.639-1.344)	0.6878
Exposure to ACE inhibitors	98 (5.2)	47 (5.0)	0.956 (0.667-1.371)	0.1005	1.140 (0.950-1.369)	0.1587
Exposure to ARBs	1346 (71.0)	702 (73.9)	1.161 (0.972-1.387)	0.1005	1.140 (0.950-1.369)	0.1587
Long-term hospitalization	221 (100)	221 (100)	1.000		1.000	
Nonexposure to RAAS inhibitors	43 (19.5)	52 (23.5)	1.000		1.000	
Exposure to RAAS inhibitors	178 (80.5)	169 (76.5)	0.785 (0.496-1.238)	0.2979	0.863 (0.533-1.397)	0.5489
Exposure to ACE inhibitors	11 (5.0)	4 (1.8)	0.352 (0.110-1.123)	0.0776	0.640 (0.175-2.334)	0.4987
Exposure to ARBs	171 (77.4)	166 (75.1)	0.883 (0.569-1.368)	0.5766	0.906 (0.567-1.448)	0.6795
Intensive care unit admission	44 (100)	22 (100)	1.000		1.000	
Nonexposure to RAAS inhibitors	11 (25.0)	4 (18.2)	1.000		1.000	
Exposure to RAAS inhibitors	33 (75.0)	18 (81.8)	1.500 (0.417-5.397)	0.5349	1.515 (0.402-5.701)	0.5392
Exposure to ACE inhibitors	1 (2.3)	2 (4.6)	2.048 (0.122-34.368)	0.6185	2.235 (0.132-37.884)	0.5775
Exposure to ARBs	32 (72.7)	18 (81.8)	1.687 (0.474-6.010)	0.4197	1.703 (0.459-6.324)	0.4265
High-flow oxygen therapy	89 (100)	47 (100)	1.000		1.000	
Nonexposure to RAAS inhibitors	16 (18.0)	11 (23.4)	1.000		1.000	
Exposure to RAAS inhibitors	73 (82.0)	36 (76.6)	0.717 (0.302-1.704)	0.4517	0.865 (0.272-1.619)	0.3675
Exposure to ACE inhibitors	10 (11.2)	2 (4.3)	0.351 (0.074-1.674)	0.1890	0.358 (0.074-1.734)	0.2020
Exposure to ARBs	66 (74.2)	35 (74.5)	1.016 (0.452-2.283)		0.972 (0.424-2.226)	0.9464
Death	64 (100)	38 (100)	1.000		1.000	
Nonexposure to RAAS inhibitors	17 (26.6)	8 (21.0)	1.000		1.000	
Exposure to RAAS inhibitors	47 (73.4)	30 (79.0)	1.356 (0.521-3.532)	0.5325	1.363 (0.513-3.662)	0.5342
Exposure to ACE inhibitors	6 (9.4)	1 (2.6)	0.261 (0.030-2.258)	0.2226	0.260 (0.030-2.247)	0.2206
Exposure to ARBs	41 (64.1)	30 (79.0)	2.104 (0.828-5.543)	0.1179	2.132 (0.829-5.489)	0.1163

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; COVID-19, coronavirus disease 2019; OR, odds ratio; and RAAS, renin-angiotensin-aldosterone system.

*Adjusted for diabetes mellitus, dyslipidemia, myocardial infarction, stroke, liver disease, cancer, chronic obstructive pulmonary disease, asthma, end-stage renal disease with dialysis, immunocompromised status, and Charlson comorbidity index in outcome of infection and long-term hospitalization; adjusted for end-stage renal disease with dialysis and Charlson comorbidity index in outcome of intensive care unit admission, high-flow oxygen therapy, and death.

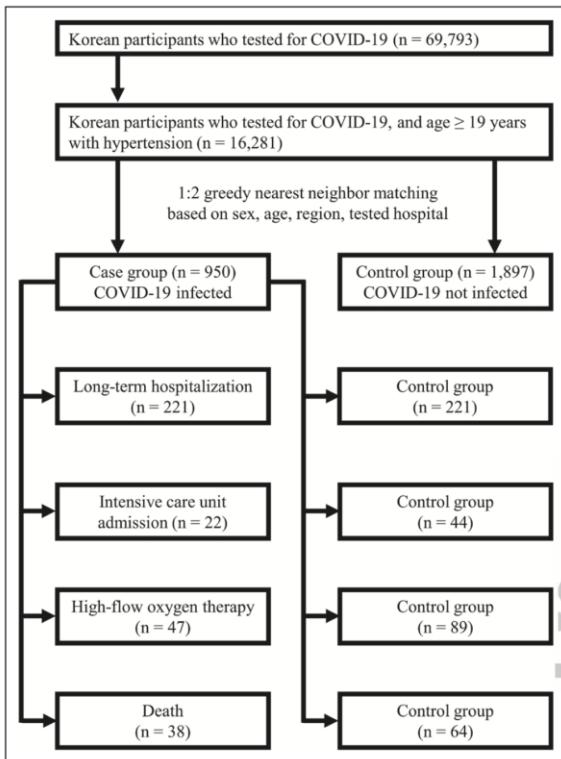


Figure. Flow of study participants.

TREATMENT OF COVID-19 - EVIDENCE-BASED OR PERSONALIZED MEDICINE?

Fang FC, Schooley RT.. Clin Infect Dis. 2020 Jul 15:ciaa996. doi: 10.1093/cid/ciaa996. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

Senior editors at Clinical Infectious Disease discuss the challenges of incorporating evidence-based medicine (EBM) into COVID-19 management, such as the difficulty of generalizing already limited data due to the variability in COVID-19's presentation and clinical course. They suggest providers must consider both EBM and personalized approaches to optimize care of COVID-19 patients (ie., taking into account of the benefit and risks of the different treatment interventions while also carefully considering the physiologic status of the individual patient).

ACUTE CARE

COVID-19 IN KIDNEY TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW OF THE CASE SERIES AVAILABLE THREE MONTHS INTO THE PANDEMIC

Oltean M, Søfteland JM, Bagge J, Ekelund J, Felldin M, Schult A, Magnusson J, Friman V, Karason K.. Infect Dis (Lond). 2020 Jul 13:1-8. doi: 10.1080/23744235.2020.1792977. Online ahead of print.

Level of Evidence: 4 - Case-series or casecontrol studies, or poor quality prognostic cohort study

BLUF

The authors conducted a systematic review of 204 kidney transplant recipients (74% men) with COVID-19 through 12 case series conducted in Spain, Iran, Italy, China, the UK, and the US from January 1 to June 4, 2020 (Figure 1), finding this patient group had a higher mortality rate of 21.2% compared with a 5.8% mortality rate in the general population. Mortality was strongly correlated to advanced age, ICU admission, and intubation. A majority of the patients were treated with immunosuppression and hydroxychloroquine, 34% of patients were admitted to the ICU and 19.7% were administered mechanical ventilation. The authors suggest that in-patient kidney transplant recipients, especially those with advanced age, may be at increased mortality risk from SARS-CoV-2 infection.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) ranges from a mild illness to acute respiratory distress syndrome (ARDS), multiorgan dysfunction, and death. Transplant recipients are vulnerable due to comorbidities and immunosuppressants that render them susceptible to infections. The information on COVID-19 in kidney transplant recipients remains limited to small case series.

METHODS: A systematic literature search was conducted, and 12 case series totalling 204 kidney transplant recipients with COVID-19 were identified. Data were extracted, pooled and analysed.

RESULTS: Most patients (74%) were men. The most frequent symptoms were fever (76%), cough (64%) and dyspnoea (43%). At admission, over 70% of the patients had abnormal radiological findings. Leukocyte counts were in the lower normal range. C-reactive protein, ferritin, and D-dimer were consistently increased. Treatments included lowering immunosuppression, hydroxychloroquine, antivirals, tocilizumab and intravenous immunoglobulins. Thirty-one percent of the patients were admitted to intensive care units (ICUs), and 16% required intubation. The overall mortality was 21.2%. Patients who died were significantly older than those who survived (61 +- 12 vs. 51 +- 15, $p < .01$). Logistic regression revealed that the odds for death increased by 4.3% for each additional year of age (odds ratio [OR] 1.043, 95% confidence interval [CI] 1.005-1.083, p value = .0265).

CONCLUSIONS: No substantial conclusions could be drawn on the efficacy of any particular treatment. More rigorous patient stratification is needed when analysing and reporting data to facilitate future meta-analyses.

FIGURES

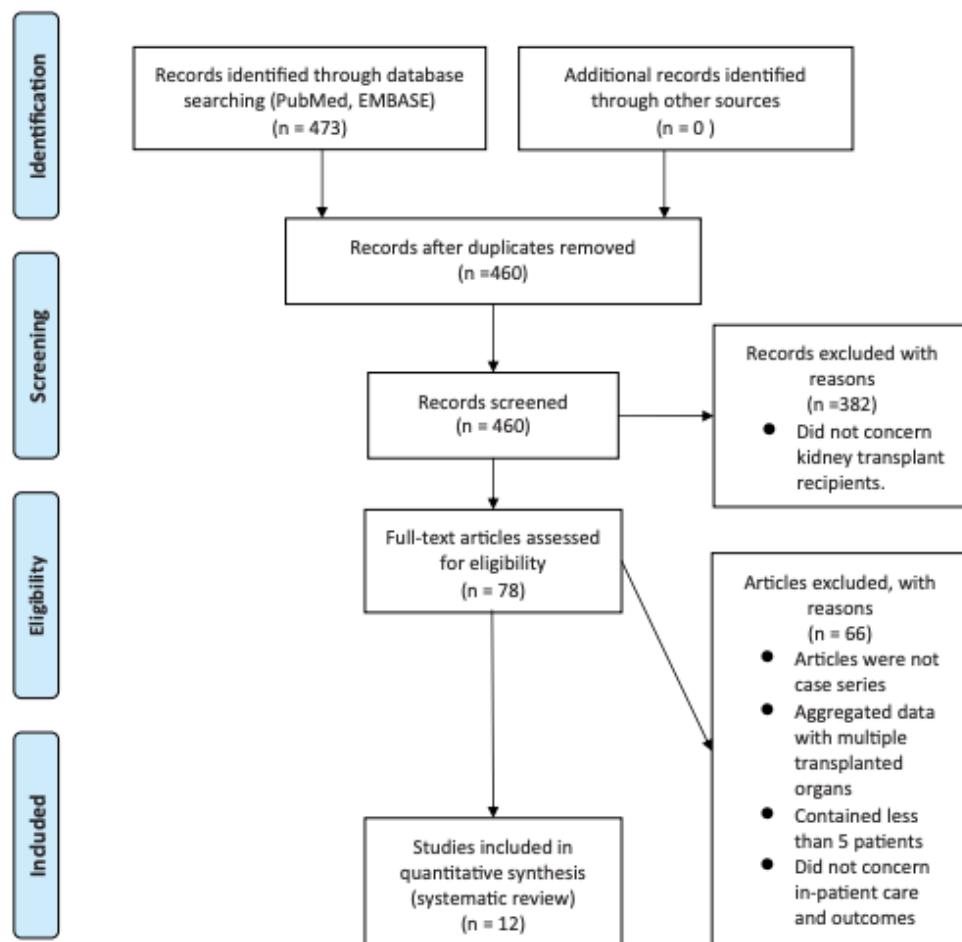


Figure 1. PRISMA flow chart.

CRITICAL CARE

COVID-19 PATIENT BRIDGED TO RECOVERY WITH VENO-VENOUS EXTRACORPOREAL MEMBRANE OXYGENATION

Rinewalt D, Coppolino A, Seethala R, Sharma N, Salim A, Keller S, Mallidi HR.. J Card Surg. 2020 Jul 15. doi: 10.1111/jocs.14829. Online ahead of print.

Level of Evidence: Other - Case Report

BLUF

Authors at Harvard Medical School presented a case report of a 49 year old female with a history of hypertension and obesity who was COVID-19 positive and treated with veno-venous (VV) ECMO due to persistent hypoxia failing mechanical ventilation. After 9 days, she was trialed off ECMO and improved with supine mechanical ventilation, she was then extubated and discharged from the hospital. Based on this case, the authors devised an approach to COVID-19 patients who require ECMO (Figure 1), suggesting that with careful monitoring and patient selection it can be a viable treatment strategy despite poor outcomes exhibited in prior studies (Henry et al, Li et al).

ABSTRACT

BACKGROUND: In severe cases, the coronavirus disease 2019 (COVID-19) viral pathogen produces hypoxic respiratory failure unable to be adequately supported by mechanical ventilation. The role of extracorporeal membrane oxygenation (ECMO) remains unknown, with the few publications to date lacking detailed patient information or management algorithms all while reporting excessive mortality.

METHODS: Case report from a prospectively maintained institutional ECMO database for COVID-19.

RESULTS: We describe veno-venous (VV) ECMO in a COVID-19-positive woman with hypoxic respiratory dysfunction failing mechanical ventilation support while prone and receiving inhaled pulmonary vasodilator therapy. After 9 days of complex management secondary to her hyperdynamic circulation, ECMO support was successfully weaned to supine mechanical ventilation and the patient was ultimately discharged from the hospital.

CONCLUSIONS: With proper patient selection and careful attention to hemodynamic management, ECMO remains a reasonable treatment option for patients with COVID-19.

FIGURES

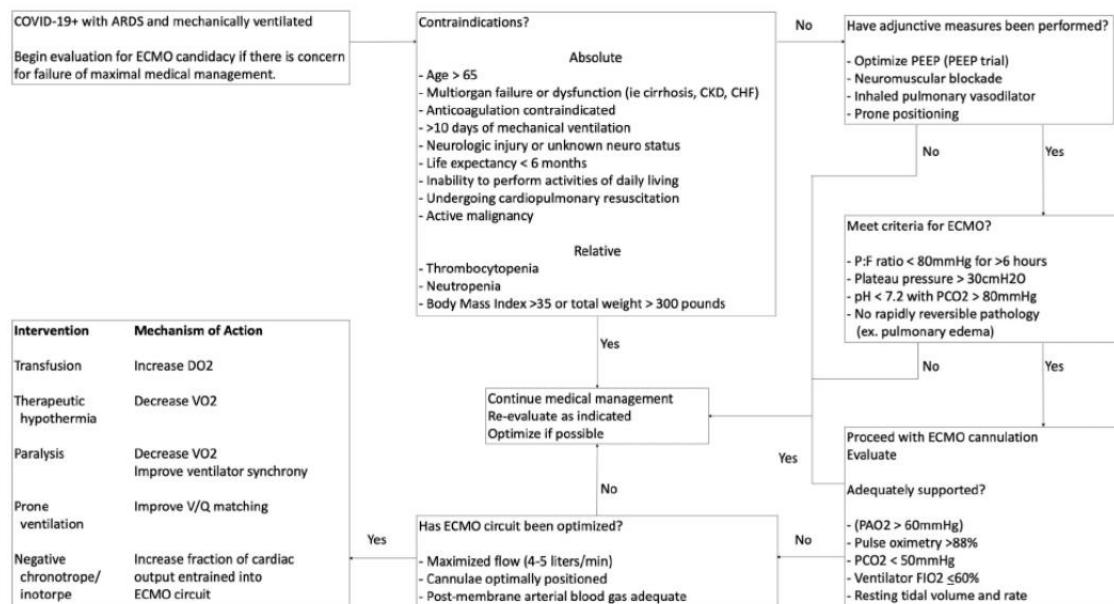


Figure 1. Patient selection, evaluation, and treatment strategies. ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; DO2, oxygen delivery; ECMO, extracorporeal membrane oxygenation; PAO2, partial pressure of oxygen; PCO2, partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; VO2, oxygen consumption; V/Q, ventilation/perfusion.

GASTROINTESTINAL MANIFESTATIONS OF COVID-19: IMPACT ON NUTRITION PRACTICES

Aguila EJT, Cua IHY, Fontanilla JAC, Yabut VLM, Causing MFP.. Nutr Clin Pract. 2020 Jul 15. doi: 10.1002/ncp.10554. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

This literature review on digestive tract issues and nutrition in the context of COVID-19 highlights the different gastrointestinal (GI) manifestations, recommends nutritional options to address symptoms of COVID-19-associated GI intolerance, stresses the importance of early enteral nutrition, and recommends various indications and routes of nutritional support (Tables 1 & 2). Additionally, the authors encourage further research on how COVID-19 complicates the management and nutrition of patients with preexisting GI disorders.

SUMMARY

GI manifestations of COVID-19 include anorexia, nausea, vomiting, diarrhea, and abdominal pain and account for several challenges healthcare providers face in maintaining COVID-19 patients' nutritional status. Based on this review, enteral nutrition is the preferred route of nutrition in these patients, even those in prone positioning. The authors recommend optimization of oral diets and oral nutrition supplements (ONSs) in addition to maintaining a high calorie and protein diet.

ABSTRACT

Although Coronavirus disease 2019 (COVID-19) is primarily a respiratory disease, growing evidence shows that it can affect the digestive system and present with gastrointestinal (GI) symptoms. Various nutrition societies have recently published their guidelines in context of the pandemic, and several points emphasize the impact of these GI manifestations on nutrition therapy. In patients with COVID-19, the normal intestinal mucosa can be disrupted by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, and this could result in GI symptoms and a compromise in nutrient absorption.

Optimization of oral diet is still recommended. However, given the GI effects of COVID-19, a fraction of infected patients have poor appetite and would not be able to meet their nutrition goals with oral diet alone. For this at-risk group, which includes those who are critically ill, enteral nutrition is the preferred route to promote gut integrity and immune function. In carrying this out, nutrition support practices have been revised in such ways to mitigate viral transmission and adapt to the pandemic. All measures in the GI and nutrition care of patients are clustered to limit exposure of healthcare workers. Among patients admitted to intensive care units, a significant barrier is GI intolerance, and it appears to be exacerbated by significant GI involvement specific to the SARS-CoV-2 infection. Nevertheless, several countermeasures can be used to ease side effects. At the end of the spectrum in which intolerance persists, the threshold for switching to parenteral nutrition may need to be lowered.

FIGURES

Table 1. Indication and Routes of Nutrition Support.

Route	Indication	Remarks
Oral diet and oral nutrition supplements (ONSs)	If able to tolerate oral diet, take high-calorie and high-protein diet	High-calorie and high-protein diet should be advised to maintain metabolic functions and body weight ¹⁹
	If nutrition targets are not met by oral diet, ONSs can be added	ONSs should be given within 24 to 48 hours of hospitalization with the ONSs providing ≥400 kcal/d and ≥30 g/d protein ¹⁶
Enteral nutrition via nasogastric or nasointestinal route	If nutrition targets cannot be met orally alone (eg, polymorbid medical inpatients, older persons)	Insertion of tubes should be done with proper personal protective equipment (PPE) ¹⁵
Parenteral nutrition	If nutrition targets cannot be met by enteral nutrition or with gastrointestinal intolerance despite different measures to address intolerance	Can be given as supplement or as parenteral nutrition ¹⁷

Table 2. Recommendations to Address Gastrointestinal (GI) Intolerance.

GI Manifestation	Recommendation	Rationale
Nausea, vomiting, or ileus	Add prokinetics (IV erythromycin, IV metoclopramide or combination)	To enhance motility
Delayed gastric emptying	Do not concentrate enteral formula Consider postpyloric feeding	To avoid delayed gastric emptying To bypass the stomach and administer feed to the small intestine because of delayed gastric emptying
Abdominal distension	Reduce feeding rate or volume	To alleviate abdominal distension and give longer time for better absorption
	Shift to energy-dense formula	To provide high-calorie feeding but with less volume for better absorption and to alleviate abdominal distension
Diarrhea	Shift to semi-elemental or predigested formula	To reduce diarrhea and for better absorption

MEDICAL SUBSPECIALTIES

SARS-COV-2 (COVID-19) AND CYSTIC FIBROSIS

Stanton BA, Hampton TH, Ashare A. Am J Physiol Lung Cell Mol Physiol. 2020 Jul 15. doi: 10.1152/ajplung.00225.2020.
Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

A literature review by authors affiliated with Dartmouth discusses the potential mechanisms by which patients with cystic fibrosis (CF) and COVID-19 have a less severe disease course than would be expected. Based on their findings (Summary), the authors suggest that many factors may contribute to decreasing SARS-CoV-2 severity in patients with CF and note several potential therapeutic targets/candidates (ecotin, SERPINB1, azithromycin, etc) that should be further studied in reducing SARS-CoV-2 severity.

SUMMARY

The main observations of this review include:

1. Polymorphisms may exist for ACE and ACE2 genes that lead to less severe symptoms from COVID-19.
2. Increased levels of ACE2 mRNA and reduced levels of TMPRSS2 (a serine protease involved in SARS-CoV-2 cell entry) mRNA were observed in CF airway epithelial cells compared to non-CF cells.
3. High levels of ACE2 in CF patients may promote production of anti-inflammatory angiotensin 1-7 (Figure 1A) while lower levels of TMPRSS2 may prevent SARS-CoV-2 cell entry, leading to overall reduced inflammation and lung injury.
4. Azithromycin and serine protease inhibitor treatment in patients with CF could contribute to milder COVID-19 symptoms (Figure 1B).
5. A CF lung has high levels of serine protease inhibitors (such as ecotin and SERPINB1), which may prevent TMPRSS2 from promoting SARS-CoV-2 cellular entry.

ABSTRACT

Cystic Fibrosis (CF) is a genetic disease caused by mutations in the CFTR gene. Although viral respiratory tract infections are, in general, more severe in patients with CF compared to the general population, a small number of studies indicate that SARS-CoV-2 does not cause a worse infection in CF. This is surprising since comorbidities including preexisting lung disease have been reported to be associated with worse outcomes in SARS-CoV-2 infections. Several recent studies provide insight into why SARS-CoV-2 may not produce more severe outcomes in CF. First, ACE and ACE2, genes that play key roles in SARS-CoV-2 infection have some variants that are predicted to reduce the severity of SARS-CoV-2 infection. Second, mRNA for ACE2 is elevated and the mRNA for TMPRSS2, a serine protease, is decreased in CF airway epithelial cells. Increased ACE2 is predicted to enhance SARS-CoV-2 binding to cells, but would increase conversion of angiotensin II, which is proinflammatory, to angiotensin-1-7, which is anti-inflammatory. Thus, increased ACE2 would reduce inflammation and lung damage due to SARS-CoV-2. Moreover, decreased TMPRSS2 would reduce SARS-CoV-2 entry into airway epithelial cells. Second, many CF patients are treated with azithromycin, which suppresses viral infection and lung inflammation, and inhibits the activity of furin, a serine protease. Finally, the CF lung contains high levels of serine protease inhibitors including ecotin and SERPINB1, which are predicted to reduce the ability of TMPRSS2 to facilitate SARS-CoV-2 entry into airway epithelial cells. Thus, a variety of factors may mitigate the severity of SARS-CoV-2 in CF.

FIGURES

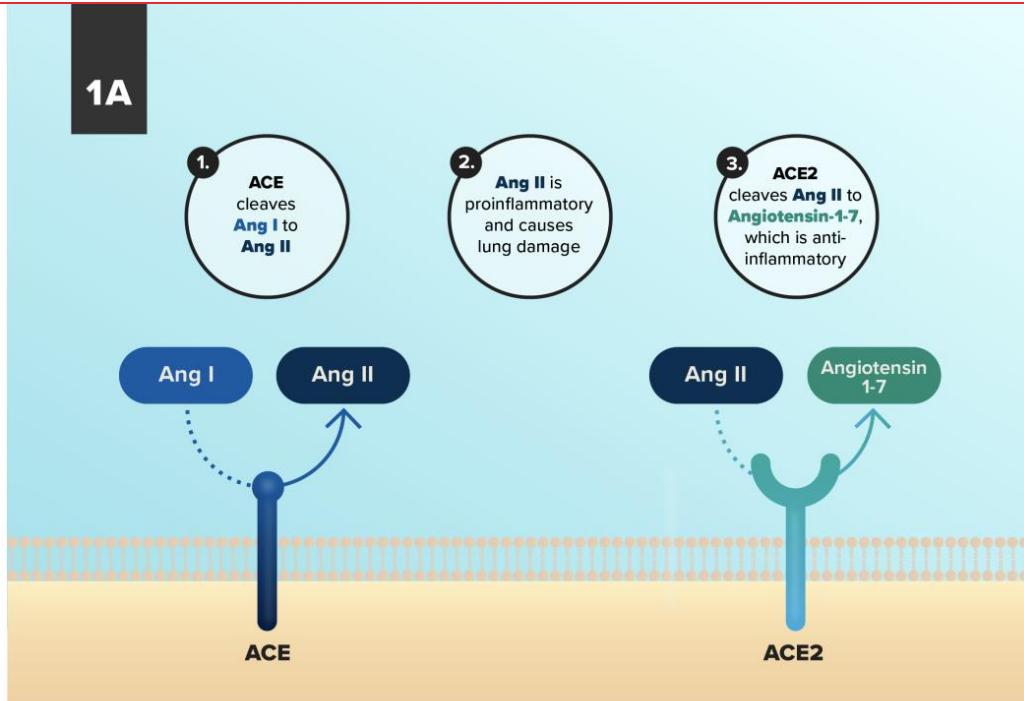


Figure 1A: Role of ACE, ACE II, TMPRSS2 in SARS-CoV-2 lung infection. (A) ACE cleaves angiotensin I (Ang I) to angiotensin II (Ang II), which is proinflammatory and causes lung damage. ACE2 processes Ang II to angiotensin-1-7, which is anti-inflammatory. Thus, a decrease in ACE and/or an increase in ACE2 would reduce inflammation and lung damage due to SARS-CoV-2.

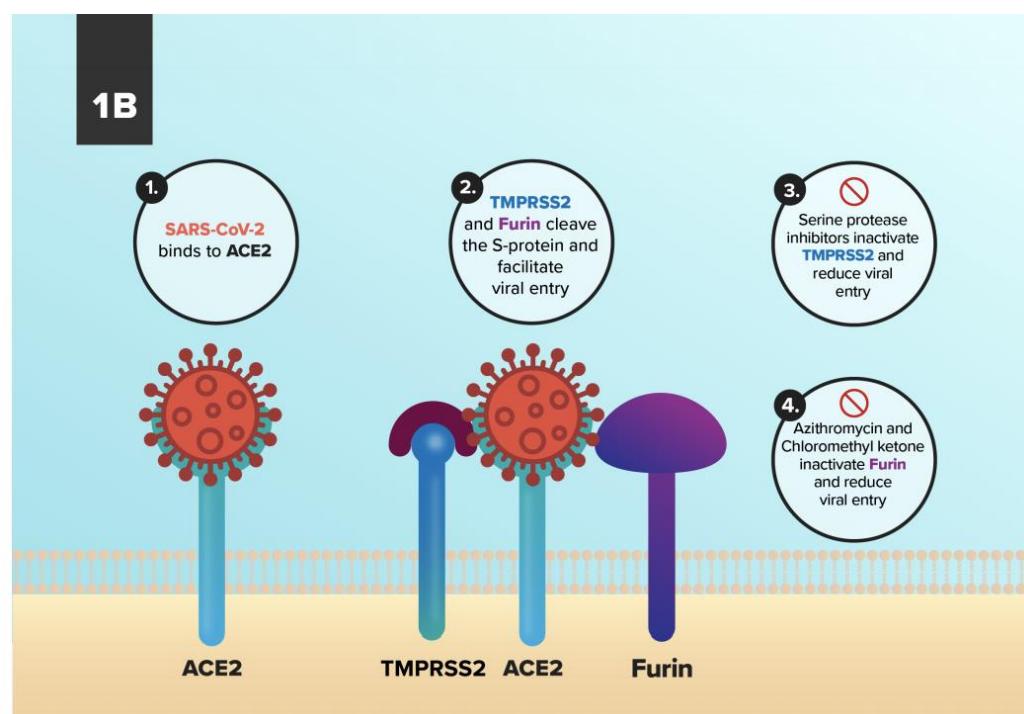


Figure 1B: SARS-CoV-2 binds to ACE2. (2) The S-protein is cleaved by TMPRSS2, and furin, which facilitates viral entry into cells. (3) Several serine protease inhibitors in the CF lung, including ecatin and SERP1NR1, and the drugs camostat mesylate, and nelfinavir mesylate inhibit TMPRSS2. (4) Azithromycin and chloromethyl ketone inhibit furin. The inhibitors of TMPRSS2 and furin are predicted to reduce SARS-CoV-2 entry into airway epithelial cells.

CLINICAL CHARACTERISTICS IN PATIENTS WITH SARS-COV-2/HBV CO-INFECTION

Chen L, Huang S, Yang J, Cheng X, Shang Z, Lu H, Cheng J.. J Viral Hepat. 2020 Jul 15. doi: 10.1111/jvh.13362. Online ahead of print.

Level of Evidence: 4 - Case-series or casecontrol studies, or poor quality prognostic cohort study

BLUF

A retrospective cohort study of 326 COVID-19 patients at Shanghai Public Health Clinical Center from 20 January to 24 February 2020 found that 20 patients who had Hepatitis B virus (HBV) co-infection (6.1%) had lower pre-albumin levels (102.3 mg/L versus 145.4 mg/L; P=.0367) yet similar liver function tests, hospital stay duration, and discharge rates compared to patients with COVID-19 alone. Although further investigation with a larger patient sample is warranted, these findings suggest that HBV does not exacerbate COVID-19-related liver damage or cause a worse prognosis for this population.

ABSTRACT

COVID-19 has become a global pandemic and garnered international attention. Although the clinical features of COVID-19 related liver injury have been investigated, there have been no reports and studies on the clinical characteristics of COVID-19 patients co-infected with Hepatitis B Virus (HBV). This study aimed to evaluate whether SARS-CoV-2/HBV co-infection could influence liver function and the disease outcome. All 326 confirmed COVID-19 cases in Shanghai Public Health Clinical Center (The COVID-19 designated hospital in Shanghai, China) from January 20, 2020 to February 24, 2020 were enrolled and followed up until February 29 in this study. The clinical, laboratory data and the length of stay were collected and analyzed retrospectively. 20 patients with HBV co-infection (6.1%) and 306 patients (93.9%) without HBV infection showed no differences in the level of liver function parameters. However, compared with HBsAg- patients [145.4 mg/L (103.9-179.2)], HBsAg+ patients had a lower level of prealbumin [(102.3 mg/L (76.22-160.2), P=.0367]. There were also no significant differences for the discharge rate and the length of stay between two groups. Taken together, we found no evidence that SARS-CoV-2/HBV co-infection could aggravate liver injury or extend duration of hospitalization.

FIGURES

Table1 Clinical characteristics in patients with SARS-CoV-2/HBV co-infection

	HBsAg+ (n=20)	HBsAg- (n=306)	P Value
Age Median (IQR)	52.5 (44-62.8)	50.5 (36-64)	0.4769
Male n (%)	13 (65%)	155 (50.7%)	0.2136
Liver function parameters	Median (IQR)		
ALT (U/L)	28 (16.25-42.25)	21 (15-35)	0.2644
AST (U/L)	27.5 (22-42.25)	23 (18.5-33)	0.1645
ALP (U/L)	60 (49.75-72)	56 (48-66.25)	0.2051

L-γ-GT (U/L)	23.5 (15.5-35.25)	24.5 (16-42)	0.4361
LDH (U/L)	242.5 (200-265.5)	224 (192-278)	0.702
TB (umol/L)	10.55 (6.825-15.73)	8.35 (6.6-10.93)	0.1406
DB (umol/L)	5.2 (2.975-7.03)	3.9 (3.1-5.43)	0.1354
Albumin (g/L)	37.88 (35.42-42.34)	40.18 (37.42-42.76)	0.2685
Globulin (g/L)	28.4 (26.96-31.36)	28.3 (25.67-31.22)	0.5371
Prealbumin (mg/L)	102.3 (76.22-160.2)	145.4 (103.9-179.2)	0.0367
Outcome			
Severe/Critically ill n (%)	2 (10%)	24 (7.8%)	0.667
Death n (%)	0	3 (0.98%)	/
Discharged n (%)	19 (95%)	245 (80%)	0.14
Hospital stays (days)	14 (10-19)	14 (11-19)	0.83

ADJUSTING PRACTICE DURING COVID-19

THE LINK BETWEEN VITAMIN D AND COVID-19: DISTINGUISHING FACTS FROM FICTION

Bergman P.. J Intern Med. 2020 Jul 11. doi: 10.1111/joim.13158. Online ahead of print.

Level of Evidence: 5 - Expert Opinion

BLUF

In this editorial, the author considers Vitamin D's role in preventing COVID-19. They reference evidence of an indirect protective link (referenced below in more detail), including Vitamin D's protective potential against acute respiratory infections (ARI), ability to increase conversion of ACE2 to ACE, and possible ability to decrease mortality at higher latitudes. Though they note that confounding factors (user effect, old age, ethnicity, male sex, obesity, diabetes, hypertension) surround this link, the author suggests that clinicians should not hesitate to provide Vitamin D supplementation to patients, particularly those with risk factors (dark skin, the elderly, patients with chronic diseases and obese patients).

SUMMARY

Suggestions from the article include, but are not limited to:

- One study referenced that Parkinson's disease patients may experience a lower likelihood of COVID-19 with vitamin D supplementation.
- Clinicians should be vigilant to special groups, including tuberculosis and sarcoidosis patients, where ectopic activation of vitamin D may lead to hypercalcemia.
- Benefits of supplementation are small and cumulative over months. Preferentially supplement the following at-risk groups (dark skin, the elderly, patients with chronic diseases and obese patients, etc).
- Doses up to 10,000 IU/day are safe though only 1000-2000 IU may be needed to obtain optimal effects on bone and immunity.
- Patients suspected of vitamin D deficiency should be tested for serum 25-OH Vitamin D-levels and only supplement those below 50 nmol/L to provide bone protection and enhance respiratory immunity against ARI.

ABSTRACT

Vitamin D is produced in the skin under the influence of UVB-light from the sun or obtained via the diet by eating fatty fish, enriched dairy products or supplements. Vitamin D is known to support a healthy bone and severe deficiency may lead to osteomalacia or the rickets, which still occur in poor areas of the world. In addition, vitamin D supports key functions in many organs, including the brain, muscle and the immune systems (Holick, 2007). In fact, the vitamin D receptor (VDR) is expressed in most cell types and may activate somewhere between 200-500 genes, many related to the immune system.

COVID-19 CONSIDERATIONS IN PEDIATRIC DENTISTRY

Bahramian H, Gharib B, Baghalian A.. JDR Clin Trans Res. 2020 Jul 14:2380084420941503. doi: 10.1177/2380084420941503. Online ahead of print.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

Authors from Iran suggest dental guidelines (summarized below) for optimized pediatric care and to minimize the risk of COVID-19 transmission during office visits and emergency situations (ie., cellulitis, severe tooth pain, and dental trauma).

SUMMARY

The suggested pediatric dentistry guidelines are the following:

- 1) All patients should have their temperature and SpO₂ checked beforehand.
- 2) Patients and companions should be given hand sanitizer and shoe covers.

- 3) Patients should wear coveralls to minimize the chance of contact with infected clothes.
- 4) For patients not suspected of having COVID-19, emergency procedures can be done with only the aforementioned guidelines.
- 5) Social distancing should be observed in the reception area.
- 6) Only one child and an accompanying adult should be in the office with the dentist.
- 7) The office should have proper ventilation.
- 8) All surfaces and devices should be sanitized after each patient.
- 9) Full PPE, including N95 respirator and eyewear, is recommended for the dentist.

ABSTRACT

One of the most important current medical concerns across the globe is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which has been designated by the World Health Organization as a novel viral pneumonia named coronavirus disease 2019 (COVID-19). COVID-19 has substantially affected all aspects of human lives and forced most people to self-quarantine themselves and stay home in order to remain safe. As pediatric dentists as a part of the health care system deferring elective procedures, we are obliged to manage emergency situations such as cellulitis, severe tooth pain, and dental trauma. Therefore, we need to beware of the symptoms and risks of the emerging disease and, accordingly, change the policies in our offices to minimize the risk of transmission while checking up and treating our patients in the safest possible way. Knowledge Transfer Statement: This article aims to acquaint clinicians treating pediatric patients with COVID-19 hazards and delineate the steps required for minimizing cross-infection in case of providing emergency treatment to children in dental offices.

MEDICAL SUBSPECIALTIES

NEPHROLOGY

COVID-19 OUTBREAK AND MANAGEMENT APPROACH FOR FAMILIES WITH CHILDREN ON LONG-TERM KIDNEY REPLACEMENT THERAPY

Zhao R, Zhou Q, Wang XW, Liu CH, Wang M, Yang Q, Zhai YH, Zhu DQ, Chen J, Fang XY, Tang XS, Zhang H, Shen Q, Xu H.. Clin J Am Soc Nephrol. 2020 Jul 14:CJN.03630320. doi: 10.2215/CJN.03630320. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A survey study of 220 participants at five major pediatric dialysis centers in China conducted by Children's Hospital of Fudan University found that among families with children on long-term kidney replacement therapy (KRT) 78% (n=171) reported COVID-19 had influenced treatment, 61% (n=135) described current difficulties, and 79% (n=173) worried about difficulties in the next 2 months (Visual abstract, Figure 2). Additionally, 13% (n=29) had depressive symptoms, and 11% (n=24) endorsed anxiety. The results suggest the COVID-19 outbreak has had a negative impact on both medical accessibility for children on long-term KRT and the mental health of their families.

ABSTRACT

BACKGROUND AND OBJECTIVES: During the coronavirus disease 2019 outbreak, the treatment of families with children on long-term KRT is challenging. This study was conducted to identify the current difficulties, worries regarding the next 2 months, and mental distress experienced by families with children on long-term KRT during the coronavirus disease 2019 outbreak and to deliver possible management approaches to ensure uninterrupted treatment for children on long-term KRT.
DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: A multicenter online survey was conducted between February 10 and 15, 2020, among the families with children on long-term KRT from five major pediatric dialysis centers in mainland China. The primary caregivers of children currently on long-term KRT were eligible and included. Demographic information, severe acute respiratory syndrome coronavirus 2 infection status, current difficulties, and worries regarding the next 2 months were surveyed using a self-developed questionnaire. The Patient Health Questionnaire-9 and the General Anxiety Disorder Scale-7 were used to screen for depressive symptoms and anxiety, respectively.

RESULTS: Among the children in the 220 families included in data analysis, 113 (51%) children were on dialysis, and the other 107 (49%) had kidney transplants. No families reported confirmed or suspected cases of coronavirus disease 2019. Overall, 135 (61%) and 173 (79%) caregivers reported having difficulties now and having worries regarding the next 2 months,

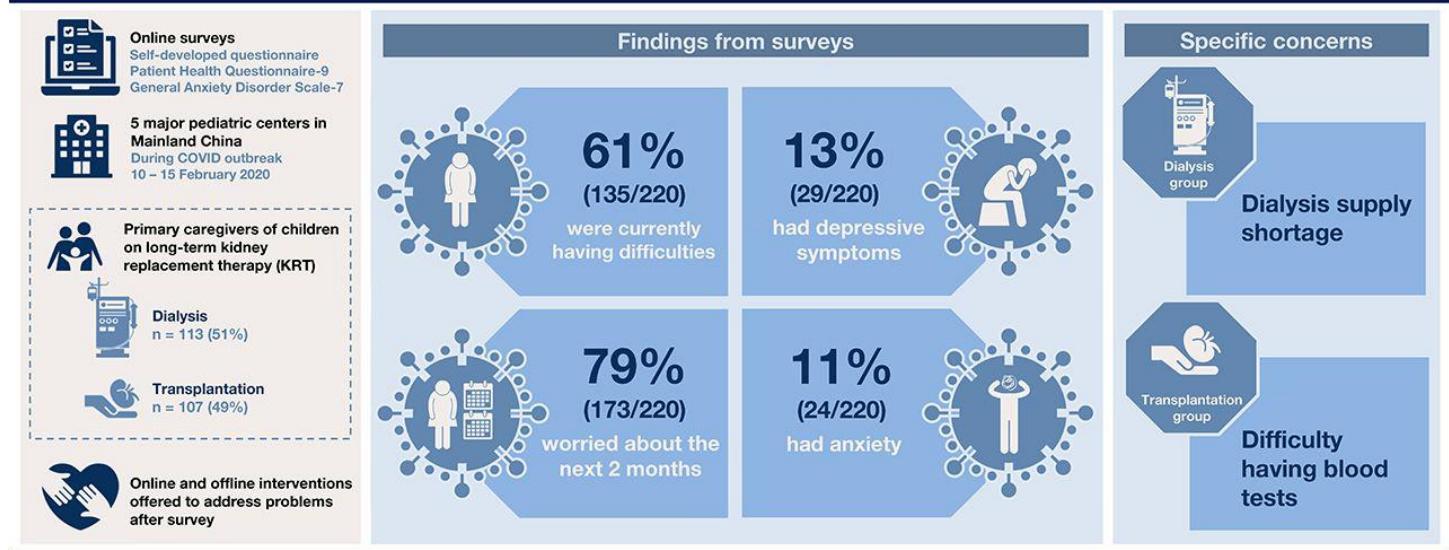
respectively. Dialysis supply shortage (dialysis group) and hard to have blood tests (kidney transplantation group) were most commonly reported. A total of 29 (13%) caregivers had depressive symptoms, and 24 (11%) had anxiety. After the survey, we offered online and offline interventions to address their problems. At the time of the submission of this paper, no treatment interruption had been reported.

CONCLUSIONS: The coronavirus disease 2019 outbreak has had physical, mental, logistical, and financial effects on families with children on long-term KRT.

FIGURES

How is the COVID-19 outbreak affecting families of children on long-term kidney replacement therapy?

CJASN
Clinical Journal of the American Society of Nephrology



Conclusions The COVID-19 outbreak has had physical, mental, logistical, and financial impacts on families with children on long-term kidney replacement therapy.

Rui Zhao, Qing Zhou, Xiaowen Wang, Cuihua Liu, et al. **COVID-19 Outbreak and Management Approach for Families with Children on Long-term Kidney Replacement Therapy.** CJASN doi: 10.2215/CJN.03630320. Visual Abstract by Michelle Lim, MBChB, MRCP

Visual Abstract

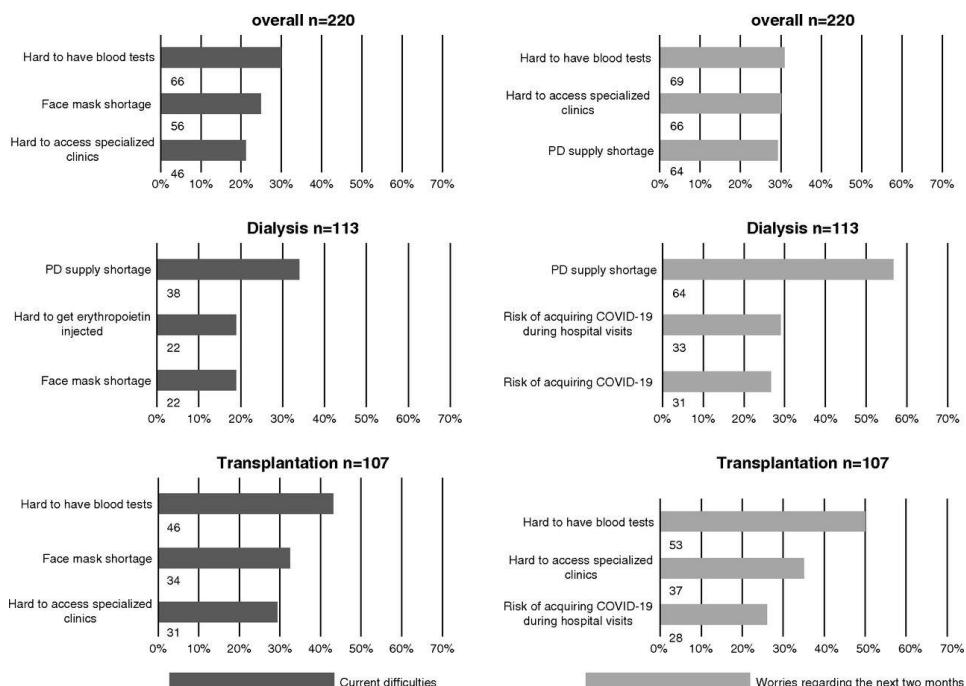


Figure 2. The top three difficulties and worries of caregivers with children on KRT varied across treatment modalities.

MEETING MATERNAL MENTAL HEALTH NEEDS DURING THE COVID-19 PANDEMIC

Hermann A, Fitelson EM, Bergink V.. JAMA Psychiatry. 2020 Jul 15. doi: 10.1001/jamapsychiatry.2020.1947. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

This expert opinion written by clinicians from New York describes the challenges that pregnant and postpartum patients have faced during the COVID-19 pandemic and presents ways to support these patients' mental health and resilience. These strategies include allowing partners to attend childbirths via video conference, using telehealth for check-ins after discharge, offering additional mental health training for clinicians, and providing proactive mental health resources for patients.

SUMMARY

Additional strategies for supporting pregnant and postpartum patients include:

1. Expansion of mental health care for providers as providers cannot effectively care for patients if they themselves are stressed from doing their jobs in a pandemic.
2. Expansion of telehealth for mental health issues so that patients have access to a holistic healthcare system remotely.
3. Proactive assessment of the mental health needs of patients already engaged in mental health treatment during pregnancy to avoid lapses in treatment postpartum.
4. Coordination of the production of healthcare guidelines and psychoeducation materials by professional societies to avoid inconsistencies and repetition. These guidelines are crucial for allowing hospital systems to create the infrastructure needed to provide coordinated care to patients.

R&D: DIAGNOSIS & TREATMENTS

CURRENT DIAGNOSTICS

ASSOCIATION BETWEEN DETECTABLE SARS-COV-2 RNA IN ANAL SWABS AND DISEASE SEVERITY IN PATIENTS WITH CORONAVIRUS DISEASE 2019

Lin W, Xie Z, Li Y, Li L, Wen C, Cao Y, Chen X, Ou X, Hu F, Li F, Tang X, Cai W, Li L.. J Med Virol. 2020 Jul 16. doi: 10.1002/jmv.26307. Online ahead of print.

Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

A longitudinal cohort study found that 21.1% of 217 laboratory confirmed patients with COVID-19 hospitalized in Guangzhou, China had detectable SARS-CoV-2 RNA in anal swabs and concluded that detectable viral RNA in anal swabs is associated with increased risks of disease severity, ICU admission, development of gastrointestinal (GI) symptoms, and a longer duration of viral RNA presence in anal compared to throat swabs (Figures 1, 3). The authors suggest that the association between detectable SARS-CoV-2 in the digestive tract and the severity of COVID-19 in patients justifies screening for viral RNA in the GI tract for early disease management.

SUMMARY

The authors indicate the large and wide distribution of angiotensin-converting enzyme 2 in esophageal, gastric, duodenal, and rectal tissues facilitates viral entry into the digestive tract, which provides SARS-CoV-2 with an additional site for replication and storage. They suggest that this may explain the delayed elimination of the virus and more severe disease progression in patients with positive anal swabs.

ABSTRACT

BACKGROUND: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) RNA was found in intestines and feces, but its clinical significance is not completely clear. We aim to characterize the longitudinal test results of SARS-CoV-2 RNA in anal swabs, and to explore the association with disease severity.

METHODS: We included laboratory-confirmed Coronavirus Disease 2019 (COVID-19) patients who hospitalized in Guangzhou Eighth People's Hospital and excluded those who had not received anal swabs for SARS-CoV-2 RNA testing. Epidemiological, clinical and laboratory data were obtained. Throat swabs and anal swabs were collected periodically for SARS-CoV-2 RNA detection.

RESULTS: 217 eligible patients (median aged 50 years, 50.2% were females) were analyzed. 21.2% (46/217) of the patients were detectable for SARS-CoV-2 RNA in anal swabs. The duration of viral RNA was longer, but the viral load was lower in anal swabs than throat swabs in the early stage of disease. During a median follow-up of 20 days, 30 (13.8%) patients admitted to intensive care unit (ICU) for high-flow nasal cannula or higher-level oxygen support measures to correct hypoxemia.

Detectable viral RNA in anal swabs (adjusted hazard ratio [aHR], 2.50; 95% CI, 1.20-5.24), increased CRP (aHR, 3.14; 95% CI, 1.35-7.32) and lymphocytopenia (aHR, 3.12; 95% CI, 1.46-6.67) were independently associated with ICU admission. The cumulative incidence of ICU admission was higher among patients with detectable viral RNA in anal swabs (26.3% vs. 10.7%, P=0.006).

CONCLUSION: Detectable SARS-CoV-2 RNA in the digestive tract was a potential warning indicator of severe disease. This article is protected by copyright. All rights reserved.

FIGURES

Figure 1. Longitudinal results of anal swabs and throat swabs among the 46 patients with detectable SARS-CoV-2 RNA in anal swab.

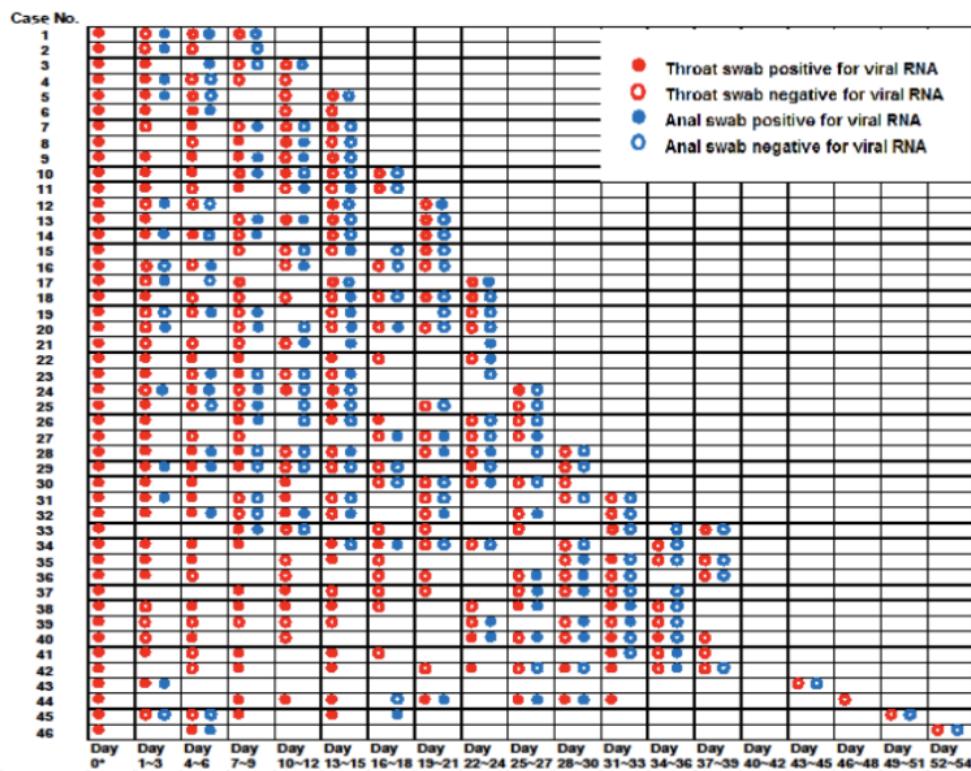
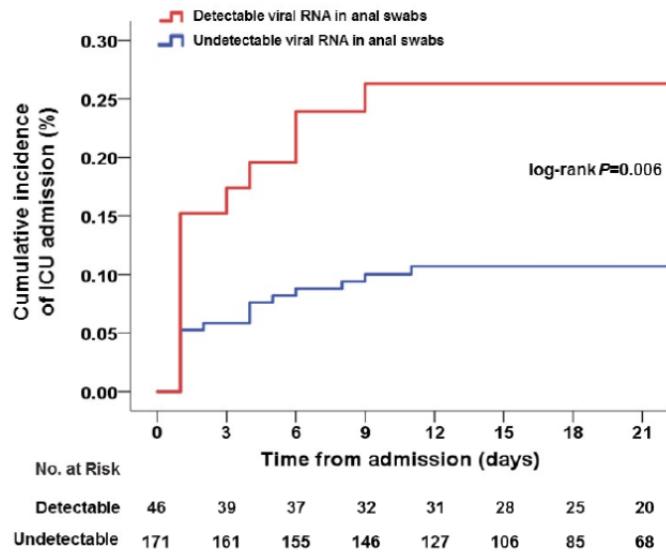


Figure 3. Cumulative incidence of intensive care unit (ICU) admission in patients with detectable and undetectable SARS-CoV-2 RNA in anal swab.



SEROLOGICAL CHEMILUMINESCENCE IMMUNOASSAY FOR THE DIAGNOSIS OF SARS-COV-2 INFECTION

Lijia S, Lihong S, Huabin W, Xiaoping X, Xiaodong L, Yixuan Z, Pin H, Yina X, Xiaoyun S, Junqi W.. J Clin Lab Anal. 2020 Jul 16:e23466. doi: 10.1002/jcla.23466. Online ahead of print.

Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

Chinese researchers monitored IgM and IgG concentrations in 15 patients with RT-PCR confirmed SARS-CoV-2 infection via chemiluminescence immunoassay (CLIA) and found the sensitivity of IgM was lower than that of IgG at the manufacturer recommended cutoff of 10 AU/mL (60% vs 86.67%), but improved to 93.33% after adjusting the cutoff to 1.83 AU/mL (Tables 2, 3). Seropositivity rates of IgM and IgG reached 100% by 14 days post-symptom onset, suggesting patients with negative serologies after two weeks of symptoms are unlikely to be infected with SARS-CoV-2 (Figure 1).

ABSTRACT

OBJECTIVE: Dynamic monitoring of the concentration variation of IgM and IgG in patients with SARS-CoV-2 infections and exploring their diagnostic value for coronavirus disease-19 (COVID-19).

METHODS: A total of 15 patients with SARS-CoV-2 infection were enrolled as the COVID-19 group, and 50 patients were enrolled as the control group. The concentrations of SARS-CoV-2-specific antibodies (IgM and IgG) were detected by a chemiluminescence immunoassay (CLIA).

RESULTS: According to the cutoff value recommended by the manufacturer (cutoff = 10 AU/mL), the sensitivity, specificity, Youden index (YI), positive predictive value (PPV), and negative predictive value (NPV) of IgM were 60%, 100%, 60%, 100%, and 89.29%, respectively; and 86.67%, 100%, 86.67%, 100%, and 96.15%, respectively, for IgG. We reassessed the cutoff value of IgM. When the cutoff value for SARS-CoV-2 IgM was 1.83 AU/mL, the sensitivity, specificity, YI, PPV, and NPV were 93.33%, 98%, 91.33%, 93.33%, and 98%, respectively. During dynamic monitoring of the concentrations of IgM and IgG in COVID-19 patients, we found the shortest times before a patient became IgM and IgG seropositive after symptom onset were 1.5 and 2 days, respectively. The longest times were 7 and 8 days, respectively. The positive rates of SARS-CoV-2 IgM and IgG both reached 100% in 8-14 days after symptom onset.

CONCLUSION: The IgM cutoff value of 1.83 AU/mL for the diagnosis of COVID-19 was much better than the cutoff suggested by the manufacturer. SARS-CoV-2 infection can be ruled out if antibodies against SARS-CoV-2 are still undetectable 14 days after symptom onset.

FIGURES

TABLE 2 SARS-CoV-2 IgM and IgG (IgM/IgG cutoff = 10.00 AU/mL)

IgM	Nucleic acid detection				Nucleic acid detection		
	Positive	Negative	Cases	IgG	Positive	Negative	Cases
Positive	9	0	9	Positive	13	0	13
Negative	6	50	56	Negative	2	50	52
Cases	15	50	65	Cases	15	50	65

TABLE 3 The diagnostic value of SARS-CoV-2 IgM and IgG

Antibody	Cutoff value	AUC	Sensitivity (%)	Specificity (%)	YI (%)	PPV (%)	NPV (%)
IgM	10.00	0.978	60	100	60	100	89.29
	1.83		93.33	98	91.33	93.33	98
IgG	10.00	1.00	86.67	100	86.67	100	96.15

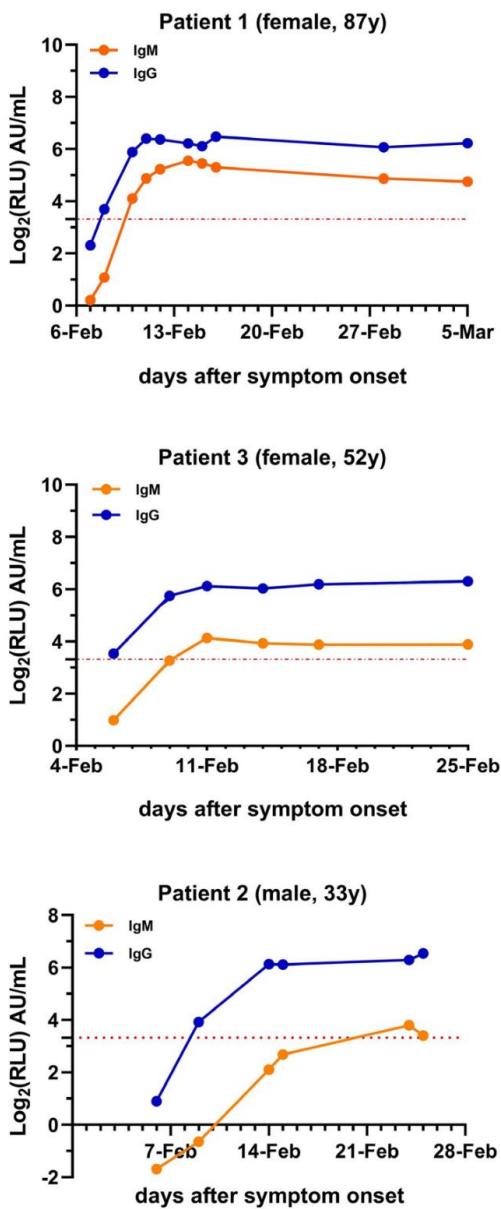


FIGURE 1 A relatively complete time course of the IgM and IgG response was observed in 3 patients. IgG is depicted in blue, and IgM is depicted in orange. The x-axis shows the synchronous date of detection of IgM and IgG from the day of symptom onset. The y-axis shows the log₂ of IgM and IgG concentrations (Log₂RLU). The red dotted line is the cutoff value $y = \log_2 10$

CT FEATURES OF COVID-19 PATIENTS WITH TWO CONSECUTIVE NEGATIVE RT-PCR TESTS AFTER TREATMENT

Fu Z, Tang N, Chen Y, Ma L, Wei Y, Lu Y, Ye K, Liu H, Tang F, Huang G, Yang Y, Xu F.. Sci Rep. 2020 Jul 14;10(1):11548. doi: 10.1038/s41598-020-68509-x.

Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

A retrospective study of 46 COVID-19 patients (n=39 severe/critical COVID-19, n=7 mild/moderate COVID-19) after treatment at the People's Hospital of Guangxi Zhuang Autonomous Region from 16 February to 8 March 2020 found residual lung lesions on CT imaging despite 2 consecutive negative reverse transcriptase polymerase chain reaction (RT-PCR) tests. Their findings include:

- 71% of the severe/critical group had peripheral and central lung lesions on CT imaging, while 85% among the mild/moderate group only demonstrated peripheral lesions.

- Mixed ground glass opacities (100% vs 44%), pulmonary consolidation (57% vs 10%), pulmonary interstitial thickening (86% vs 59%), and higher CT scores (16-20 vs 0-5) were more prevalent in the severe/critical group compared to the moderate/mild group (Table 2).

These findings suggest that chest CT may serve as a more accurate indicator of COVID-19 treatment efficacy and recovery compared to nucleic acid testing.

ABSTRACT

The objective of this study is to expound the CT features of COVID-19 patients whose throat swab samples were negative for two consecutive nucleic acid tests after treatment. We retrospectively reviewed 46 COVID-19 patients with two consecutive negative RT-PCR tests after treatment. The cases were divided into moderate group and severe/critical group according to disease severity. Clinical and CT scanning data were collected. CT signs of pulmonary lesions and the score of lung involvement were expounded. Thirty-nine moderate cases and seven severe/critical cases were included. Residual pulmonary lesions were visible in CT images. Moderate patients showed peripheral lesions while severe/critical cases exhibited both central and peripheral lesions with all lobes involvement. Mixed ground glass opacity (GGO) and pulmonary consolidation were noted. A larger proportion of severe patients showed reticular pulmonary interstitium thickening. Air bronchogram, pleural effusion, vascular enlargement, bronchial wall thickening, bronchiectasis, pleural thickening and pleural adhesion were more frequently observed in severe/critical group. The severe/critical group showed higher CT score. Pulmonary lesions persisted even after twice consecutive negative nucleic acid tests. We strongly recommended regular follow-up of CT scans after nucleic acid tests conversion. Evaluation of complete remission should base on chest CT.

FIGURES

Feature	Moderate group n=39	Severe/critical group n=7	P value
Number			
Unique	3 (8%)	0 (%)	–
Multiple	36 (92%)	7 (100%)	1.0
Distribution			
Peripheral	33 (85%)	2 (29%)	0.005
Peripheral involving central	6 (15%)	5 (71%)	0.005
Lobes involved			
Single lobe	9 (23%)	0 (0%)	–
2–4 lobes	13 (33%)	0 (0%)	–
5 lobes	17 (44%)	7 (100%)	0.01
Density			
Ground glass opacity	38 (97%)	7 (100%)	1.0
Mixed ground glass opacity	16 (41%)	7 (100%)	0.009
Consolidation	4 (10%)	4 (57%)	0.012
Shape			
Circular	18 (46%)	3 (43%)	1.0
Fan-shaped	19 (49%)	7 (100%)	0.014
Irregular	34 (87%)	7 (100%)	1.0
Pulmonary fibrosis	22 (56%)	5 (71%)	0.682
Pulmonary interstitium thickening			
Linear	5 (13%)	1 (14%)	1.0
Reticular	23 (59%)	6 (86%)	0.043
Other findings			
Air bronchogram	1 (3%)	4 (57%)	0.003
Vascular enlargement	30 (77%)	7 (100%)	0.316
Bronchial wall thickening	3 (8%)	2 (29%)	0.160
Bronchiectasis	5 (13%)	3 (43%)	0.089
Pleural thickening	19 (49%)	6 (86%)	0.106
Pleural adhesion	12 (31%)	5 (71%)	0.083
Pleural effusion	1 (3%)	3 (43%)	0.009
Total CT score			
0–5	29 (74%)	0 (0%)	–
6–10	8 (21%)	2 (29%)	0.636
11–15	0 (%)	1 (14%)	–
16–20	2 (5%)	4 (57%)	0.003

Table 2: Residual Chest CT findings in patients with two consecutive negative COVID-19 RT-PCR results

DEVELOPMENTS IN DIAGNOSTICS

AUTOMATED DETECTION AND QUANTIFICATION OF COVID-19 PNEUMONIA: CT IMAGING ANALYSIS BY A DEEP LEARNING-BASED SOFTWARE

Zhang HT, Zhang JS, Zhang HH, Nan YD, Zhao Y, Fu EQ, Xie YH, Liu W, Li WP, Zhang HJ, Jiang H, Li CM, Li YY, Ma RN, Dang SK, Gao BB, Zhang XJ, Zhang T.. Eur J Nucl Med Mol Imaging. 2020 Jul 14. doi: 10.1007/s00259-020-04953-1. Online ahead of print.

Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

This retrospective cohort study used a deep learning-based software to analyze chest CT scans (Figure 1) of 2460 SARS-CoV-2-positive patients in Wuhan, China and found that common CT features of COVID-19 pneumonia include multifocal bilateral ground glass opacities (90%; Table 2), with the dorsal segment of the right lower lobe being the most common infection site in this cohort. These findings suggest the utility of deep-learning methods to accurately quantify and detect COVID-19 lung changes, which would efficiently assist clinicians in diagnosis and management.

ABSTRACT

BACKGROUND: The novel coronavirus disease 2019 (COVID-19) is an emerging worldwide threat to public health. While chest computed tomography (CT) plays an indispensable role in its diagnosis, the quantification and localization of lesions cannot be accurately assessed manually. We employed deep learning-based software to aid in detection, localization and quantification of COVID-19 pneumonia.

METHODS: A total of 2460 RT-PCR tested SARS-CoV-2-positive patients (1250 men and 1210 women; mean age, 57.7 +- 14.0 years (age range, 11-93 years) were retrospectively identified from Huoshenshan Hospital in Wuhan from February 11 to March 16, 2020. Basic clinical characteristics were reviewed. The uAI Intelligent Assistant Analysis System was used to assess the CT scans.

RESULTS: CT scans of 2215 patients (90%) showed multiple lesions of which 36 (1%) and 50 patients (2%) had left and right lung infections, respectively (> 50% of each affected lung's volume), while 27 (1%) had total lung infection (> 50% of the total volume of both lungs). Overall, 298 (12%), 778 (32%) and 1300 (53%) patients exhibited pure ground glass opacities (GGOs), GGOs with sub-solid lesions and GGOs with both sub-solid and solid lesions, respectively. Moreover, 2305 (94%) and 71 (3%) patients presented primarily with GGOs and sub-solid lesions, respectively. Elderly patients (>= 60 years) were more likely to exhibit sub-solid lesions. The generalized linear mixed model showed that the dorsal segment of the right lower lobe was the favoured site of COVID-19 pneumonia.

CONCLUSION: Chest CT combined with analysis by the uAI Intelligent Assistant Analysis System can accurately evaluate pneumonia in COVID-19 patients.

FIGURES

CT feature	No. (%) of patients
Lesion presentation on scan	
Negative	84 (3%)
Unilateral infection	167 (7%)
Only right lung	81 (3%)
Only left lung	86 (3%)
Bilateral infection	2215 (90%)
Left lung infection volume greater than 50%	36 (1%)
Right lung infection volume greater than 50%	50(2%)
Total lung infection volume greater than 50%	27 (1%)
CT signs	
Pure GGO	298 (12%)
GGO + sub-solid	778 (32%)
GGO + sub-solid + solid	1300 (53%)
GGO as the main lesion	2305 (94%)
Sub-solid as the main lesion	71 (3%)

CT computed tomography, GGO ground glass opacity

Table 2. Chest CT features of patients with COVID-19.

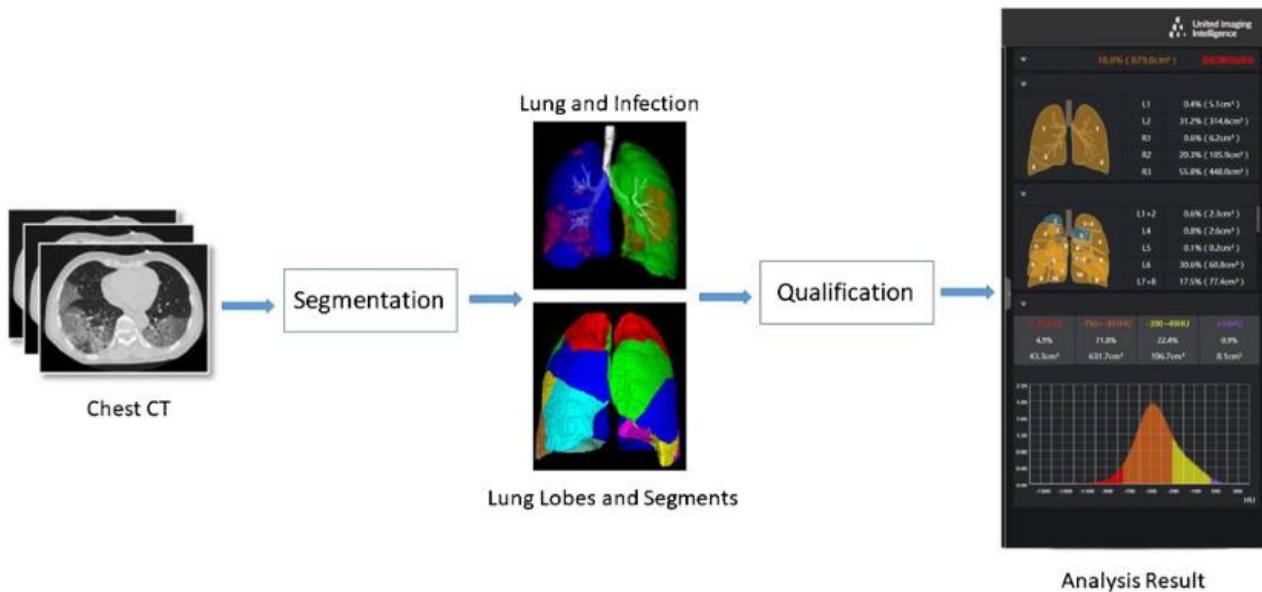


Figure 1. Pipeline for quantifying COVID-19 infection. A chest CT scan is first fed into the deep learning-based segmentation system. Then, quantitative metrics are calculated to characterize infection regions in the CT scan, including but not limited to the following: infection volumes, and percentages of infection (POIs) in the whole lung, lung lobes, and bronchopulmonary segments.

EVALUATION OF SIX COMMERCIAL MID TO HIGH VOLUME ANTIBODY AND SIX POINT OF CARE LATERAL FLOW ASSAYS FOR DETECTION OF SARS-COV-2 ANTIBODIES

Charlton CL, Kanji JN, Johal K, Bailey A, Plitt SS, MacDonald C, Kunst A, Buss E, Burnes LE, Fonseca K, Berenger BM, Schnabl K, Hu J, Stokes W, Zelyas N, Tipples G.. J Clin Microbiol. 2020 Jul 14;JCM.01361-20. doi: 10.1128/JCM.01361-20. Online ahead of print.

Level of Evidence: 4 - Case-control studies, or “poor or non-independent reference standard

BLUF

This study compared the ability of 6 commercial enzyme assays (EIA) and 8 lateral flow point of care assays (POCT) to test for antibodies to SARS-CoV-2 in the serum of 28 COVID-19 patients from the University of Alberta Hospital against negative control serum stored from healthy patients before November 2019, for a total of 161 samples (Table 1). Results revealed that while EIA and POCT were both able to detect SARS-CoV-2, Abbott, Affinity, and BioRad EIAs had the highest clinical sensitivity and specificity tested (Tables 3 and 4). Although these assays are an effective way for detection of COVID-19, there is concern for cross-reactivity with other respiratory viruses, especially other coronaviruses, and therefore these assays should not be used in acute patient diagnosis, but rather to aid in the investigation of previous exposure and seroprevalence within a population.

ABSTRACT

Background: COVID serological tests are essential to determine the overall seroprevalence of a population, and to facilitate exposure estimates within that population.

Methods: We performed a head-to-head assessment of enzyme immunoassays (EIA) and point of care lateral flow assays (POCT) to detect SARS-CoV-2 antibodies. Demographics, symptoms, co-morbidities, treatment, and mortality of patients whose sera was used were also reviewed.

Results: Six EIAs (Abbott, Affinity, BioRad, DiaSorin, Euroimmun, and Roche), and six POCTs (BTNX, Biolidics, Deep Blue, Genrui, Getein BioTech, and Innovita) were evaluated for the detection of SARS-CoV-2 antibodies in known COVID-19 infected individuals. Sensitivity of EIAs ranged from 50-100%, with only four assays having overall sensitivities >95% after 21 days post symptom onset. Notably, cross-reactivity with other respiratory viruses (PIV-4 (n=5), hMPV (n=3), rhinovirus/enterovirus (n=1), CoV-229E (n=2), CoV-NL63 (n=2), and CoV-OC43 (n=2) was observed; however, overall specificity for EIAs was good (92-100%; where all but one assay had specificity above 95%). POCTs were 0-100% sensitive >21 days post onset, with specificity ranging from 96-100%. However, many POCTs had faint banding and were often difficult to interpret.

Conclusions: Serology assays can detect SARS-CoV-2 antibodies as early as 10 days post onset. Serology assays vary in their sensitivity based on the marker (IgA/M vs. IgG vs. total) and by manufacturer; however, overall only 4 EIA and 4 POCT assays had sensitivities >95% >21 days post symptom onset. Cross-reactivity with other seasonal coronaviruses is of concern. The use of serology assays should not be used for the diagnosis of acute infection, but rather for use in carefully designed serosurveys to facilitate understanding of seroprevalence in a population and to identify previous exposure to SARS-CoV-2.

FIGURES

Company	Detection of Antibody Class	Type of Assay	Volume and Estimated TAT	Assay Target	Approvals	Notes
Abbott	IgG	CMIA	High throughput 45 min per sample	Recombinant antigen nucleocapsid protein	FDA EUA granted April 26, 2020 HC Approved May 14, 2020	A clean of the instrument before and after running SARS-CoV-2 samples is required (~40 min total)
Affinity	IgM and IgG	ELISA	Mid volume 4 hours per 96-well plate	Recombinant antigens of the RBD and spike protein	CE Marked	Package insert recommends testing each sample in duplicate
BioRad	IgM and IgG	ELISA	Mid volume 4 hours per 96-well plate	Antibodies recognizing recombinant nucleocapsid proteins and peptides	Submitted to HC	Package insert recommends testing each sample in duplicate
Diasorin	IgG	CLIA	High throughput 40 min per sample	IgG antibodies directed against the S1 and S2 domains of the spike protein	FDA EUA granted April 24, 2020 HC Approved May 12, 2020	
EuroImmun	IgA and IgG	ELISA	Mid volume 4 hours per 96-well plate	Recombinant S1 domain of the structural protein	FDA EUA granted May 4, 2020 CE Marked	Package insert recommends testing each sample in duplicate
Roche	IgG	ECLIA	High throughput 45 min per sample	Recombinant protein representing the nucleocapsid antigen	FDA EUA granted May 2, 2020	
BTNX	IgM and IgG	Lateral flow	POCT 15 min per sample	Target unspecified		
Biolidics	IgM and IgG	Lateral flow	POCT 15 min per sample	Recombinant protein, target unspecified		
Deep Blue	IgM and IgG	Lateral flow	POCT 15 min per sample	Target unspecified	Removed from FDA EUA	
Genrui	IgM and IgG	Lateral flow	POCT 15 min per sample	Target unspecified		
Getein BioTech	IgM and IgG	Lateral flow	POCT 15 min per sample	Recombinant nucleocapsid and spike proteins		
Innovita	IgM and IgG	Lateral flow	POCT 15 min per sample	Target unspecified		

Table 1: Description of serology assays used in this study.

Table 3. Performance of six SARS-CoV-2 EIAs by date of serum collection relative to date of symptom onset

Assay	Positive Samples																		Negative Samples (serum collected pre Nov 2019)																
	0-14 days									15-21 days									>21 days									All time points							
	Neg	Equ	Pos	Sens	Sens ¹	Cl ²	Neg	Equ	Pos	Sens	Sens ¹	Cl ²	Neg	Equ	Pos	Sens	Sens ¹	Cl ²	Neg	Equ	Pos	Sens	Sens ¹	Cl ²	n ³	Neg	Equ	Pos	Spec	Spec ⁴	Cl ²				
Abbott	IgG	6	0	15	71	71 48-89	2	0	9	82	82 48-98	0	0	10	100	100 69-100	8	0	34	81	81 66-91	42	49	0	1	98	98	89-100							
Affinity	IgM	5	0	16	76	76 53-92	0	0	11	100	100 72-100	0	0	8	100	100 63-100	5	0	35	88	88 73-96	40	47	0	0	100	100	92-100							
	IgG	8	0	13	62	62 38-82	3	1	7	64	73 31-89	1	0	7	88	88 47-100	12	1	27	68	70 51-81	40	47	0	0	100	100	92-100							
Overall	IgM/IgG	2	0	19	90	90 70-99	0	0	11	100	100 72-100	0	0	8	100	100 63-100	2	0	38	95	95 83-99	40	47	0	0	100	100	92-100							
BioRad	IgM	9	0	12	57	57 34-78	4	1	6	55	64 23-83	5	0	5	50	50 19-81	18	1	23	55	57 39-70	42	49	1	0	98	100	89-100							
	IgG	4	0	17	81	81 58-95	1	2	8	73	91 39-94	0	0	10	100	100 69-100	5	2	35	83	88 69-93	42	50	0	0	100	100	93-100							
Overall	IgM/IgG	4	0	17	81	81 58-95	1	0	10	91	91 59-100	0	0	10	100	100 69-100	5	0	37	88	88 74-96	42	50	0	0	100	100	93-100							
Diasorin	IgG	11	1	9	43	48 22-66	3	0	8	73	73 39-94	1	0	9	90	90 55-100	15	1	26	62	64 46-76	42	48	1	1	96	98	86-100							
Euroimmun	IgA	7	0	14	67	67 43-85	2	0	9	82	82 48-98	0	1	7	88	100 47-100	9	1	30	75	78 59-87	40	46	4	0	92	100	81-98							
	IgG	11	0	10	48	48 26-70	3	0	8	73	73 39-94	1	0	7	88	88 47-100	15	0	25	63	63 46-77	40	50	0	0	100	100	93-100							
Overall	IgA/IgG	5	0	16	76	76 53-92	2	0	9	82	82 48-98	0	0	8	100	100 63-100	7	0	33	83	83 67-93	40	50	0	0	100	100	93-100							
Roche	Total AB	7	0	14	67	67 43-85	3	0	8	73	73 39-94	2	0	8	80	80 44-97	12	0	30	71	71 55-84	42	50	0	0	100	100	93-100							

¹Sensitivity if equivocal is considered positive

²Confidence intervals (CI) are calculated for sensitivity and specificity where equivocals are considered negative

³Two invalid samples were observed for Affinity and for Euroimmun (total n = 40)

⁴Specificity if equivocal is considered positive

Table 4: Performance of six SARS-CoV-2 lateral flow assays (POCT) by date of serum collection relative to date of symptom onset

Assay	Positive Samples																		Negative Samples (serum collected pre Nov 2019)																
	0-14 days									15-21 days									>21 days									All time points							
	Neg	Equ	Pos	Sens	Sens ¹	Cl ²	Neg	Equ	Pos	Sens	Sens ¹	Cl ²	Neg	Equ	Pos	Sens	Sens ¹	Cl ²	Neg	Equ	Pos	Sens	Sens ¹	Cl ²	n ³	Neg	Equ	Pos	Spec	Spec ⁴	Cl ²				
BTNX	IgM	7	5	8	40	65 19-64	3	1	6	60	70 26-88	0	4	6	60	100 26-88	10	10	20	50	75 34-66	40	50	0	0	100	100	93-100							
	IgG	8	1	11	55	60 32-77	3	0	7	70	70 35-93	1	0	9	90	90 55-100	12	1	27	68	70 51-81	40	50	0	0	100	100	93-100							
Overall	IgM/IgG	6	1	13	65	70 41-85	2	0	8	80	80 44-97	0	1	9	90	100 55-100	8	2	30	75	80 59-87	40	50	0	0	100	100	93-100							
Bolidics	IgM	14	2	4	20	30 6-44	8	0	2	20	20 3-56	6	3	1	10	40 0-45	28	5	7	18	30 7-33	40	48	1	1	96	98	86-100							
	IgG	6	1	13	65	70 41-85	2	0	8	80	80 44-97	0	0	10	100	100 69-100	8	1	31	78	80 62-89	40	50	0	0	100	100	93-100							
Overall	IgM/IgG	6	1	13	65	70 41-85	2	0	8	80	80 44-97	0	0	10	100	100 69-100	8	1	31	78	80 62-89	40	50	0	0	100	100	93-100							
Deep Blue	IgM	5	4	11	55	75 32-77	3	1	6	60	70 26-88	0	0	10	100	100 69-100	8	5	27	68	80 51-81	40	49	1	0	98	100	89-100							
	IgG	11	3	6	30	45 12-54	3	1	6	60	70 26-88	1	0	9	90	90 55-100	15	4	21	53	63 36-68	40	50	0	0	100	100	93-100							
Overall	IgM/IgG	5	4	11	55	75 32-77	2	1	7	70	80 35-93	0	0	10	100	100 69-100	7	5	28	70	83 53-83	40	50	0	0	100	100	93-100							
Genru	IgM	6	0	14	70	70 46-88	2	0	8	80	80 44-97	0	0	10	100	100 69-100	8	0	32	80	80 64-91	40	48	2	0	96	100	86-100							
	IgG	10	0	10	50	50 27-73	3	0	7	70	70 35-93	1	0	9	90	90 55-100	14	0	26	65	65 48-79	40	50	0	0	100	100	93-100							
Overall	IgM/IgG	6	0	14	70	70 46-88	2	0	8	80	80 44-97	0	0	10	100	100 69-100	8	0	32	80	80 64-91	40	50	0	0	100	100	93-100							
Getein BioTech	IgM	19	0	0	0	0 0-18	9	0	1	10	10 0-45	10	0	0	0	0 0-31	38	0	1	3	3 0-13	39	50	0	0	100	100	93-100							
	IgG	11	0	8	42	42 20-67	3	0	7	70	70 35-93	0	0	10	100	100 69-100	14	0	25	64	64 47-79	39	50	0	0	100	100	93-100							
Overall	IgM/IgG	11	0	8	42	42 20-67	3	0	7	70	70 35-93	0	0	10	100	100 69-100	14	0	25	64	64 47-79	39	50	0	0	100	100	93-100							
Innova	IgM	9	8	3	15	55 3-38	5	2	3	30	50 7-65	5	3	2	20	50 3-56	19	13	8	20	53 9-36	40	50	0	0	100	100	93-100							
	IgG	12	4	4	20	40 6-44	3	1	6	60	70 26-88	1	3	6	60	90 26-88	16	8	16	40	60 25-57	40	50	0	0	100	100	93-100							
Overall	IgM/IgG	8	7	5	25	60 9-49	2	1	7	70	80 35-93	1	3	6	60	90 26-88	11	11	18	45	73 29-62	40	50	0	0	100	100	93-100							

DEVELOPMENTS IN TREATMENTS

TOCILIZUMAB FOR THE TREATMENT OF ADULT PATIENTS WITH SEVERE COVID-19 PNEUMONIA: A SINGLE-CENTER COHORT STUDY

Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A retrospective observational study conducted in Madrid March 16-27 found that tocilizumab (TCZ), an anti-interleukin-6 monoclonal antibody, was safe and effective for patients with severe COVID-19-induced pneumonia, with 44.3% (39/88) and 73.9% (65/88) of patients showing clinical improvement ("hospital discharge and/or a decrease of ≥2 points from baseline [day 0] on the six-point ordinal scale") after 7 and 14 days, respectively (Figures 1-3). These findings suggest that TCZ may be an effective treatment in patients with severe COVID-19 pneumonia and an otherwise poor prognosis.

ABSTRACT

OBJECTIVES: Coronavirus Disease 2019 (COVID-19) can lead to a massive cytokine release. The use of the anti-interleukin-6 receptor monoclonal antibody tocilizumab (TCZ) has been proposed in this hyperinflammatory phase, although supporting evidence is limited.

METHODS: We retrospectively analyzed 88 consecutive patients with COVID-19 pneumonia that received at least one dose of intravenous TCZ in our institution between March 16 and 27, 2020. Clinical status from day 0 (first TCZ dose) through day 14 was assessed by a six-point ordinal scale. The primary outcome was clinical improvement (hospital discharge and/or a decrease of ≥=2 points on the six-point scale) by day 7. Secondary outcomes included clinical improvement by day 14 and dynamics of vital signs and laboratory values.

RESULTS: Rates of clinical improvement by days 7 and 14 were 44.3% (39/88) and 73.9% (65/88). Previous or concomitant receipt of subcutaneous interferon-beta (adjusted odds ratio [aOR]: 0.23; 95% confidence interval [CI]: 0.06 - 0.94; P-value = 0.041) and serum lactate dehydrogenase >450 U/L at day 0 (aOR: 0.25; 95% CI: 0.06 - 0.99; P-value = 0.048) were negatively associated with clinical improvement by day 7. All-cause mortality was 6.8% (6/88). Body temperature and respiratory and cardiac rates significantly decreased by day 1 compared to day 0. Lymphocyte count and pulse oximetry oxygen saturation/FiO₂ ratio increased by days 3 and 5, whereas C-reactive protein levels dropped by day 2. There were no TCZ-attributable adverse events.

CONCLUSIONS: In this observational single-center study, TCZ appeared to be useful and safe as immunomodulatory therapy for severe COVID-19 pneumonia. This article is protected by copyright. All rights reserved.

FIGURES

Figure 1. Patient status according to the six-point ordinal scale at different times following the administration of the first dose of TCZ (day 0). ECMO: extracorporeal membrane oxygenation; IMV: invasive mechanical ventilation; TCZ: tocilizumab.

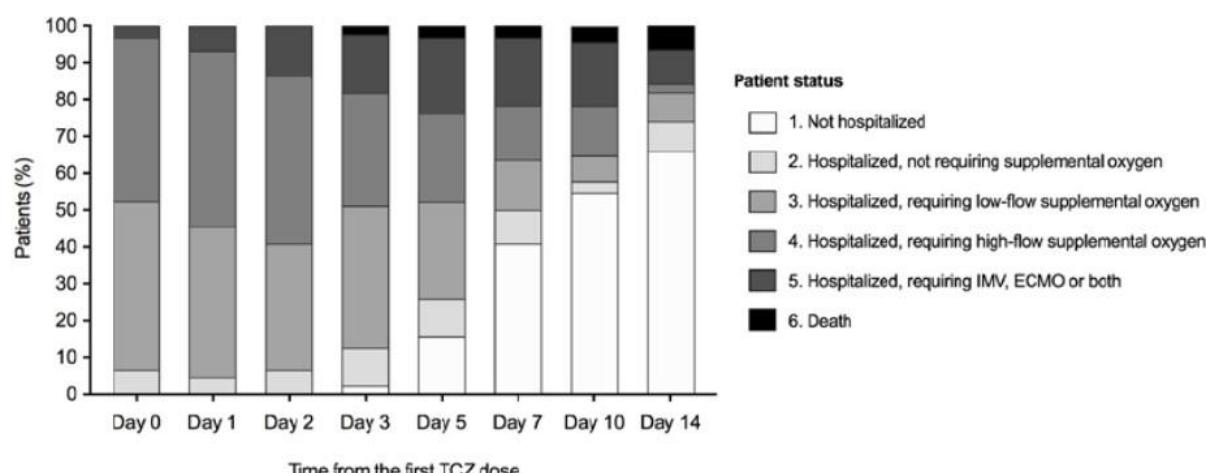


Figure 2. Evolution of vital signs following the administration of the first TCZ dose: (a) axillary temperature; (b) respiratory rate; (c) heart rate; and (d) SpO₂/FiO₂ ratio. *P-value <0.05; **P-value <0.01; ***P-value <0.0001 (statistical test for repeated measures was used). SpO₂/FiO₂: pulse oximetry oxygen saturation/fraction of inspired oxygen; TCZ: tocilizumab.

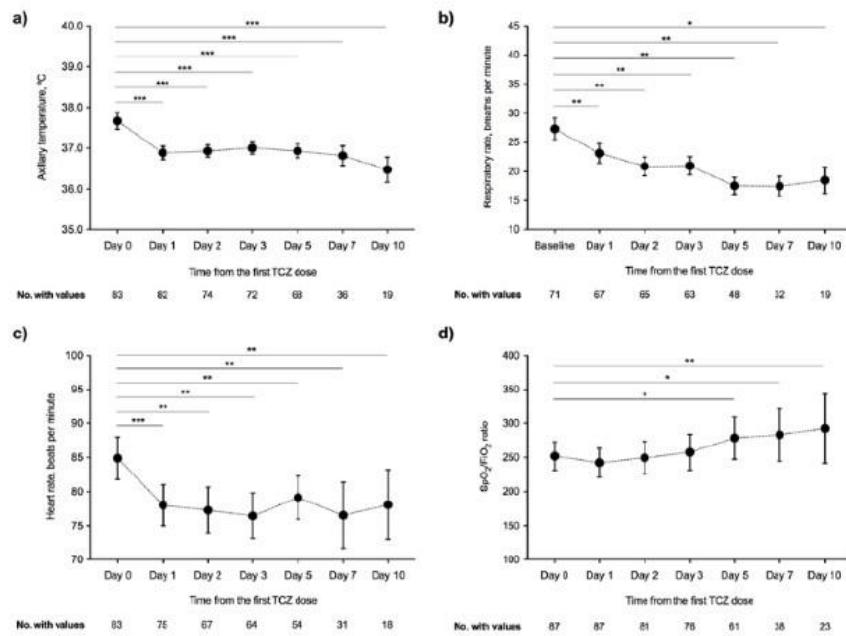
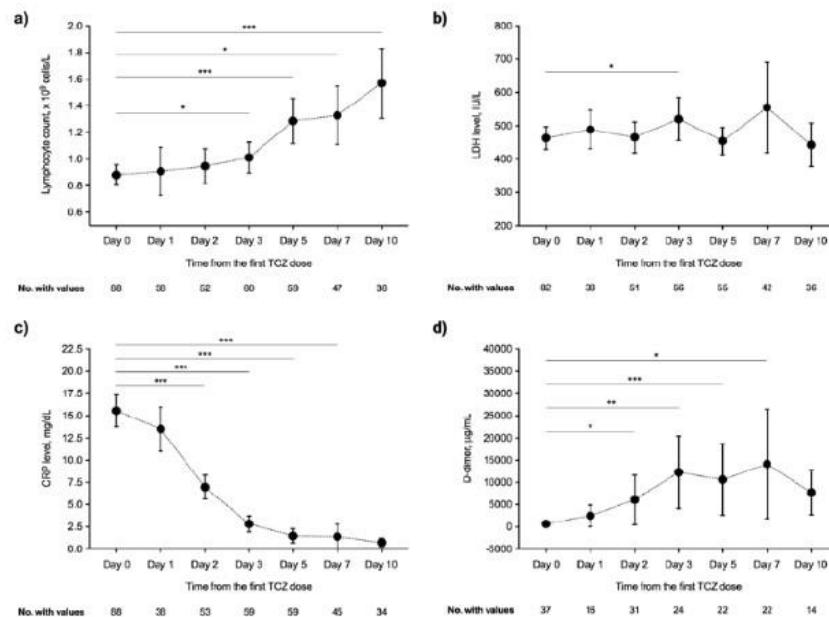


Figure 3. Evolution of laboratory values following the administration of the first TCZ dose: (a) lymphocyte count; (b) LDH level; (c) CRP level; and (d) D-dimer level. *P-value <0.05; **P-value <0.01; ***P-value <0.0001 (statistical test for repeated measures was used). CRP: C reactive protein; LDH: lactate dehydrogenase; TCZ: tocilizumab.



POTENTLY NEUTRALIZING AND PROTECTIVE HUMAN ANTIBODIES AGAINST SARS-COV-2

Zost SJ, Gilchuk P, Case JB, Binshtein E, Chen RE, Nkolola JP, Schäfer A, Reidy JX, Trivette A, Nargi RS, Sutton RE, Suryadevara N, Martinez DR, Williamson LE, Chen EC, Jones T, Day S, Myers L, Hassan AO, Kafai NM, Winkler ES, Fox JM, Shrihari S, Mueller BK, Meiler J, Chandrashekhar A, Mercado NB, Steinhardt JJ, Ren K, Loo YM, Kallewaard NL, McCune BT, Keeler SP, Holtzman MJ, Barouch DH, Gralinski LE, Baric RS, Thackray LB, Diamond MS, Carnahan RH, Crowe JE Jr. *Nature*. 2020 Jul 15. doi: 10.1038/s41586-020-2548-6. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A case-control study using animal models was conducted by the Vanderbilt Vaccine Center to assess the effectiveness of human monoclonal antibodies against SARS-CoV-2. Researchers found that the more potent monoclonal antibodies recognized two overlapping epitopes, COV2-2196 and COV2-2130 (Figure 1), while also binding the receptor binding domain of SARS-CoV-2. These effects resulted in neutralization of the virus, observed through reduced inflammation and viral burden in mice as well as a protective effect in rhesus monkeys after exposure to these monoclonal antibodies. These results suggest that a small subset of known monoclonal antibodies recognize these key epitopes and are therefore effective in neutralizing the virus and useful as a framework for a potential vaccine/immunotherapy for COVID-19.

ABSTRACT

The COVID-19 pandemic is a major threat to global health¹ for which there are limited medical countermeasures^{2,3}. Moreover, we currently lack a thorough understanding of mechanisms of humoral immunity⁴. From a larger panel of human monoclonal antibodies (mAbs) targeting the spike (S) glycoprotein⁵, we identified several that exhibited potent neutralizing activity and fully blocked the receptor-binding domain of S (SRBD) from interacting with human ACE2 (hACE2). Competition binding, structural, and functional studies allowed clustering of the mAbs into classes recognizing distinct epitopes on the SRBD as well as distinct conformational states of the S trimer. Potent neutralizing mAbs recognizing non-overlapping sites, COV2-2196 and COV2-2130, bound simultaneously to S and synergistically neutralized authentic SARS-CoV-2 virus. In two mouse models of SARS-CoV-2 infection, passive transfer of either COV2-2196 or COV2-2130 alone or a combination of both mAbs protected mice from weight loss and reduced viral burden and inflammation in the lung. In addition, passive transfer of each of two of the most potently ACE2 blocking mAbs (COV2-2196 or COV2-2381) as monotherapy protected rhesus macaques from SARS-CoV-2 infection. These results identify protective epitopes on SRBD and provide a structure-based framework for rational vaccine design and the selection of robust immunotherapeutics.

FIGURES

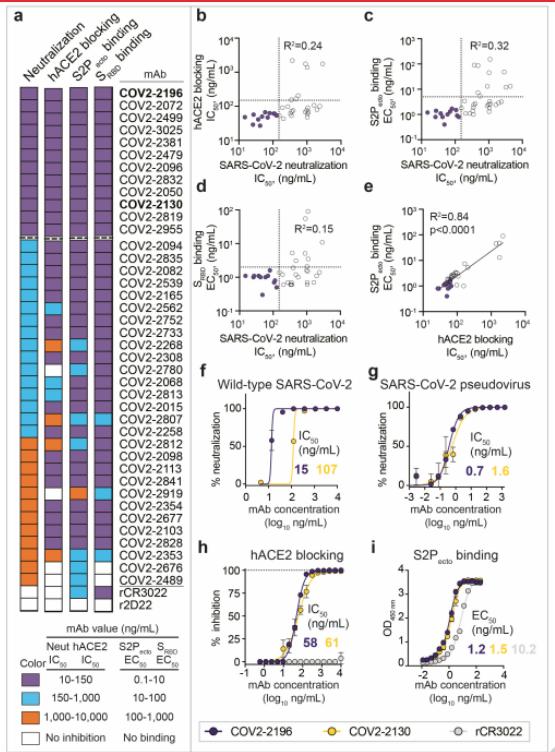


Fig. 1 | Functional characteristics of neutralizing SARS-CoV-2 mAbs.

a. Heatmap of mAb neutralization activity, hACE2 blocking activity, and binding to either trimeric S2P_{ecto} protein or monomeric S_{RBD}. mAbs are ordered by neutralization potency, and dashed lines indicate the 12 antibodies with a neutralization IC₅₀ value lower than 150 ng/mL. IC₅₀ values are visualized for viral neutralization and hACE2 blocking, while EC₅₀ values are visualized for binding. The cross-reactive SARS-CoV S_{RBD} mAb rCR3022 is shown as a positive control, while the anti-dengue mAb r2D22 is shown as a negative control. Data are representative of at least 2 independent experiments performed in technical duplicate. No inhibition or no binding indicates an IC₅₀ or EC₅₀ value of >10,000 ng/mL, respectively.

b-d. Correlation of hACE2 blocking, S2P_{ecto} trimer binding, or S_{RBD} binding of mAbs with their neutralization activity.

e. Correlation of hACE2 blocking and S2P_{ecto} trimer binding. R² values are shown for linear regression analysis of log-transformed values. Purple circles indicate mAbs with a neutralization IC₅₀ value lower than 150 ng/mL.

f. Neutralization curves for COV2-2196 and COV2-2130 against authentic SARS-CoV-2 virus. Calculated IC₅₀ values are denoted on the graph. Error bars denote the standard deviation of each point. Data are representative of at least 2 independent experiments, each performed in technical duplicate.

g. Neutralization curves for COV2-2196 and COV2-2130 in a pseudovirus neutralization assay. Error bars denote the standard deviation of each point. Values shown are technical duplicates from a single experiment. Calculated IC₅₀ values from a minimum of 6 experiments are denoted on the graph.

h. hACE2 blocking curves for COV2-2196, COV2-2130, and the non-blocking SARS-CoV mAb rCR3022 in the hACE2 blocking ELISA. Calculated IC₅₀ values are denoted on the graph.. Mean ± SD of technical triplicates are shown from a representative experiment repeated twice.

i. ELISA binding of COV2-2196, COV2-2130, and rCR3022 to trimeric S2P_{ecto}. Calculated EC₅₀ values are denoted on the graph. Mean ± SD of technical triplicates are shown from a representative experiment repeated twice.

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