The Daily COVID-19 Literature Surveillance Summary

January 11, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Epidemiology

- Do we need routine COVID-19 testing of Emergency Department staff? A study from the University of Washington uses a mathematical model based on the Diamond Princess cruise ship data to predict detection of SARS-CoV-2 in asymptomatic health care workers (HCWs) in the emergency department in regions with high COVID-19 rates. Results revealed that within six months, weekly testing in asymptomatic HCWs would reduce infection rates by 3 to 5.9% when the transmission constant is 1.219e-4 new infections/person^2, while a transmission constant of 3.660e-4 new infections/person^2 would result in reduction of infections by 11 to 23%. The authors urge more frequent testing in asymptomatic HCWs to help reduce the rate of SARS-CoV-2 infection.

Understanding the Pathology

- Dynamic changes are witnessed in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery in a retrospective analysis by bioinformatics and global health specialists in Jiangsu, China where 1,850 hospitalized patients with COVID-19 were analyzed and those with mild or moderate disease were found to develop IgG antibodies one week earlier than patients with severe disease. While spike protein and receptor-binding domain specific IgG levels were 1.5- and 2-fold higher in critically ill hospitalized patients and SARS-CoV-2 RNA-negative recovered patients, respectively, compared to those who are remained RNA-positive. These data suggest earlier development of antibodies may be protective against developing severe disease; however, those who recover from more severe disease may also have higher levels of antibodies and a shorter duration of viral shedding.

Management

- Coronary calcium scoring was found to be a predictor for outcome in COVID-19. A retrospective cohort study conducted at the University of Munich by a team of internal medicine and radiology specialists found the coronary artery calcification (CAC) score to be a significant prognostic indicator based on 109 SARS-CoV-2-infected patients. Authors found the median CAC to be 140 [IQR 1–1165] in patients with critical COVID-19, and 160 [IQR: 88–562] in patients with fatal outcome. Authors note limitations due to retrospective design and small sample size, however, these findings suggest that coronary artery disease is significantly associated with an adverse clinical outcome in COVID-19.

- Oxygen saturation/fraction of inhaled oxygen is associated with mortality in patients with COVID-19 associated pneumonia requiring oxygen therapy. A retrospective cohort study from a group of South Korean Internists analyzed 59 hospitalized COVID-19 patients in hypoxic respiratory failure , and found that the SpO2:FiO2 (SF ratio) was predictive of ARDS occurrence ($p < .001$). Results also demonstrated that the SF ratio at exacerbation (HR, 0.916; 95% CI, 0.846-0.991; P = 0.029) and National Early Warning Score (NEWS) (HR, 1.277; 95% CI, 1.010-1.615; P = 0.041) were significant predictors of mortality. These findings are clinically significant because predicting development of ARDS and mortality allows physicians to effectively triage and treat the highest risk patients. Additionally, the SF ratio has many advantages over the traditionally used P:F ratio (PaO2:FiO2) during the COVID-19 pandemic because it does not require measurement of arterial blood gas, thus conserving valuable time and resources.

Adjusting Practice During COVID-19

- There is a high prevalence of deep venous thrombosis in non-severe COVID-19 patients hospitalized for a neurovascular disease. This prospective study from Strasbourg University Hospital, France evaluates 13 patients with non-severe COVID-19 and concurrent neurovascular disease for deep venous thrombosis (DVT) via doppler ultrasound scanning (DUS) of the lower limbs. Results showed that despite thromboprophylaxis, the prevalence of asymptomatic DVT was 38.5%. The authors thus advocate for the use of bedside DUS to identify DVT in patients with COVID-19 given that D-dimer, the classic marker of DVT, has been shown to correlate with COVID-19 severity and may be elevated in this population regardless of coagulable state.

R&D: Diagnosis & Treatments

- What have we learned about viral cultures and COVID-19 infectious potential? A review, conducted at University of Oxford, analyzes 29 studies that attempted to culture SARS-CoV-2 to estimate potential or observed infectivity. The authors state an apparent correlation between length of time between specimen collection and test, cycle threshold, and symptom severity. Furthermore, they found cycle threshold to be a good surrogate for viral load as it correlated with increased infection of Vero E6 cells by SARS-CoV-2. Inconsistency in culturing methods limit study power, highlighting the need for standardization of this process.

- Inconclusive COVID-19 PCR results have high rates of false positive tests. Infectious disease physicians from UCLA analyzed inconclusive SARS-CoV-2 RT-PCR tests (18 cases from a CDC assay and 51 from the TaqPath assay) to determine rates of false positive tests and to create an algorithm to make determinations on inconclusive tests. The authors found that the rate of false positives in the inconclusive tests ranged between 14-39% and that lowering the cycle threshold cutoff from 40 to 37 in the TaqPath assay significantly lowered the false-positive rate. This study demonstrates that there is a significant rate of false positive RT-PCR SARS-CoV-2 tests, which can be corrected through additional testing and changing of cycle thresholds, though this may make false negative results more likely.

- Hydroxychloroquine with or without azithromycin was found to have no effect in mild-to-moderate COVID-19. A multicenter randomized controlled trial conducted by HCor Research Institute in Sao Paulo, Brazil across 55 hospitals in Brazil included 667 adult patients hospitalized with suspected or confirmed mild-moderate COVID-19 (receiving < 4L/min O2) with less than 14 days since symptom onset who received: standard care, standard care plus hydroxychloroquine 400 mg twice daily, or standard care plus hydroxychloroquine 400 mg twice daily plus azithromycin 500 mg once daily for 7 days. It was determined that a higher ordinal score (worse prognosis) at 15 days was not affected by hydroxychloroquine or hydroxychloroquine plus azithromycin treatment and did not change with amount of time since randomization. This suggests use of hydroxychloroquine, with or without azithromycin, in mild-to-moderate COVID-19 infection has no effect on improving clinical status at 15 days compared to standard care.

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CLIMATE

DO PEOPLE ACTUALLY "LISTEN TO THE EXPERTS"? A CAUTIONARY NOTE ON ASSUMING EXPERT CREDIBILITY AND PERSUASIVENESS ON PUBLIC HEALTH POLICY ADVOCACY

Geiger N.. Health Commun. 2020 Dec 28:1-8. doi: 10.1080/10410236.2020.1862449. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

Nathaniel Geiger, from the Media School at Indiana University explores the relationship between the persuasiveness and credibility of experts versus non-experts in policy advocacy, comparing climate change to COVID-19. Using Bayesian analyses, he found that experts were neither more nor less persuasive than non-experts. He suggests that further work is needed to explore the conditions under which experts can gain or increase trust and persuasiveness, and suggests a role for non-experts as ambassadors for public health issues and policy change.

ABSTRACT

The present work empirically explores whether experts are trusted more or more persuasive than an "average Joe" when engaging in policy advocacy on public health topics. I conducted a 2 (topic: climate change vs. COVID-19) X 2 (source: expert vs. nonexpert) experimental study with an US adult sample (N = 486). Using Bayes factors to quantify evidence for null and alternative hypothesis, I find substantial evidence that at least under the conditions present in the study, experts are perceived to be higher in expertise, but equal in trustworthiness to the "average Joe". In turn, experts are equally persuasive to nonexperts on both topics. My work suggests that when engaging in policy advocacy on public health matters, the fact that an advocate is an expert on a topic can be acknowledged by audiences, but this may not necessarily help (nor necessarily harm) one's perceived trustworthiness or ability to persuade an audience. More research is needed to understand how experts can bolster their trustworthiness and persuasiveness when advocating for public health policies.

EVALUATING THE NEED FOR ROUTINE COVID-19 TESTING OF EMERGENCY DEPARTMENT STAFF: QUANTITATIVE ANALYSIS

Zhang Y, Cheng SR.. JMIR Public Health Surveill. 2020 Dec 3;6(4):e20260. doi: 10.2196/20260.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

This study from the University of Washington uses a mathematical model based on the Diamond Princess cruise ship data to predict detection of SARS-CoV-2 in asymptomatic health care workers (HCWs) in the emergency department in regions with high COVID-19 rates (Figure 1). Results revealed that within six months, weekly testing in asymptomatic HCWs would reduce infection rates by 3 to 5.9% when the transmission constant is 1.219e-4 new infections/person^2, while a transmission constant of 3.660e-4 new infections/person^2 would result in reduction of infections by 11 to 23%. The authors urge more frequent testing in asymptomatic HCWs to help reduce the rate of SARS-CoV-2 infection.

ABSTRACT

BACKGROUND: As the number of COVID-19 cases in the US continues to rise and hospitals are experiencing personal protective equipment (PPE) shortages, healthcare workers have been disproportionately affected by COVID-19 infection. Since COVID-19 testing is now available, some have raised the question of whether we should be routinely testing asymptomatic healthcare workers. OBJECTIVE: To provide a quantitative analysis of the predicted impact that regular COVID-19 testing of healthcare workers may have on COVID-19 infection prevention in emergency department patients and staff. METHODS: Using publicly available data on COVID-19 infections and emergency department visits, as well as internal hospital staffing information, we generated a mathematical model to predict the impact of periodic COVID-19 testing in asymptomatic members of the emergency department staff in regions affected by COVID-19 infection. We calculated various transmission constants based on the Diamond Princess cruise ship data, used a logistic model to calculate new infections, and we created a Markov model according to average COVID-19 incubation time. RESULTS: Our model predicts that after 180 days, with a transmission constant of 1.219e-4 new infections per person2, weekly COVID-19 testing of healthcare workers (HCW) would reduce new HCW and patient infections by 3~5.9% and bi-weekly testing would reduce both by 1~2.1%. At a transmission constant of 3.660e-4 new infections per person2, weekly testing would reduce infections by 11~23% and bi-weekly testing would reduce infections by 5.5~13%. For a lower transmission constant of 4.067e-5 new infections per person2, weekly and biweekly HCW testing would result in a 1% and 0.5~0.8% reduction in infections respectively. CONCLUSIONS: Periodic COVID-19 testing for emergency department staff in regions that are heavily-affected by COVID-19 and/or facing resource constraints may reduce COVID-19 transmission significantly among healthcare workers and previously-uninfected patients.

FIGURES

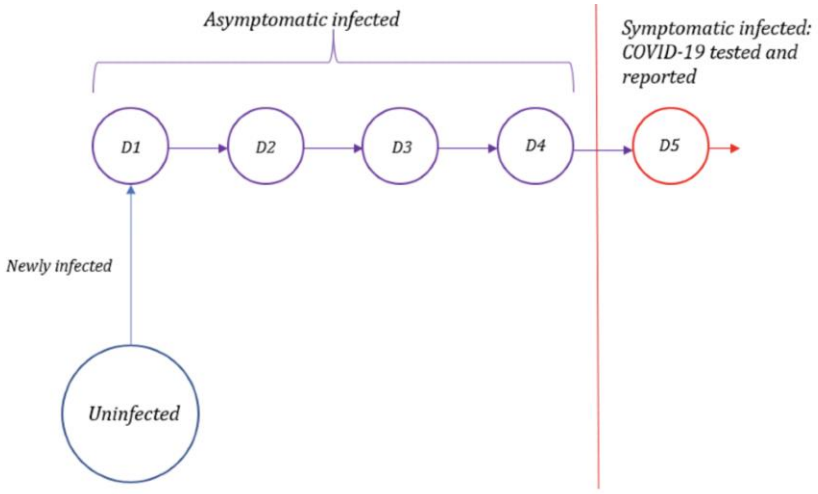

Figure 1. Timeline of infection for confirmed COVID-19 cases. After infection, an individual can transmit the infection to others but does not become symptomatic until day 5.

COMPREHENSIVE HEALTH ASSESSMENT THREE MONTHS AFTER RECOVERY FROM ACUTE COVID-19

van den Borst B, Peters JB, Brink M, Schoon Y, Bleeker-Rovers CP, Schers H, van Hees HWH, van Helvoort H, van den Boogaard M, van der Hoeven H, Reijers MH, Prokop M, Vercoulen J, van den Heuvel M.. Clin Infect Dis. 2020 Nov 21:ciaa1750. doi: 10.1093/cid/ciaa1750. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A cohort study conducted at Radboud University Medical Center investigated the health of 124 discharged COVID-19 patients by completing lung function tests, chest CT/X-ray, a 6-minute walking test, body composition, and questionnaires on mental, cognitive, health status, and quality of life. While ground-glass opacity in CT images was improved in 99% of patients and normal chest X-rays were observed in 93% of patients with mild disease, 91% of discharged patients had residual lung parenchymal abnormalities (Table 2). Some patients also showed low exercise capacity, low fat-free mass index, or cognitive deficits (Table 3), while the survey revealed high self-reported relative functional impairment, fatigue, and reduced quality of life (Figure 3b). This study adds to the growing concerns regarding long-term prognosis of COVID-19 patients that will likely require sustained care.

ABSTRACT

BACKGROUND: Long-term health sequelae of COVID-19 may be multiple but have thus far not been systematically studied. METHODS: All patients discharged after COVID-19 from the Radboud university medical centre, Nijmegen, The Netherlands, were consecutively invited to a multidisciplinary outpatient facility. Also, non-admitted patients with mild disease but with symptoms persisting >6 weeks could be referred by general practitioners. Patients underwent a standardized assessment including measurements of lung function, chest CT/X-ray, 6-minute walking test, body composition, and questionnaires on mental, cognitive, health status and quality of life (QoL). RESULTS: 124 patients (age 59+-14 years, 60% male) were included; 27 with mild, 51 with moderate, 26 with severe and 20 with critical disease. Lung diffusion capacity was below lower limit of normal in 42% of discharged patients. Ninety-nine percent of discharged patients had reduced ground-glass opacification on repeat CT imaging, and normal chest X-rays were found in 93% of patients with mild diseases. Residual pulmonary parenchymal abnormalities were present in 91% of discharged patients, and correlated with reduced lung diffusion capacity. Twenty-two percent had low exercise capacity, 19% low fat-free mass index, and problems in mental and/or cognitive function were found in 36% of the patients. Health status was generally poor, particularly in the domains functional impairment (64%), fatigue (69%) and QoL (72%). CONCLUSIONS: This comprehensive health assessment revealed severe problems in several health domains in a substantial number of ex-COVID-19 patients. Longer follow-up studies are warranted to elucidate natural trajectories and to find predictors of complicated long-term trajectories of recovery.

	No. of patients with missing data (n)	All patients (N=124)	Critical disease patients (n=20)	Severe disease patients (n=26)	Moderate disease patients (n=51)	Referred mild disease patients (n=27)	p-value
			a	b	c	d	
Dyspnea							
mMRC, median (IQR)	0	1 (0-2)	1 (0-1)	1 (0-2)	1 (0-1)	2 (1-2)	<0.001 [a-d, c-d]
Pulmonary function							
Resting oxygen saturation, mean (SD), %	15	96 (1)	96 (1)	96 (1)	96 (2)	97 (1)	0.387
VCmax, mean (SD), %predicted	2	99 (16)	98 (15)	92 (17)	102 (18)	100 (9)	0.111
VCmax<LLN, No. (%)		8 (7)	1 (5)	2 (8)	5 (10)	0 (0)	0.378
FEV1, mean (SD), %predicted	2	97 (16)	101 (16)	91 (24)	97 (19)	99 (13)	0.254
FEV1<LLN, No. (%)	2	12 (10)	1 (5)	3 (12)	6 (12)	2 (7)	0.774
FEV1/VCmax, mean (SD), %	2	76 (11)	81 (6)	75 (12)	75 (10)	76 (16)	0.253
FEV1/VCmax<LLN, No. (%)	2	13 (11)	0 (0)	4 (15)	6 (12)	3 (11)	0.372
DLCO, mean (SD), %predicted	2	81 (17)	77 (14)	75 (17)	80 (17)	93 (10)	<0.001 [a-d, b-d, c-d]
DLCO<LLN, No. (%)	2	41 (34)	11 (55)	14 (54)	16 (33)	0 (0)	<0.001
TLC, mean (SD), %predicted	2	99 (14)	94 (16)	95 (14)	101 (14)	104 (9)	0.013 [a-d]
TLC<LLN, No. (%)	5	15 (13)	4 (20)	3 (12)	7 (15)	1 (4)	0.355
RV, mean (SD), %predicted	5	100 (22)	86 (19)	101 (25)	101 (21)	107 (20)	0.009 [a-c, a-d]
RV<LLN, No. (%)	5	10 (8)	2 (15)	1 (4)	4 (9)	2 (7)	0.599
Imaging							
Available CT at follow-up, No. (%)	13	84 (87)	17 (85)	22 (85)	45 (88)	NA	-
Extent of residual CT abnormalities, median (IQR)	13	8 (6)	12 (6)	8 (6)	6 (4)	NA	0.019 [a-c]
Type of residual CT abnormalities present, No. (%)	13						
Ground-glass opacity		73 (86)	16 (89)	18 (86)	39 (85)	NA	0.914
Bronchi(ol)ectasis		51 (60)	12 (67)	10 (48)	29 (63)	NA	0.396
Lines and bands		54 (64)	15 (83)	13 (62)	26 (57)	NA	0.132
Fibrosis		22 (26)	9 (50)	5 (24)	8 (17)	NA	0.027

TABLE 2. Dyspnea, pulmonary function and chest CT imaging results three months after recovery from acute COVID-19

	No. of patients with missing data (n)	All patients (N=124)	Critical disease patients (n=20)	Severe disease patients (n=26)	Moderate disease patients (n=51)	Referred mild disease patients (n=27)	p-value
Physical functioning							
CFS, No. (%)	3						
Not Frail		104 (84)	18 (90)	21 (81)	43 (84)	22 (92)	0.577
Somewhat frail		6 (5)	0 (0)	2 (12)	2 (4)	1 (4)	
Frail		11 (9)	2 (10)	2 (8)	6 (12)	1 (4)	
6MWD, mean (SD), %predicted	9	92 (18)	99 (16)	83 (17)	91 (17)	95 (22)	0.134
6MWD <80%predicted, No. (%)		25 (22)	1 (5)	8 (32)	13 (28)	3 (12)	0.068
Desaturation >=4% upon 6MWT, No. (%)	14	20 (16)	4 (22)	4 (17)	11 (25)	1 (4)	0.194
Body composition							
BMI, mean (SD), kg/m^2	0	28.3 (5.4)	27.2 (3.2)	29.6 (4.6)	27.9 (4.8)	28.8 (7.8)	0.387
FFMI, mean (SD), kg/m^2	7	19.4 (2.6)	19.2 (1.7)	20.2 (2.3)	19.4 (2.7)	18.6 (3.1)	0.157
FFMI<LLN , No. (%)		23 (19)	4 (21)	7 (27)	5 (11)	7 (27)	0.260
Mental and cognitive status							
HADS-anxiety >10, No. (%)	0	12 (10)	2 (10)	2 (8)	6 (12)	2 (7)	0.912
HADS-depression >10, No. (%)	0	14 (12)	2 (10)	2 (8)	4 (8)	6 (22)	0.241
TICS <34, No. (%)	0	19 (15)	1 (5)	6 (23)	9 (18)	3 (11)	0.330
CFQ >43 , No. (%)	0	21 (17)	3 (17)	8 (17)	6 (12)	4 (15)	0.210
PCL-5 >33, No. (%)	0	9 (7)	1 (5)	3 (12)	3 (6)	2 (7)	0.800
IES-R >33, No. (%)	2	12 (10)	0 (0)	3 (12)	7 (14)	2 (7)	0.339
Normal scores on all mental and cognitive status questionnaires, No. (%)	2	79 (64)	14 (70)	14 (54)	35 (69)	16 (59)	0.532

Abbreviations 6MWD, 6 minute walking distance; 6MWT, 6 minute walking test; BMI, body mass index; CFQ, cognitive failure questionnaire; CFS, clinical frailty scale; FFMI, fat-free mass index; HADS, hospital anxiety and depression scale; IES-R, impact of event scale-revisited; LLN: lower limit of normal (ie.5^{th} percentile); PCL-5, post-traumatic stress checklist according to the diagnostic statistic manual-5; TICS, telephone interview of cognitive status.

TABLE 3. Physical functioning, body composition, mental and cognitive status three months after recovery from acute COVID-19

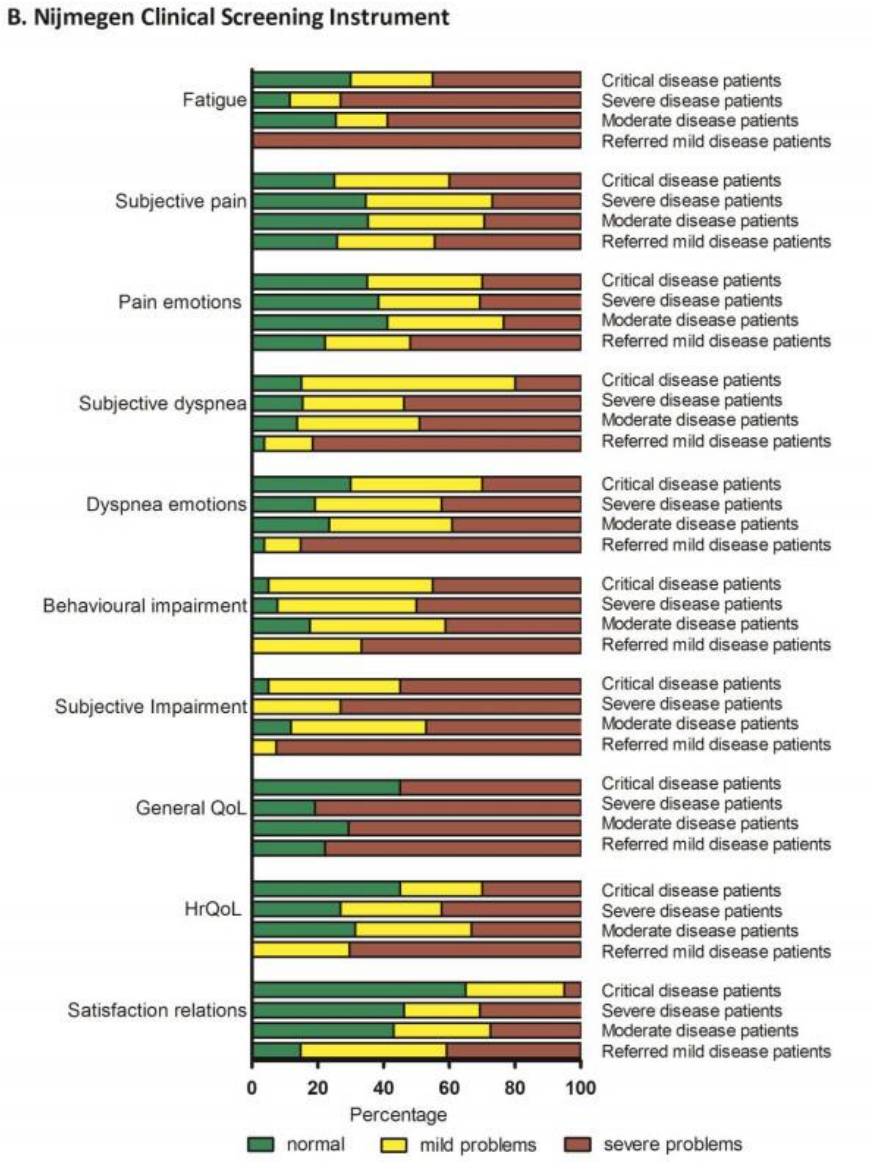

Figure 3B. Health status on domains of the SF-36 (A) and on sub-domains of the NCSI (B) three months after recovery from acute COVID-19

PEDIATRICS

STRONG IMMUNITY AGAINST COVID-19 IN THE EARLY TWO YEARS OF AGE LINKS TO FREQUENT IMMUNIZATION OF ROUTINE VACCINES

Qiu L, Zhang C, Wu J, Luo J, Netea MG, Luo Z, Leng Q.. Sci Bull (Beijing). 2020 Dec 30;65(24):2057-2060. doi: 10.1016/j.scib.2020.08.012. Epub 2020 Aug 8.
Level of Evidence: 4 - Case-series

BLUF

A retrospective study examined the course of COVID-19 in 25 pediatric patients in Taihe Hospital, Hubei Province, China. They found that younger patients, especially those less than 2 years, and those who were up to date with routine immunizations had faster recovery and milder symptoms (Figure 1). Thus, the authors argue that routine vaccinations may prevent severe COVID-19 in pediatric patients through eliciting heterologous immunity.

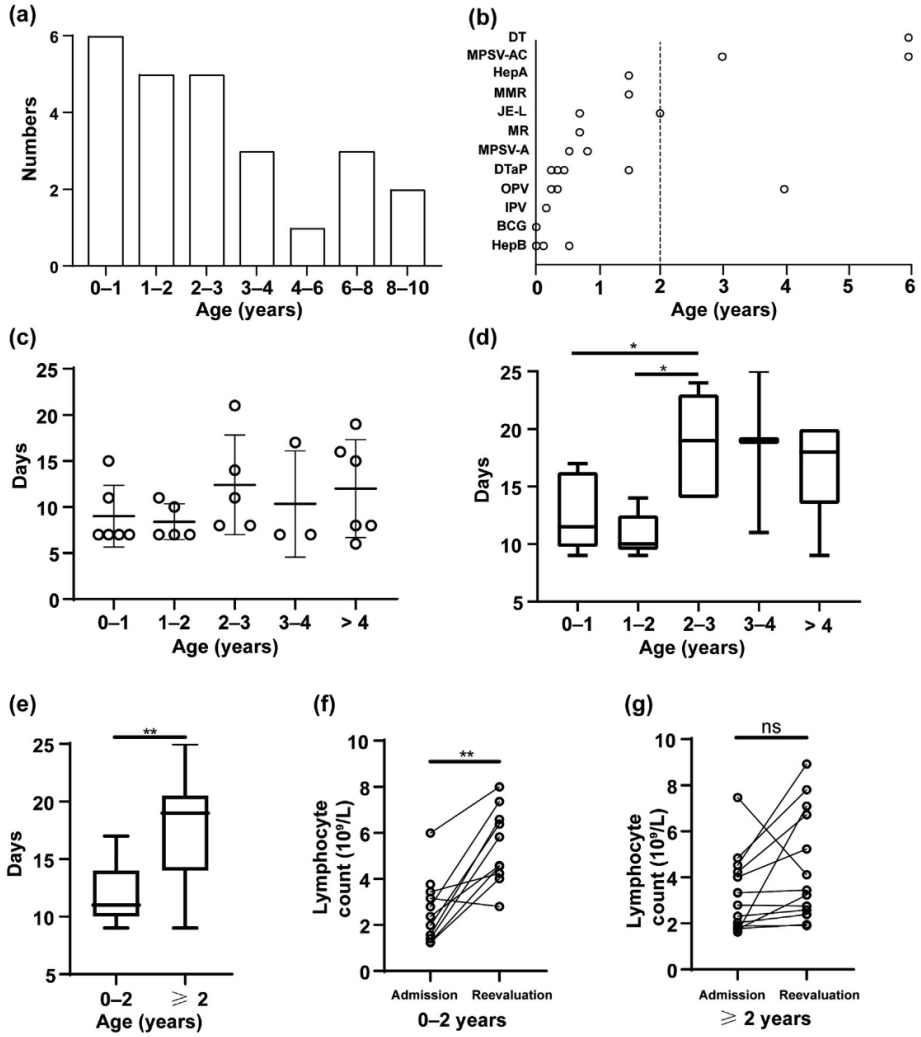

Figure 1. Potential factors that determine the better COVID-19 outcomes in children under 2 years old. (a) Age distribution of 25 pediatric patients under 10 years old. (b)Immunization schedules of pre-school children in China. (c) Duration from SARS-CoV-2 RNA-positive detection to subsequent negative SARS-CoV-2 PCR results for patientswith the indicated ages. Data are presented as the medians and IQRs (interquartile ranges); empty circles represent individual patients. (d) Duration from disease onset tosubsequent negative SARS-CoV-2 PCR results for patients with the indicated ages. Data are presented as the medians and IQRs;P-values were calculated by a Mann-Whitneynonparametrict-test. (e) Duration from disease onset to subsequent negative SARS-CoV-2 PCR results for patients under and over 2 years old. Data are presented as themedians and IQRs;p-value was calculated by a Mann-Whitney nonparametrict-test. (f) Lymphocyte counts at admission and at the time of subsequent negative SARS-CoV-2PCR results for patients under 2 years old. Empty circles represent individual lymphocyte counts;P-value was calculated by a pairedt-test. (g) Lymphocyte counts atadmission and at the time of subsequent negative SARS-CoV-2 PCR results for patients over 2 years old. Empty circles represent individual lymphocytecounts;P-value wascalculated by a pairedt-test. All theP-values from statistical tests were from two-sided evaluations. *:P< 0.05; **:P< 0.01; ns: non-significant. HepB: Hepatitis B vaccine;BCG:BacillusCalmette-Guerin vaccine; IPV: Inactivated polio vaccine; OPV: Oral polio vaccine; DTaP: Diphtheria and tetanus toxoid with acellular pertussis vaccine; MPSV-A:Meningococcal polysaccharide vaccine A; MR: Measles and rubella vaccine; JE-L: Live attenuated Japanese encephalitis vaccine; MMR: Measles, mumps and rubella vaccine;HepA: Hepatitis A vaccine; MPSV-AC: Meningococcal polysaccharide vaccine A + C; DT: Diphtheria and tetanus toxoid children's dose.

IGA DOMINATES THE EARLY NEUTRALIZING ANTIBODY RESPONSE TO SARS-COV-2

Sterlin D, Mathian A, Miyara M, Mohr A, Anna F, Claër L, Quentric P, Fadlallah J, Devilliers H, Ghillani P, Gunn C, Hockett R, Mudumba S, Guihot A, Luyt CE, Mayaux J, Beurton A, Fourati S, Bruel T, Schwartz O, Lacorte JM, Yssel H, Parizot C, Dorgham K, Charneau P, Amoura Z, Gorochov G.. Sci Transl Med. 2020 Dec 7:eabd2223. doi: 10.1126/scitranslmed.abd2223. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

In a study of 159 hospitalized patients with COVID-19, researchers from France found that mucosal IgA neutralizing antibodies dominated the early part of the humoral response against SARS-CoV-2, with levels remaining detectable up to 73 days after symptom onset (Figures 1, 2). The authors report that while serum IgA was a potent early SARS-CoV-2 neutralizing agent, it was not associated with severe COVID-19 disease. They suggest that IgA-mediated mucosal immunity is a major defense mechanism against SARS-CoV-2 that can reduce the infectivity of mucosal secretions and viral transmission (Figure 3) and that this finding might contribute to the development of specific IgA-based vaccines to SARS-CoV-2.

ABSTRACT

Humoral immune responses are typically characterized by primary IgM antibody responses followed by secondary antibody responses associated with immune memory and comprised of of IgG, IgA and IgE. Here we measured acute humoral responses to SARS-CoV-2, including the frequency of antibody-secreting cells and the presence of SARS-CoV-2-specific neutralizing antibodies in the serum, saliva and broncho-alveolar fluid of 159 patients with COVID-19. Early SARS-CoV-2-specific humoral responses were dominated by IgA antibodies. Peripheral expansion of IgA plasmablasts with mucosal-homing potential was detected shortly after the onset of symptoms and peaked during the third week of the disease. The virus-specific antibody responses included IgG, IgM and IgA, but IgA contributed to virus neutralization to a greater extent compared with IgG. Specific IgA serum concentrations decreased notably one month after the onset of symptoms, but neutralizing IgA remained detectable in saliva for a longer time (days 49 to 73 post symptoms). These results represent a critical observation given the emerging information as to the types of antibodies associated with optimal protection against re-infection, and whether vaccine regimens should consider targeting a potent but potentially short-lived IgA response.

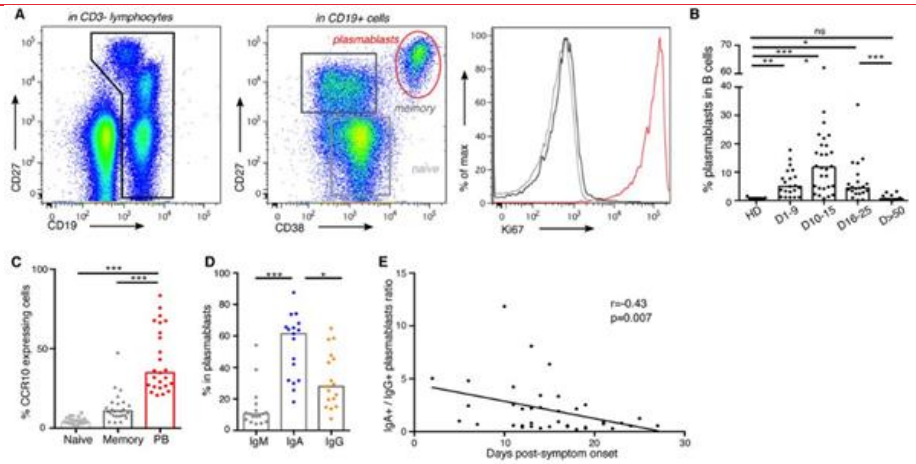

Fig. 1 Plasmablast dynamics following SARS-CoV-2 infection.
A. Representative flow cytometry analysis of B cell subpopulations in the blood of SARS-CoV-2 infected patients. Doublets and dead cells were excluded before CD3-CD19+ gating. Plasmablasts are defined as CD19lowCD27highCD38highKi67+ cells, memory B cells as CD19+CD27+IgD-Ki67- and naïve B cells as CD19+CD27-IgD+Ki67- cells B. Plasmablast frequency in B cell compartment in blood of SARS-CoV-2 infected patients (n=38, clinical characteristics in Table S1) compared with healthy donors (n=9). Histograms represent medians. P-values were calculated using Dunn's multiple comparison test (* p<0.05; ** p<0.01; *** p<0.001). C. Flow cytometry analysis of CCR10 expression in B cell subpopulations in blood of SARS-CoV-2 infected patients (n=25). Samples used in this analysis were collected from day 3 to 27 after symptom onset. Histograms represent medians. P-values were calculated using Wilcoxon test (*** p<0.001). D. Intracellular antibody expression in circulating plasmablasts in blood of SARS-CoV-2 infected patients (n=17) using flow cytometry. Samples used in this analysis were collected from day 2 to 23 after symptom onset. Histograms represent medians. P-values were calculated using Dunn's multiple comparison test (* p<0.05; *** p<0.001). E. Intracellular IgA versus IgG expression in plasmablasts according to disease duration. Each dot represents one patient. Non-parametric Spearman correlation was calculated.

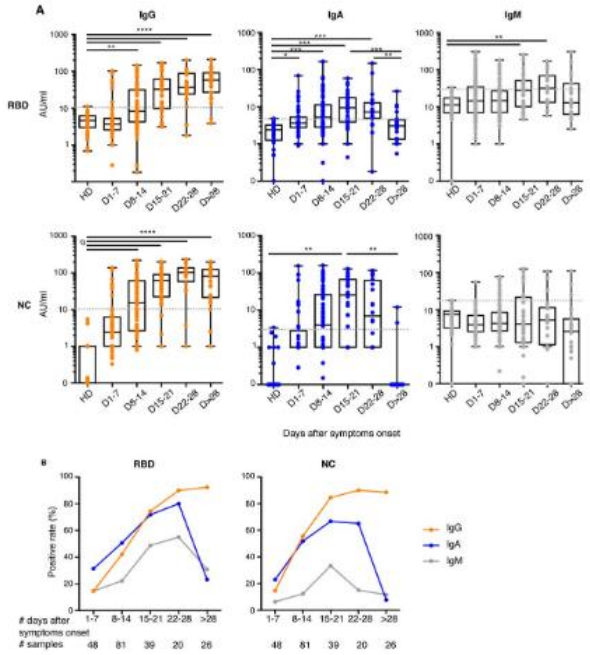

Fig. 2 Antibody responses kinetics to SARS-CoV-2 proteins.
A. Specific IgG, IgA, and IgM against spike-1 receptor binding domain (RBD) and Nucleocapsid protein (NC) were measured using photonic ring immunoassay in 132 patients (clinical characteristics detailed in Tables S2-S3). Antibody levels are expressed as arbitrary units/ml (AU/ml). Cut-off lines are represented as grey dotted lines. The boxplots show medians (middle line) and first and third quartiles and the whiskers indicate minimal and maximal values. P-value was calculated using Dunn's multiple comparison test (* p<0.05; **p<0.01: ***p<0.001; ****p<0.0001). B. Positive rates of specific serum IgG, IgA, and IgM in 132 patients at different times after symptom onset, from day 1 to 78.

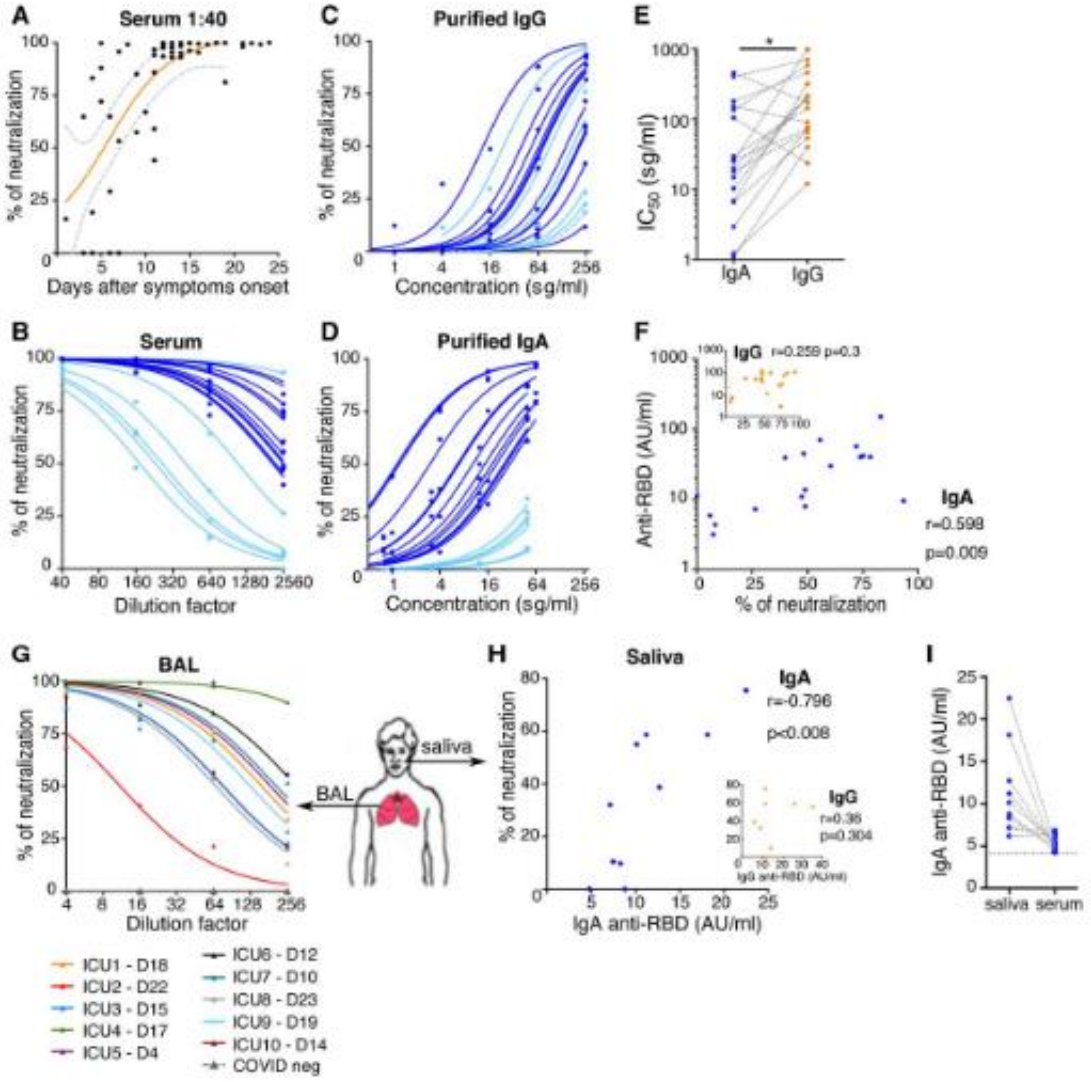

Fig. 3 Neutralizing activity of serum antibodies to SARS-CoV-2.
A. Neutralizing activity of 52 sera (dilution 1:40) from 38 SARS-CoV-2 infected patients (see clinical characteristics in Table S1) was determined using a pseudovirus neutralization assay. Orange curve represents significant sigmoidal interpolation (p=0.0082). Grey dotted curves represent 95% confidence intervals. B. Neutralizing activity of 18 sera measured by pseudovirus neutralization assay at different indicated dilutions. Samples used for this analysis were collected between day 6 and 24 after symptom onset. Light blue color corresponds to samples with low IgA neutralization potential. C. Neutralizing activity of purified IgG was measured at indicated concentrations from 18 sera collected between day 6 and day 24 post-symptom onset. Curves were drawn according to non-linear regression. Light blue color corresponds to samples with low IgA neutralization potential. D. Neutralizing activity of purified IgA from paired samples in Fig. 3C. Light blue color corresponds to samples with low IgA neutralization potential. E. Paired purified IgA and IgG IC50 values in samples tested in Figs. 3C and D. P-value was calculated using Wilcoxon test (* p<0.05). F. Comparison of serum anti-RBD IgA (main panel) or IgG (insert) levels measured by photonic ring immunoassay with neutralizing capacity of corresponding purified isotypes measured by pseudovirus neutralization assay. Spearman coefficient (r) and P-value (p) are indicated. G. Neutralizing activity of bronchoalveolar lavages (BAL) collected in 10 SARS-CoV-2 patients between day 4 and 23 after symptom onset (clinical characteristics are detailed in Table S5). Indicated BAL dilutions were tested using pseudovirus neutralization assay. Bronchoalveolar lavages obtained from SARS-CoV-2 negative patients (n=3) showed no neutralization activity (dotted grey lines). Each colored line represents one patient. H. Neutralizing activity and anti-RBD IgA levels (both tested at dilution 1:4) of saliva collected in 10 SARS-CoV-2 patients between day 49 and 73 after symptom onset. Spearman coefficient (r) and P-value (p) are indicated. I. Anti-RBD levels in paired saliva and serum from patients tested in Fig. 3H. P-value was calculated using Wilcoxon test (** p<0.01).

DYNAMIC CHANGES IN ANTI-SARS-COV-2 ANTIBODIES DURING SARS-COV-2 INFECTION AND RECOVERY FROM COVID-19

Li K, Huang B, Wu M, Zhong A, Li L, Cai Y, Wang Z, Wu L, Zhu M, Li J, Wang Z, Wu W, Li W, Bosco B, Gan Z, Qiao Q, Wu J, Wang Q, Wang S, Xia X.. Nat Commun. 2020 Nov 27;11(1):6044. doi: 10.1038/s41467-020-19943-y.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A retrospective analysis by bioinformatics and global health specialists in Jiangsu, China analyzed hospitalized patients with COVID-19 (n=1,850) and found those with mild or moderate disease developed IgG antibodies one week earlier than patients with severe disease. While spike protein and receptor-binding domain specific IgG levels were 1.5- and 2-fold higher in critically ill hospitalized patients and SARS-CoV-2 RNA-negative recovered patients, respectively, compared to those who are remained RNA-positive (Figure 2). These data suggest earlier development of antibodies may be protective against developing severe disease; however, those who recover from more severe disease may also have higher levels of antibodies and a shorter duration of viral shedding.

ABSTRACT

Deciphering the dynamic changes in antibodies against SARS-CoV-2 is essential for understanding the immune response in COVID-19 patients. Here we analyze the laboratory findings of 1,850 patients to describe the dynamic changes of the total antibody, spike protein (S)-, receptor-binding domain (RBD)-, and nucleoprotein (N)-specific immunoglobulin M (IgM) and G (IgG) levels during SARS-CoV-2 infection and recovery. The generation of S-, RBD-, and N-specific IgG occurs one week later in patients with severe/critical COVID-19 compared to patients with mild/moderate disease, while S- and RBD-specific IgG levels are 1.5-fold higher in severe/critical patients during hospitalization. The RBD-specific IgG levels are 4-fold higher in older patients than in younger patients during hospitalization. In addition, the S- and RBD-specific IgG levels are 2-fold higher in the recovered patients who are SARS-CoV-2 RNA negative than those who are RNA positive. Lower S-, RBD-, and N-specific IgG levels are associated with a lower lymphocyte percentage, higher neutrophil percentage, and a longer duration of viral shedding. Patients with low antibody levels on discharge might thereby have a high chance of being tested positive for SARS-CoV-2 RNA after recovery. Our study provides important information for COVID-19 diagnosis, treatment, and vaccine development.

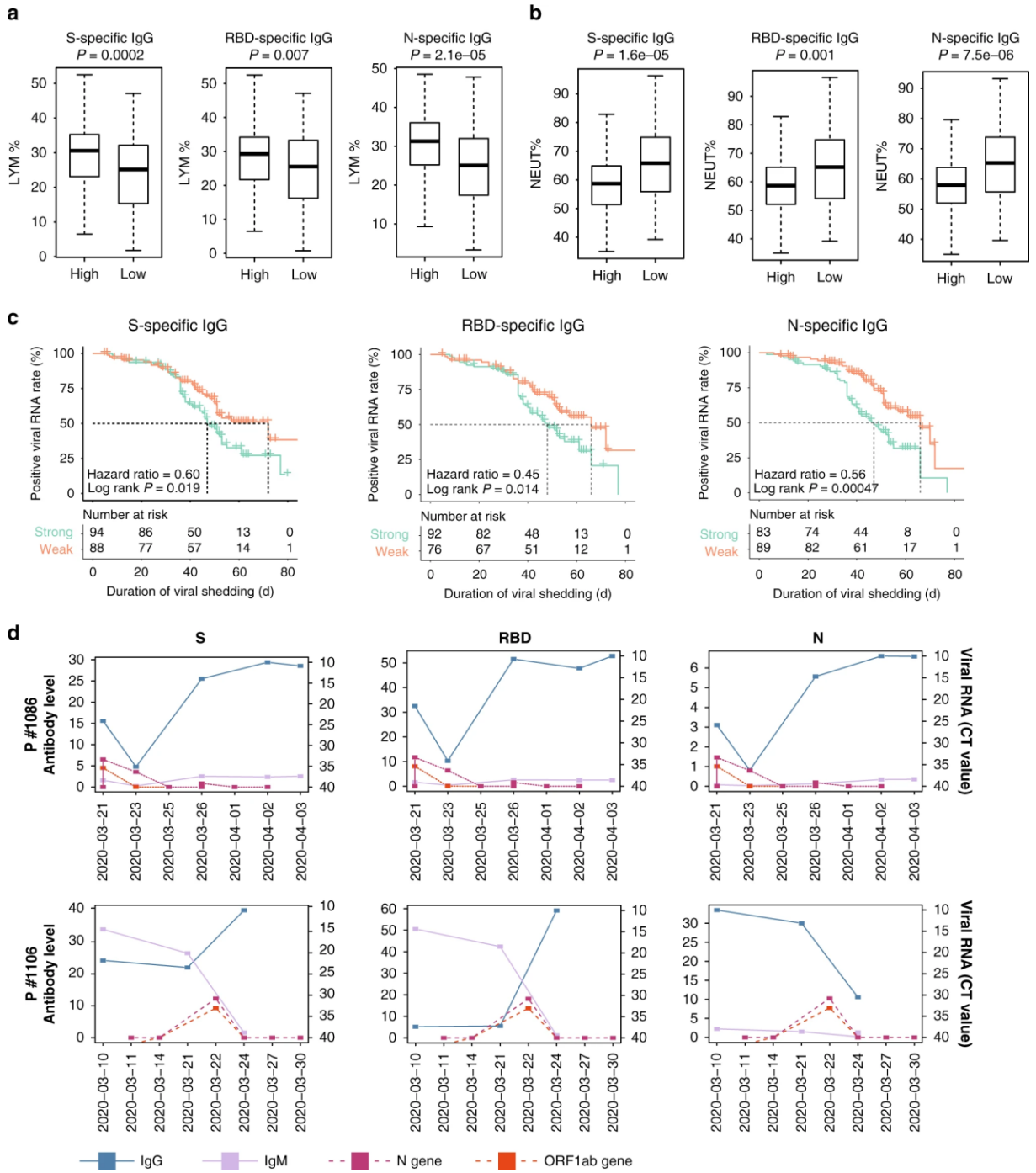

Figure 2. The percentage of lymphocytes (a) and neutrophils (b) in severe/critical COVID-19 patients with different N-, RBD-, and S-specific IgG levels. Antibody levels and lymphocyte/neutrophil percentages were measured on the same day, with 112 sets of measurements for both the low- and high-antibody groups. Horizontal lines in the boxplots represent the median, the lower, and the upper hinges correspond to the first and third quartiles, and the whiskers extend from the hinge up to 1.5 times the interquartile range from the hinge. P values were calculated with a two-sided Wilcoxon rank-sum test. c Kaplan–Meier analysis of the viral shedding time in patients with strong and weak antibody responses. The X axis represents the duration of viral shedding (days). The Y axis represents the positive rate of viral RNA. P values were calculated with the log-rank test. d The dynamic changes in antibody levels and virus RNA load in Patients #1086 and #1106. The X axis represents the detection date. The Y axis on the left represents the antibody level, and the Y axis on the right represents the cycle threshold (CT) value of PCR for the detection of viral RNA load. A CT value <40 was defined as SARS-CoV-2 viral positive. Blue dots represent IgG levels, purple dots represent IgM levels. The ORF1ab and N genes of SARS-CoV-2 were represented as pink and orange dots, respectively.

MOUSE MODEL OF SARS-COV-2 REVEALS INFLAMMATORY ROLE OF TYPE I INTERFERON SIGNALING

Israelow B, Song E, Mao T, Lu P, Meir A, Liu F, Alfajaro MM, Wei J, Dong H, Homer RJ, Ring A, Wilen CB, Iwasaki A.. J Exp Med. 2020 Dec 7;217(12):e20201241. doi: 10.1084/jem.20201241.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A group of physicians from Yale University developed a new mouse model (with patient-derived virus in mice of diverse genetic backgrounds) to study infection, replication, pathogenesis, and protection of SARS-CoV-2 based on adeno-associated virus (AAV)–mediated expression of hACE2 (human entry receptor angiotensin-converting enzyme 2, Figure 1). Overall, this new mouse model provides a new, powerful tool for detailed investigation of SARS-CoV2 pathogenesis and will allow scientists to identify key factors in anti–SARS-CoV-2 immunity while also reducing costs and time.

SUMMARY

This discovery is especially significant because previous laboratory mouse models were unable to be infected by SARS-CoV-2 due to "the virus's inability to use the mouse orthologue of its hACE2." With this new mouse model, they found that by 7 days post-infection, mice developed SARS-CoV-specific IgG, neutralizing antibodies, and gene signatures of acute interferon-stimulated genes cluster most closely with a type I IFN (Interferon) response, which is similar to lung samples of COVID-19 patients.

ABSTRACT

Severe acute respiratory syndrome-coronavirus 2 (SARS-Cov-2) has caused over 13,000,000 cases of coronavirus disease (COVID-19) with a significant fatality rate. Laboratory mice have been the stalwart of therapeutic and vaccine development; however, they do not support infection by SARS-CoV-2 due to the virus's inability to use the mouse orthologue of its human entry receptor angiotensin-converting enzyme 2 (hACE2). While hACE2 transgenic mice support infection and pathogenesis, these mice are currently limited in availability and are restricted to a single genetic background. Here we report the development of a mouse model of SARS-CoV-2 based on adeno-associated virus (AAV)-mediated expression of hACE2. These mice support viral replication and exhibit pathological findings found in COVID-19 patients. Moreover, we show that type I interferons do not control SARS-CoV-2 replication in vivo but are significant drivers of pathological responses. Thus, the AAV-hACE2 mouse model enables rapid deployment for in-depth analysis following robust SARS-CoV-2 infection with authentic patient-derived virus in mice of diverse genetic backgrounds.

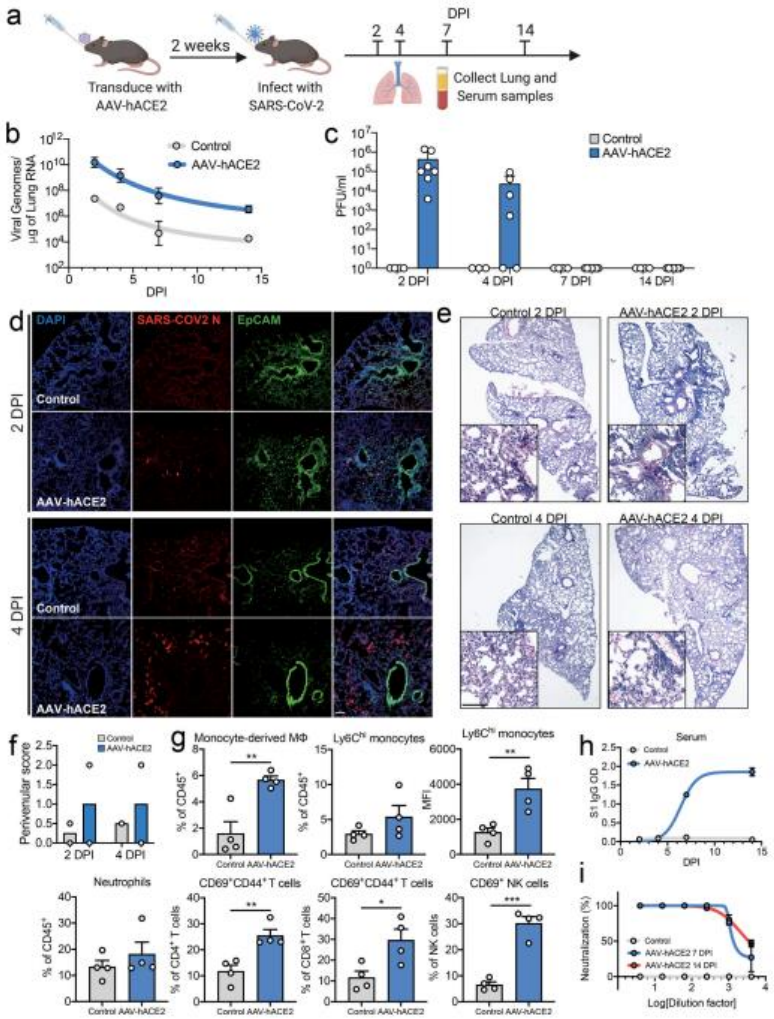

Figure 1

(a) Schematic of experimental plans. C57BL/6J mice were transduced intra-tracheally with an AAV coding for hACE2 (AAV-hACE2) or control (AAV-GFP or PBS) and infected with SARS-CoV-2 2 weeks after. Lung and blood samples were collected at days 2, 4, 7, and 14 for analysis.
(b) Viral RNA from lung homogenates were measured using quantitative PCR against SARS-CoV-2.
(c) Viral titers from lung homogenates were performed by plaque assay on VeroE6 cells (AAV-hACE2 values noted as mean ± SEM from three independent experiments; n = 7 at 2 and 14 DPI; n = 6 at 4 and 7 DPI. Control values noted as mean ± SEM from two independent experiments; n = 4 at 2, 7, and 14 DPI; n = 3 at 4 DPI).
(d) Frozen lung tissue was stained for SARS-CoV-2 N protein (red) and epithelial cells (EpCAM, green).
(e) Fixed lung tissue was paraffin-embedded and stained with H&E. Magnified panels highlight leukocyte infiltration and perivenular inflammation.
(f) Images from panel e were scored by a pulmonary pathologist for perivenular inflammation (n = 2).
(g) At 2 DPI, single-cell suspensions of lung were analyzed by flow cytometry. Data are shown as frequency of CD45+ cells (monocyte-derived macrophages, Ly6Chi monocytes, and neutrophils), frequency of parent cells (CD44+CD69+CD4+ T cells, CD44+CD69+CD8+
T cells, and CD69+ NK cells), or mean fluorescence intensity of CD64 (Ly6Chi monocytes; AAV-hACE2 and control values noted as mean ± SEM from two independent experiments, n = 4).
(h) Serum antibodies were measured against spike protein using an ELISA. (i) Day 7 and 14 sera from panel h were used to perform a PRNT on VeroE6 cells incubated with SARS-CoV-2 (AAV-hACE2 noted as mean ± SEM from two independent experiments, n = 4; control value, n = 1). P values were calculated by two-tailed unpaired Student's t test. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$. Scale bars, 100 µm.

MANAGEMENT

ACUTE CARE

CORONARY CALCIUM SCORING ASSESSED ON NATIVE SCREENING CHEST CT IMAGING AS PREDICTOR FOR OUTCOME IN COVID-19: AN ANALYSIS OF A HOSPITALIZED GERMAN COHORT

Zimmermann GS, Fingerle AA, Müller-Leisse C, Gassert F, von Schacky CE, Ibrahim T, Laugwitz KL, Geisler F, Spinner C, Haller B, Makowski MR, Nadjiri J.. PLoS One. 2020 Dec 30;15(12):e0244707. doi: 10.1371/journal.pone.0244707. eCollection 2020.

Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A retrospective cohort study conducted at the University of Munich by a team of internal medicine and radiology specialists found the coronary artery calcification (CAC) score to be a significant prognostic indicator in SARS-CoV-2-infected patients (n=109). Authors found the median CAC to be 140 [IQR 1–1165] in patients with critical COVID-19, and 160 [IQR: 88–562] in patients with fatal outcome. Authors note limitations due to retrospective design and small sample size, however, these findings suggest that Coronary Artery Disease is significantly associated with an adverse clinical outcome in COVID-19.

ABSTRACT

BACKGROUND: Since the outbreak of the COVID-19 pandemic, a number of risk factors for a poor outcome have been identified. Thereby, cardiovascular comorbidity has a major impact on mortality. We investigated whether coronary calcification as a marker for coronary artery disease (CAD) is appropriate for risk prediction in COVID-19. METHODS: Hospitalized patients with COVID-19 (n = 109) were analyzed regarding clinical outcome after native computed tomography (CT) imaging for COVID-19 screening. CAC (coronary calcium score) and clinical outcome (need for intensive care treatment or death) data were calculated following a standardized protocol. We defined three endpoints: critical COVID-19 and transfer to ICU, fatal COVID-19 and death, composite endpoint critical and fatal COVID-19, a composite of ICU treatment and death. We evaluated the association of clinical outcome with the CAC. Patients were dichotomized by the median of CAC. Hazard ratios and odds ratios were calculated for the events death or ICU or a composite of death and ICU. RESULTS: We observed significantly more events for patients with CAC above the group's median of 31 for critical outcome (HR: 1.97[1.09,3.57], p = 0.026), for fatal outcome (HR: 4.95[1.07,22.9], p = 0.041) and the composite endpoint (HR: 2.31[1.28,4.17], p = 0.0056. Also, odds ratio was significantly increased for critical outcome (OR: 3.01 [1.37, 6.61], p = 0.01) and for fatal outcome (OR: 5.3 [1.09, 25.8], p = 0.02). CONCLUSION: The results indicate a significant association between CAC and clinical outcome in COVID-19. Our data therefore suggest that CAC might be useful in risk prediction in patients with COVID-19.

CRITICAL CARE

ASSOCIATION BETWEEN OXYGEN SATURATION/FRACTION OF INHALED OXYGEN AND MORTALITY IN PATIENTS WITH COVID-19 ASSOCIATED PNEUMONIA REQUIRING OXYGEN THERAPY

Choi KJ, Hong HL, Kim EJ.. Tuberc Respir Dis (Seoul). 2020 Dec 28. doi: 10.4046/trd.2020.0126. Online ahead of print.

Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A retrospective cohort study from a group of South Korean Internists analyzed 59 hospitalized COVID-19 patients in hypoxic respiratory failure (Figure 1), and found that the SpO2:FiO2 (SF ratio) was predictive of ARDS occurrence ($p < .001$) (Figure 2). Results also demonstrated that the SF ratio at exacerbation (HR, 0.916; 95% CI, 0.846-0.991; P = 0.029) and National Early Warning Score (NEWS) (HR, 1.277; 95% CI, 1.010-1.615; P = 0.041) were significant predictors of mortality (Figure 3). These findings are clinically significant because predicting development of ARDS and mortality allows physicians to effectively triage and treat the highest risk patients. Additionally, the SF ratio has many advantages over the traditionally used P:F ratio (PaO2:FiO2) during the COVID-19 pandemic because it does not require measurement of arterial blood gas, thus conserving valuable time and resources.

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) can manifest from asymptomatic to acute respiratory distress syndrome (ARDS). COVID-19 associated pneumonia develops into ARDS due to rapid progression of hypoxia. Although arterial blood gas analysis (ABGA) should be implemented to confirm this deterioration, it is not easy to obtain such tests in the COVID-19 environment. Therefore, this study was conducted to determine whether oxygen saturation (SpO2) and SpO2/fraction of inhaled oxygen (FiO2) (SF ratio) predicts ARDS and mortality. Methods: This was a retrospective cohort study that enrolled COVID-19 pneumonia patients requiring oxygen therapy from Feb 2020 to May 2020. Of 100 COVID-19 pneumonia cases, we compared 59 cases of pneumonia requiring oxygen, divided into ARDS and non-ARDS pneumonia requiring oxygen. The factors affecting mortality were investigated. Results: At the time of admission, the SpO2, FiO2, and SF ratios of the ARDS group were significantly different from those of the non-ARDS pneumonia requiring oxygen support group (P <0.001, respectively). With respect to predicting occurrence of ARDS, the SF ratio on admission and the SF ratio at exacerbation showed an overall area under the curve of 85.7% and 88.8% (P < 0.001, respectively). Multivariate Cox regression analysis identified the SF ratio at exacerbation (HR, 0.916; 95% CI, 0.846-0.991; P = 0.029) and National Early Warning Score (NEWS) (HR, 1.277; 95% CI, 1.010-1.615; P = 0.041) as significant predictors of mortality. Conclusions: The SF ratio on admission and the SF ratio at exacerbation can predict occurrence of ARDS. The SF ratio at exacerbation and NEWS has a significant effect on mortality.

FIGURES

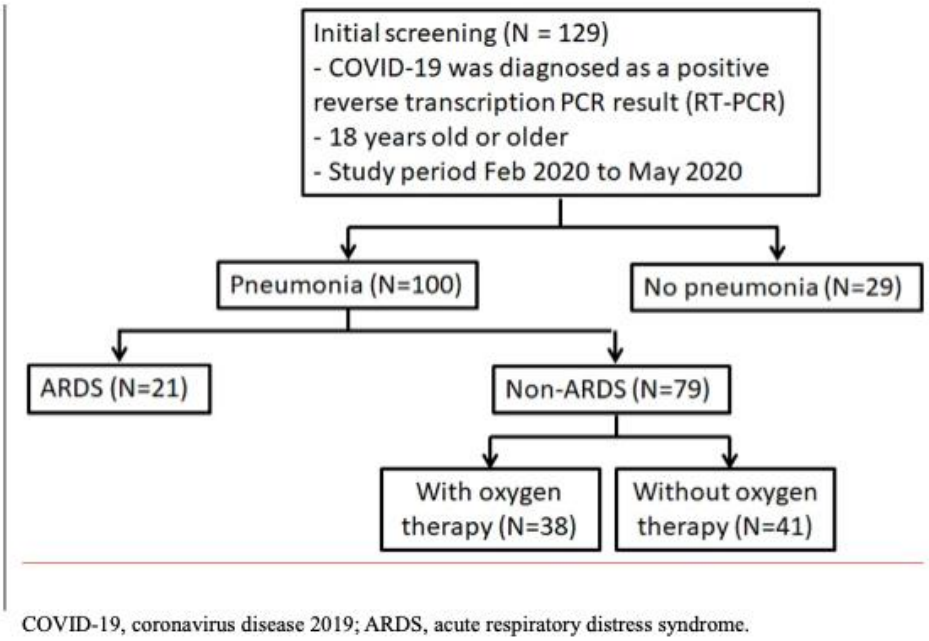

Figure 1. Flow chart for the study. A total of 129 patients aged ≥ 18 years were diagnosed as COVID- 19-positive by reverse transcription polymerase chain reaction. Among them, 100 cases (77.5%) had COVID-19-associated pneumonia. Of these, 21 cases (16.3%) had acute respiratory distress syndrome (ARDS), and 79 (61.2%) had non-ARDS pneumonia. Among the 79 cases of non-ARDS pneumonia, 38 (29.5%) required oxygen support. Data from 21 cases in the ARDS group and 38 cases in the non- ARDS requiring oxygen support group were compared.

	ARDS N=21	Non-ARDS pneumonia requiring oxygen N= 38	*P*-value
SpO_2 on admission, %	91.0 (88.0–92.0)	95.0 (92.0–96.0)	<0.001*
FiO_2 on admission	0.32 (0.21–0.60)	0.21 (0.21–0.21)	<0.001*
PaO_2 on admission, mmHg	78.7 (54.5–85.7) (n=11)	83.6 (66.1–110.0) (n=5)	0.583
PF ratio on admission	135.8 (111.3–262.2) (n=11)	398.1 (314.8–519.4) (n=5)	0.013*
SF ratio on admission	287.5 (135.0–433.3)	452.4 (438.1–457.1)	<0.001*
Time from start oxygen therapy to maintain to the highest FiO_2, hours	16.0 (9.5–46.0) (n=21)	27.0 (7.0–92.0) (n=20)	0.569
SpO_2 at exacerbation, %	94.0 (90.0–98.0) (n=21)	96.5 (93.0–98.0) (n=20)	0.305
FiO_2 at exacerbation	0.80 (0.70–0.90) (n=21)	0.30 (0.28–0.40) (n=20)	<0.001*
PaO_2 at exacerbation, mmHg	66.8 (55.1–84.0) (n=19)	56.1 (52.6–59.6) (n=2)	0.343
PF ratio at exacerbation	118.3 (78.5–153.0) (n=19)	179.5 (146.1–212.9) (n=2)	0.238
SF ratio at exacerbation	111.1 (102.2–139.0) (n=21)	319.0 (247.5–346.4) (n=20)	<0.001*
Duration of oxygen therapy, days	24.0 (13.0–40.0)	19.0 (12.5–23.5)	0.181

Values are presented as the median (interquartile range) or as number (%).

*Statistically significant difference between the ARDS and non-ARDS pneumonia requiring oxygen support groups; $P < 0.05$ (Mann–Whitney U-test).

ARDS, acute respiratory distress syndrome; SpO_2, oxygen saturation by pulse oximetry; FiO_2, fraction of inhaled oxygen; PaO_2, partial pressure of oxygen in arterial blood; PF ratio, PaO_2/FiO_2 ratio; SF ratio, SpO_2/FiO_2 ratio.

Figure 2. Risk factors as hazard ratios for mortality in 59 patients with coronavirus disease 2019-associated pneumonia.

	Univariate, unadjusted		Multivariate*	
	HRs (95% CIs)	*P*-value	HRs (95% CIs)	*P*-value
Sex	2.222 (0.615–8.026)	0.223		
NEWS	1.388 (1.145–1.684)	0.001	1.277 (1.010-1.615)	0.041
SF ratio on admission	0.992 (0.987–0.997)	0.001		
SF ratio at exacerbation	0.962 (0.923–1.002)	0.065	0.916 (0.846-0.991)	0.029
Neutrophil count	1.073 (1.001–1.150)	0.046	1.082 (0.995-1.177)	0.066
Monocyte count	0.763 (0.609-0.957)	0.019		
LDH	1.002 (0.999–1.006)	0.140	0.994 (0.998-1.000)	0.050
Sodium	0.813 (0.728–0.909)	<0.001		

*Sex, NEWS, SF ratio on admission, SF ratio at exacerbation, segmented neutrophil, monocyte, LDH, and sodium.

CIs, confidence intervals; HRs, hazard ratios; NEWS, National Early Warning Score; SF ratio, oxygen saturation by pulse oximetry/fraction of inhaled oxygen ratio; LDH, lactate dehydrogenase.

Figure 3. Risk factors as hazard ratios for mortality in 59 patients with coronavirus disease 2019-associated pneumonia

NEUROLOGY

HIGH PREVALENCE OF DEEP VENOUS THROMBOSIS IN NON-SEVERE COVID-19 PATIENTS HOSPITALIZED FOR A NEUROVASCULAR DISEASE

Rouyer O, Pierre-Paul IN, Balde AT, Jupiter D, Bindila D, Geny B, Wolff V.. Cerebrovasc Dis Extra. 2020 Dec 7;10(3):174-180. doi: 10.1159/000513295. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

This prospective study from Strasbourg University Hospital, France evaluates 13 patients with non-severe COVID-19 and concurrent neurovascular disease for deep venous thrombosis (DVT) via doppler ultrasound scanning (DUS) of the lower limbs. Results showed that despite thromboprophylaxis, the prevalence of asymptomatic DVT was 38.5%. The authors thus advocate for the use of bedside DUS to identify DVT in patients with COVID-19 given that D-dimer, the classic marker of DVT, has been shown to correlate with COVID-19 severity and may be elevated in this population regardless of coagulable state.

ABSTRACT

INTRODUCTION: Severe SARS-CoV-2 infection induces COVID-19 along with venous thromboembolic occurrences particularly in intensive care units. For non-severe COVID-19 patients affected by neurovascular diseases, the prevalence of deep venous thrombosis (DVT) is unknown. The aim of our study was to report data obtained after systematic Doppler ultrasound scanning (DUS) of lower limbs in such patients. METHODS: Between March 20 and May 2, 2020, the deep venous system of 13 consecutive patients diagnosed with neurovascular diseases and non-severe COVID-19 was investigated with a systematic bedside DUS. RESULTS: Thirteen patients were enrolled in the study including 9 acute ischaemic strokes, 1 occlusion of the ophthalmic artery, 1 transient ischaemic attack, 1 cerebral venous thrombosis and 1 haemorrhagic stroke. On admission, the median National Institute of Health Stroke Scale (NIHSS) score was of 6 (IQR, 0-20). During the first week after admission, and despite thromboprophylaxis, we found a prevalence of 38.5% of asymptomatic calves' DVT (n = 5). One patient developed a symptomatic pulmonary embolism and 2 other patients died during hospitalization. The outcome was positive for the other patients with a discharge median NIHSS score of 1 (IQR, 0-11). DISCUSSION/CONCLUSION: Despite thromboprophylaxis, systematic bedside DUS showed a high prevalence (38.5%) of asymptomatic DVT in non-severe COVID-19 patients suffering from a neurovascular disease. In the absence of a reliable marker of DVT, we suggest that this non-invasive investigation could be an interesting tool to monitor peripheral venous thrombotic complications in such patients.

VIRAL CULTURES FOR COVID-19 INFECTIOUS POTENTIAL ASSESSMENT - A SYSTEMATIC REVIEW

Jefferson T, Spencer EA, Brassey J, Heneghan C.. Clin Infect Dis. 2020 Dec 3:ciaa1764. doi: 10.1093/cid/ciaa1764. Online ahead of print.

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

BLUF

A review, conducted at University of Oxford, analyzes 29 studies from before September 10, 2020 that attempted to culture SARS-CoV-2 to estimate potential or observed infectivity (Figure 1). The authors state an apparent correlation between length of time between specimen collection and test, cycle threshold, and symptom severity. Furthermore, they found cycle threshold to be a good surrogate for viral load as it correlated with increased infection of Vero E6 cells by SARS-CoV-2. Inconsistency in culturing methods limit study power, highlighting the need for standardization of this process.

ABSTRACT

OBJECTIVE: to review the evidence from studies relating SARS-CoV-2 culture with the results of reverse transcriptase polymerase chain reaction (RT-PCR) and other variables which may influence the interpretation of the test, such as time from symptom onset. METHODS: We searched LitCovid, medRxiv, Google Scholar and the WHO Covid-19 database for Covid-19 to 10 September 2020. We included studies attempting to culture or observe SARS-CoV-2 in specimens with RT-PCR positivity. Studies were dual extracted and the data summarised narratively by specimen type. Where necessary we contacted corresponding authors of included papers for additional information. We assessed quality using a modified QUADAS 2 risk of bias tool. RESULTS: We included 29 studies reporting attempts at culturing, or observing tissue infection by, SARS-CoV-2 in sputum, nasopharyngeal or oropharyngeal, urine, stool, blood and environmental specimens. The quality of the studies was moderate with lack of standardised reporting. The data suggest a relationship between the time from onset of symptom to the timing of the specimen test, cycle threshold (Ct) and symptom severity. Twelve studies reported that Ct values were significantly lower and log copies higher in specimens producing live virus culture. Two studies reported the odds of live virus culture reduced by approximately 33% for every one unit increase in Ct. Six of eight studies reported detectable RNA for longer than 14 days but infectious potential declined after day 8 even among cases with ongoing high viral loads. Four studies reported viral culture from stool specimens. CONCLUSION: Complete live viruses are necessary for transmission, not the fragments identified by PCR. Prospective routine testing of reference and culture specimens and their relationship to symptoms, signs and patient co-factors should be used to define the reliability of PCR for assessing infectious potential. Those with high cycle threshold are unlikely to have infectious potential.

FIGURES

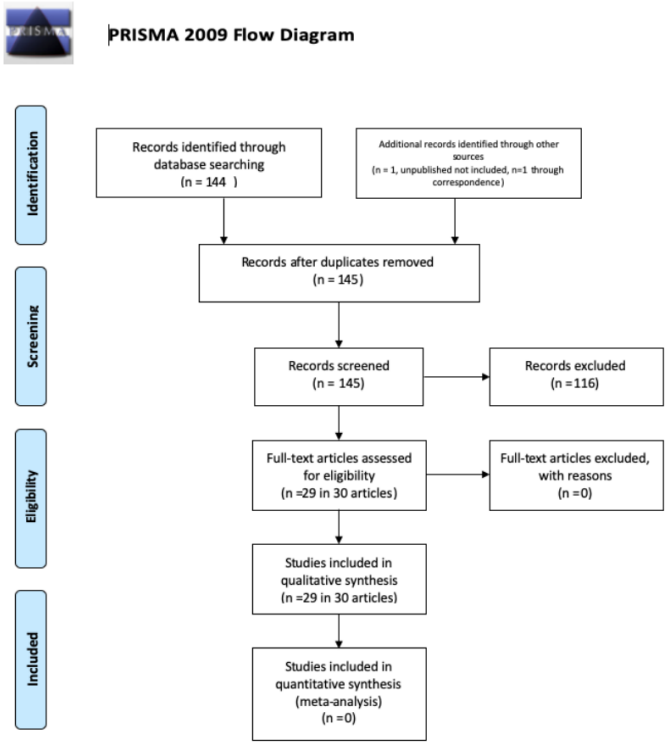

Figure 1. PRISMA flow diagram

OPTIMAL CYCLE THRESHOLDS FOR COVID-19 SCREENING - ROC-BASED METHODS HIGHLIGHT BETWEEN-STUDY DIFFERENCES

Hirschfeld G, von Glischinski M, Thiele C.. Clin Infect Dis. 2020 Dec 23:ciaa1883. doi: 10.1093/cid/ciaa1883. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

After reviewing four studies, German researchers propose using receiver-operating-characteristic based methods to determine cut off scores for cycle thresholds (CT) of RT-PCR-based COVID-19 diagnostic tests. Two of the studies indicate the optimal range of CT scores to be 26 to 37 (Figure 1), while the other two studies provide optimal points at 29 and 31. These findings are clinically relevant because incorporating CT values into RT-PCR test interpretation may improve the accuracy and predictive value.

FIGURES

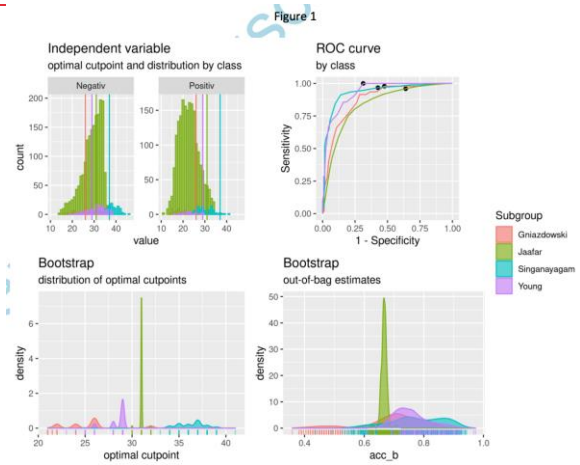

Figure 1. Optimal cut off scores for cycle thresholds

CLINICAL AND EPIDEMIOLOGIC EVALUATION OF INCONCLUSIVE COVID-19 PCR RESULTS USING A QUANTITATIVE ALGORITHM

Yang S, Stanzione N, Uslan DZ, Garner OB, de St Maurice A.. Am J Clin Pathol. 2020 Dec 4:aqaa251. doi: 10.1093/ajcp/aqaa251. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Infectious disease physicians from UCLA analyzed inconclusive SARS-CoV-2 RT-PCR tests (18 cases from a CDC assay and 51 from the TaqPath assay) to determine rates of false positive tests and to create an algorithm to make determinations on inconclusive tests (Table 1). The authors found that the rate of false positives in the inconclusive tests ranged between 14-39% (Table 2) and that lowering the cycle threshold cutoff from 40 to 37 in the TaqPath assay significantly lowered the false-positive rate. This study demonstrates that there is a significant rate of false positive RT-PCR SARS-CoV-2 tests, which can be corrected through additional testing and changing of cycle thresholds, though this may make false negative results more likely.

ABSTRACT

OBJECTIVES: The inconclusive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) result causes confusion and delay for infection prevention precautions and patient management. We aimed to develop a quantitative algorithm to assess and interpret these inconclusive results. METHODS: We created a score-based algorithm by combining laboratory, clinical, and epidemiologic data to evaluate 69 cases with inconclusive coronavirus disease 2019 (COVID-19) PCR results from the Centers for Disease Control and Prevention (CDC) assay (18 cases) and the TaqPath assay (51 cases). RESULTS: We determined 5 (28%) of 18 (CDC assay) and 20 (39%) of 51 (TaqPath assay) cases to be false positive. Lowering the cycle threshold cutoff from 40 to 37 in the TaqPath assay resulted in a dramatic reduction of the false-positive rate to 14%. We also showed testing of asymptomatic individuals is associated with a significantly higher probability of having a false-positive result. CONCLUSIONS: A substantial percentage of inconclusive SARS-CoV-2 PCR results can be false positive, especially among asymptomatic patients. The quantitative algorithm we created was shown to be effective and could provide a useful tool for clinicians and hospital epidemiologists to interpret inconclusive COVID-19 PCR results and provide clinical guidance when additional PCR or antibody test results are available.

FIGURES

Parameter	Result	Score	Rationale
Symptoms consistent with COVID-19	Yes	1	Nonspecific symptom is a weak support for COVID-19.
	No or unclear	0	
Symptoms highly suspected for COVID-19	Yes	3	More specific symptom is a stronger support for COVID-19.
	No or unclear	0	
Sick contact	Yes	1	Sick contact alone is a weak support for COVID-19.
	No or unclear	0	
Additional PCR test results	Positive	5	An additional inconclusive PCR result is a moderate support for COVID-19.
	Inconclusive	2	
	Negative or NA	0	
Antibody (IgG) test results	Positive	4	A positive antibody result is a strong support for COVID-19.
	Negative or unclear	0	

COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; NA, not available; PCR, polymerase chain reaction.
[a]See the definition of each parameter in the text. Score interpretation: >5: confirmed positive; 3-5: most likely true positive; <3: most likely false positive.

Table 1. Scoring Scheme for Case Review

Assay	Factor	Confirmed Positive, No. (%)	Most Likely True Positive, No. (%)	Confirmed and Most Likely True Positive, No. (%)	Most Likely False Positive, No. (%)	χ^2 Statistic	*P* Value
Combined cases	Total cases (*n* = *69*)	41 (60)	3 (4)	*44* (64)	*25* (36)		
	Asymptomatic (n = 16)	3	0	3 **[7]**	13 **[52]**	18.272	<.001[b]
CDC assay	Total cases (*n* = *18*)	13 (72)	0 (0)	***13*** (72)	***5*** (28)		
	Asymptomatic (n = 5)	2	0	2 **[15]**	3 **[60]**	3.583	.058
TaqPath assay (Ct cutoff = 40)	Total cases (*n* = *51*)	28 (55)	3 (6)	***31*** (61)	***20*** (39)		
	Asymptomatic (n = 11)	1	0	1 **[3]**	10 **[50]**	15.723	<.001[b]
	Preoperative (n = 12)	2	0	2 **[6]**	10 **[50]**	14.373	<.001[b]
	HCW (n = 13)	6	2	8 **[26]**	5 **[25]**	0.004	.949
TaqPath assay (Ct cutoff = 37)	Total cases (*n* = *28*)	21 (75)	3 (6)	***24*** (86)	***4*** (14)		
	Asymptomatic (n = 2)	0	0	0 **[0]**	2 **[50]**	12.923	.001[b]
	Preoperative (n = 5)	2	0	2 **[8]**	3 **[75]**	10.388	.001[b]
	HCW (n = 6)	3	2	5 **[21]**	1 **[25]**	0.035	.851

CDC, Centers for Disease Control and Prevention; HCW, health care worker.
[a]Percentages in parentheses (%) were calculated using the overall total case number (italicized) as the denominator. Percentages in brackets **[%]** were calculated using the categorial total case number (bolded) as the denominator.
[b]Statistically significant.

Table 2. Analysis of Cases With Inconclusive PCR Results

HYDROXYCHLOROQUINE WITH OR WITHOUT AZITHROMYCIN IN MILD-TO-MODERATE COVID-19

Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, Junqueira DLM, de Barros E Silva PGM, Tramujas L, Abreu-Silva EO, Laranjeira LN, Soares AT, Echenique LS, Pereira AJ, Freitas FGR, Gebara OCE, Dantas VCS, Furtado RHM, Milan EP, Golin NA, Cardoso FF, Maia IS, Hoffmann Filho CR, Kormann APM, Amazonas RB, Bocchi de Oliveira MF, Serpa-Neto A, Falavigna M, Lopes RD, Machado FR, Berwanger O; Coalition Covid-19 Brazil I Investigators.. N Engl J Med. 2020 Nov 19;383(21):2041-2052. doi: 10.1056/NEJMoa2019014. Epub 2020 Jul 23.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

A multicenter randomized controlled trial conducted by HCor Research Institute in Sao Paulo, Brazil across 55 hospitals in Brazil included 667 adult patients hospitalized with suspected or confirmed mild-moderate COVID-19 (receiving < 4L/min O2) with less than 14 days since symptom onset (Table 1) who received: standard care, standard care plus hydroxychloroquine 400 mg twice daily, or standard care plus hydroxychloroquine 400 mg twice daily plus azithromycin 500 mg once daily for 7 days. It was determined that a higher ordinal score (worse prognosis) at 15 days was not affected by hydroxychloroquine or hydroxychloroquine plus azithromycin treatment (Figure 1) and did not change with amount of time since randomization (Figure 2). This suggests use of hydroxychloroquine, with or without azithromycin, in mild-to-moderate COVID-19 infection has no effect on improving clinical status at 15 days compared to standard care.

ABSTRACT

BACKGROUND: Hydroxychloroquine and azithromycin have been used to treat patients with coronavirus disease 2019 (Covid-19). However, evidence on the safety and efficacy of these therapies is limited. METHODS: We conducted a multicenter, randomized, open-label, three-group, controlled trial involving hospitalized patients with suspected or confirmed Covid-19 who were receiving either no supplemental oxygen or a maximum of 4 liters per minute of supplemental oxygen. Patients were randomly assigned in a 1:1:1 ratio to receive standard care, standard care plus hydroxychloroquine at a dose of 400 mg twice daily, or standard care plus hydroxychloroquine at a dose of 400 mg twice daily plus azithromycin at a dose of 500 mg once daily for 7 days. The primary outcome was clinical status at 15 days as assessed with the use of a seven-level ordinal scale (with levels ranging from one to seven and higher scores indicating a worse condition) in the modified intention-to-treat population (patients with a confirmed diagnosis of Covid-19). Safety was also assessed. RESULTS: A total of 667 patients underwent randomization; 504 patients had confirmed Covid-19 and were included in the modified intention-to-treat analysis. As compared with standard care, the proportional odds of having a higher score on the seven-point ordinal scale at 15 days was not affected by either hydroxychloroquine alone (odds ratio, 1.21; 95% confidence interval [CI], 0.69 to 2.11; P = 1.00) or hydroxychloroquine plus azithromycin (odds ratio, 0.99; 95% CI, 0.57 to 1.73; P = 1.00). Prolongation of the corrected QT interval and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin, than in those who were not receiving either agent. CONCLUSIONS: Among patients hospitalized with mild-to-moderate Covid-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care. (Funded by the Coalition Covid-19 Brazil and EMS Pharma; ClinicalTrials.gov number, NCT04322123.).

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Hydroxychloroquine plus Azithromycin (N=217)	Hydroxychloroquine (N=221)	Control (N=227)	Total (N=665)
Age — yr	49.6±14.2	51.3±14.5	49.9±15.1	50.3±14.6
Male sex — no. (%)	123 (56.7)	142 (64.3)	123 (54.2)	388 (58.3)
Coexisting condition — no. (%)				
Hypertension	81 (37.3)	94 (42.5)	83 (36.6)	258 (38.8)
Diabetes	40 (18.4)	47 (21.3)	40 (17.6)	127 (19.1)
Current or former smoking	17 (7.8)	12 (5.4)	15 (6.6)	44 (6.6)
Obesity	29 (13.4)	37 (16.7)	37 (16.3)	103 (15.5)
Cancer	7 (3.2)	4 (1.8)	8 (3.5)	19 (2.9)
Heart failure	4 (1.8)	3 (1.4)	3 (1.3)	10 (1.5)
COPD	4 (1.8)	4 (1.8)	4 (1.8)	12 (1.8)
AIDS	1 (0.5)	0	3 (1.3)	4 (0.6)
Chronic renal disease	2 (0.9)	1 (0.5)	2 (0.9)	5 (0.8)
Asthma	16 (7.4)	9 (4.1)	15 (6.6)	40 (6.0)
Previous medication use — no. (%)				
Glucocorticoid	4 (1.8)	1 (0.5)	3 (1.3)	8 (1.2)
ACE inhibitor	16 (7.4)	19 (8.6)	13 (5.7)	48 (7.2)
Angiotensin II–receptor antagonist	39 (18.0)	36 (16.3)	41 (18.1)	116 (17.4)
NSAID	8 (3.7)	12 (5.4)	9 (4.0)	29 (4.4)
Randomization location — no. (%)				
Emergency department or ward	187 (86.2)	189 (85.5)	197 (86.8)	573 (86.2)
ICU	30 (13.8)	32 (14.5)	30 (13.2)	92 (13.8)
Testing for Covid-19 — no. (%)				
Positive on RT-PCR	172 (79.3)	159 (71.9)	173 (76.2)	504 (75.8)
Negative on RT-PCR or unavailable	45 (20.7)	62 (28.1)	54 (23.8)	161 (24.2)
Score on seven-level ordinal scale — no. (%)†				
3: Hospitalized and not receiving supplemental oxygen	125 (57.6)	132 (59.7)	130 (57.3)	387 (58.2)
4: Hospitalized and receiving supplemental oxygen	92 (42.4)	89 (40.3)	97 (42.7)	278 (41.8)
Use of trial medication‡				
Hydroxychloroquine — no. (%)	23 (10.6)	20 (9.0)	19 (8.4)	62 (9.3)
Azithromycin — no./total no. (%)	74/217 (34.1)	76/221 (34.4)	90/226 (39.8)	240/664 (36.1)
Median time from admission to randomization (IQR) — days	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)
Median time from symptom onset to randomization (IQR) — days	7 (5–9)	7 (5–8)	7 (4–9)	7 (5–9)

* Plus-minus values are means ±SD. The intention-to-treat population included all the patients who had undergone randomization. Information on coexisting conditions was obtained from the medical records. The values shown are based on available data. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, AIDS acquired immunodeficiency syndrome, COPD chronic obstructive pulmonary disease, ICU intensive care unit, IQR interquartile range, NSAID nonsteroidal antiinflammatory drug, and RT-PCR reverse transcriptase–polymerase chain reaction.

† Only hospitalized patients who were not receiving supplemental oxygen or who were receiving up to 4 liters per minute of supplemental oxygen were eligible for the trial. Patients who had scores on other levels of the seven-level ordinal scale were not eligible.

‡ Use of trial medication was defined as the use of hydroxychloroquine or azithromycin before randomization. Details are provided in the Supplementary Appendix.

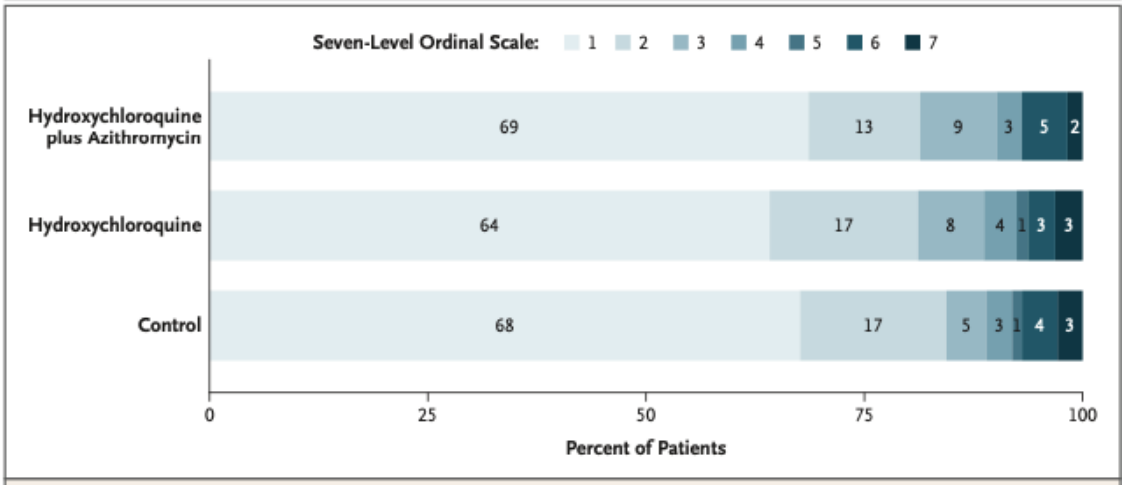

Figure 1. Status of Patients on Day 15.

The primary outcome was clinical status evaluated at 15 days according to a seven-level ordinal scale. The scores on the scale were defined as follows: a score of 1 indicated not hospitalized with no limitations on activities; 2, not hospitalized but with limitations on activities; 3, hospitalized and not receiving supplemental oxygen; 4, hospitalized and receiving supplemental oxygen; 5, hospitalized and receiving oxygen supplementation administered by a high-flow nasal cannula or noninvasive ventilation; 6, hospitalized and receiving mechanical ventilation; and 7, death. The percentages shown have been rounded to whole numbers.

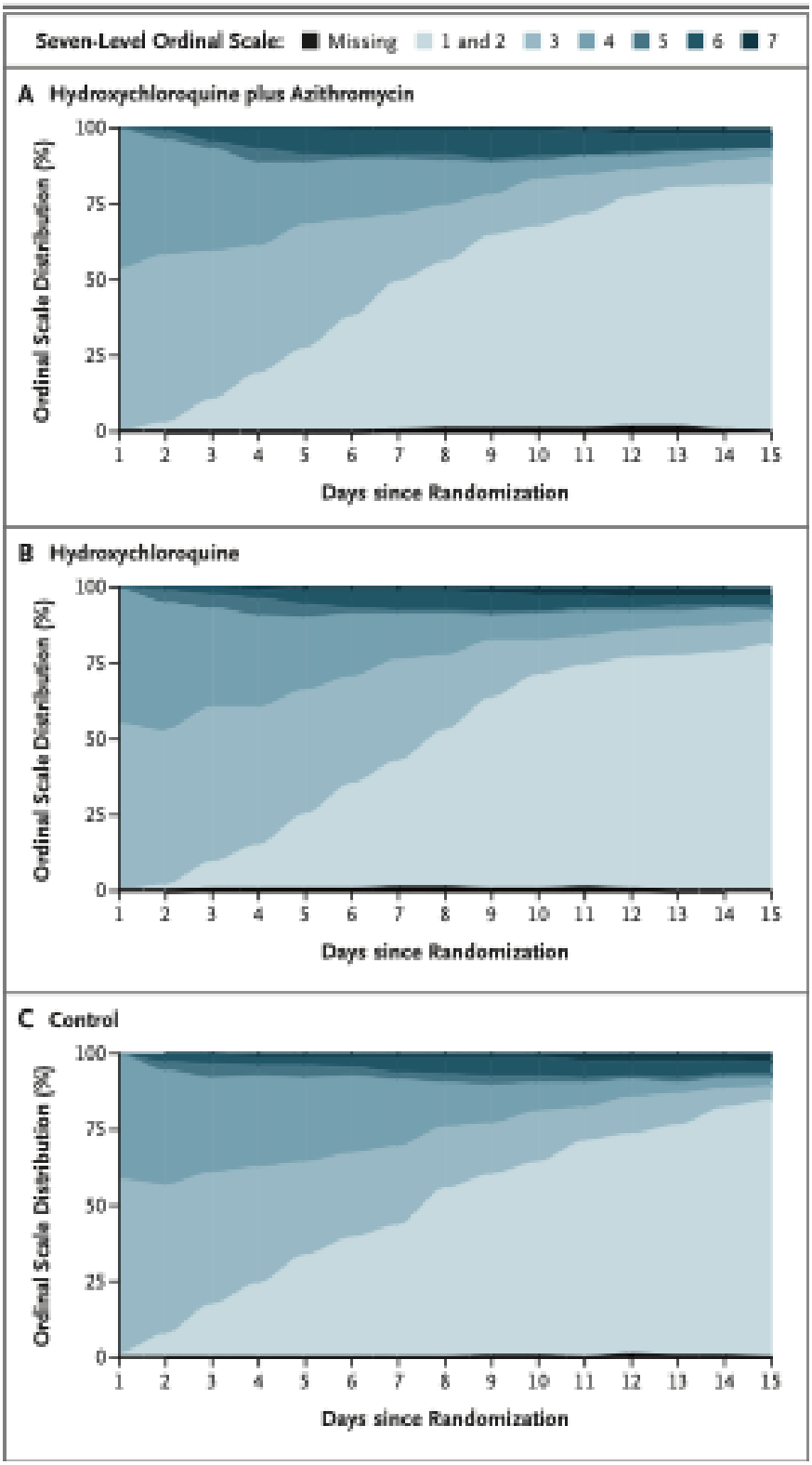

Figure 2. Distribution of the Ordinal-Scale Results over Time.

Shown is the course of ordinal-scale results as assessed over the time since randomization. However, not all levels of the seven-level scale are shown. Because data on activity limitation were not available on a daily basis for outpatients, levels 1 and 2 (i.e., the levels for patients who were not hospitalized and had no limitations on activities and for those who were not hospitalized but who had limitations on activities, respectively) were combined (equivalent to the six-level scale described in the Methods section). Thus, in this figure, levels 1 and 2 indicate not hospitalized. A total of 36 patients were discharged after a 1-day hospital stay (7 patients who had been assigned to receive hydroxychloroquine plus azithromycin, 8 in the hydroxychloroquine alone group, and 21 in the control group). Missing data are shown at the bottom of the graphs.

PSYCHOLOGICAL CONSEQUENCES OF SURVIVORS OF COVID-19 PNEUMONIA 1 MONTH AFTER DISCHARGE

Park HY, Jung J, Park HY, Lee SH, Kim ES, Kim HB, Song KH.. J Korean Med Sci. 2020 Dec 7;35(47):e409. doi: 10.3346/jkms.2020.35.e409.
Level of Evidence: 3 - Local non-random sample

BLUF

A cross-sectional study conducted at Seoul National University Hospital and National Medical Center used self-reported questionnaires, including PHQ-9, GAD-7 Scale, and Impact of Event Scale-Revised Korean version in patients (n=10) who were in the high-level isolation unit in Seoul National University Bundang Hospital between January to 31 May, 2020 one month after recovery from COVID-19 pneumonia without complications. The surveys revealed 50% reported depression during treatment and 10% reported depression and PTSD after treatment, with high-perceived stigma and previous history of psychiatric treatment correlating to higher scores for PTSD symptoms, but previous psychiatric treatment having no significant difference on depression and anxiety reporting (See Table 1). These findings suggest a low risk for post-discharge anxiety or depression among patients completely cured of COVID-19 pneumonia; however, it is important for these patients to receive psychosocial support after discharge to combat the fear of infecting others, discrimination from neighbors, and the COVID-19 associated stigma.

ABSTRACT

As the coronavirus disease 2019 (COVID-19) has rapidly spread worldwide, there are growing concerns about patients' mental health. We investigated psychological problems in COVID-19 patients assessed with self-reported questionnaires including the Patient Health Questionnaire-9, Generalized Anxiety Disorder-7 scale, and Impact of Event Scale-Revised Korean version. Ten patients who recovered from COVID-19 pneumonia without complications underwent self-reported questionnaires about 1 month after discharge. Of them, 10% reported depression and posttraumatic stress disorder (PTSD) while 50% had depression during the treatment. Perceived stigma and history of psychiatric treatment affected PTSD symptom severity, consistent with previous emerging infectious diseases. Survivors also reported that they were concerned about infecting others and being discriminated and that they chose to avoid others after discharge. Further support and strategy to minimize their psychosocial difficulties after discharge should be considered.

Table 1. Participants' demographic and clinical characteristics and mental health status at 1 month after discharge from COVID-19 pneumonia in Korea

Characteristics	Variables	Total (n = 10)	Case No.									
			1	2	3	4	5	6	7	8	9	10
Sex	Male/Female	8/2	M	M	M	F	M	M	M	M	M	F
Age, yr	Mean (SD)	62.6 (14.9)	67	81	56	63	82	60	29	55	65	68
Marriage status	Married = yes	7	Yes	Yes	Yes	Yes		Yes		Yes	Yes	
Income	> 3,500 USD/mon = yes	6	Yes		Yes			Yes	Yes	Yes	Yes	NA
Job	Employed = yes	6			Yes	Yes		Yes	Yes	Yes	Yes	
Religion	Having = yes	5		Yes		Yes	Yes				Yes	Yes
Underlying physical illness	Type of disease	6	HTN	HTN, DL	HTN, LC		HTN, CVD	CVD, DM		HTN		
Previous history of psychiatric treatment	Yes	3			Yes			Yes				Yes
Duration of hospitalization, day	Median (range)	20.9 (13–38)	13	22	19	17	15	26	15	21	23	38
Interval between follow-up visit and discharge, day	Median (range)	25.0 (13–50)	35	16	16	18	20	50	36	30	47	13
Pneumonia	Yes	10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Required oxygen supplement therapy	Yes	5		Yes				Yes		Yes	Yes	Yes
Mechanical ventilation	Yes	0										
Having a family member or an acquaintance who was infected by COVID-19	Yes	4			Yes	Yes			Yes	Yes		
Having a family member or an acquaintance who died from COVID-19	Yes	2	Yes		Yes							
Mental health status												
During admission[a]	Depression (PHQ-9)	5[b]	NA	2	20	19	17	11	11	4	4	6
	Anxiety (GAD-7)	1[c]	NA	0	10	5	8	2	6	0	0	1
Post-discharge at 1 month	Depression (PHQ-9)	1[b]	0	2	0	7	2	0	0	0	0	15
	Anxiety (GAD-7)	0[c]	0	0	0	2	0	0	0	0	0	2
	PTSD (IES-R-K)	1[d]	5	7	12	5	0	15	4	2	2	34
	Intrusion score		1	3	3	3	0	5	0	2	2	10
	Avoidance score		3	1	4	2	0	4	0	0	0	7
	Hyperarousal score		0	1	2	0	0	3	3	0	0	11
	Numbness score		1	2	3	0	0	3	1	0	0	6
Psychosocial experiences & patients' needs												
Perceived stigma regarding COVID-19		4[e]	2	6	14	8	7	14	17	9	2	21
Worry about infecting others		4		Yes	Yes			Yes		Yes		
Being discriminated against by neighbors owing to their history of COVID-19 diagnosis		4		Yes	Yes			Yes				Yes
Worry about invasion of privacy		3				Yes		Yes				Yes
Avoiding other people		3		Yes				Yes				Yes
Need for support from family members		5			Yes	Yes	Yes	Yes			Yes	
Need for support from the neighborhood		6			Yes	Yes	Yes	Yes		Yes	Yes	
Need for regular medical check-ups after discharge		5		Yes	Yes		Yes	Yes				Yes
Need for psychiatric service		3	Yes				Yes	Yes				
Need for accurate information from the government		4	Yes				Yes	Yes			Yes	

COVID-19 = coronavirus disease 2019, SD = standard deviation, PHQ-9 = Patient Health Questionnaire-9, GAD-7 = Generalized Anxiety Disorder-7, PTSD = posttraumatic stress disorder, IES-R-K = Impact of Event Scale-Revised Korean version, HTN = hypertension, DL = dyslipidemia, LC = liver cirrhosis, CVD = cardiovascular disease, DM = diabetes mellitus, NA = not available.

[a]The data were acquired by recall; [b]Number of patients with PHQ-9 ≥ 10; [c]Number of patients with GAD-7 ≥ 10; [d]Number of patients with IES-R-K ≥ 25; [e]Number of patients with the perceived stigma score > 11.1. Perceived stigma regarding COVID-19 was assessed with an 8-item questionnaire which was used in a previous study.[3] The range of the score was 0–24. High level of perceived stigma was defined as scores above > 11.1, which was two SD = 2.7 from the mean = 5.7.

Table 1. Participants' demographic and clinical characteristics and mental health status at 1 month after discharge from COVID-19 pneumonia in Korea

ACKNOWLEDGEMENTS

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