The Daily COVID-19 Literature Surveillance Summary

February 04, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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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			
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

- A multidisciplinary team of researchers from various hospitals use a stem cell donor registry in Dresden, Germany to conduct a cross-sectional study among 6257 COVID-positive patients found blood group A was a risk factor for contracting SARS-CoV-2 compared to blood group O. The data also demonstrated blood group B was associated with higher risk of severe respiratory tract infection and respiratory hospitalizations compared to blood group O. These findings provide insight into the association between genetic variance in ABO blood type genes and risk for COVID-19 infection and associated severe disease complications.

- Researchers from Stanford University utilize data-driven modeling from data reported by 30 colleges during Fall of 2020 to assess COVID-19 transmission associated with reopening campuses. Results demonstrated a spike in infections during the first 2 weeks of in-person or hybrid instruction in nearly half of the institutions (14/30), with peak seven-day instances well above 1,000 per 100,000. They also found that while all colleges were able to quickly reduce transmission on campus, many failed to control the spread of the virus into the surrounding communities. These results suggest that the first 2 weeks of college reopenings are an especially high risk time period, with potential to cause superspreader events. The authors call for better control of viral spreading when reopening campuses, implementing limitation of the number of students during the initial weeks, regulation of testing, stressing the importance of isolation and quarantine, and continued rapid response regarding outbreaks.

- The Geneva Pediatric COVID Group characterized viral co-infections in 51 children infected with SARS-CoV-2 between March 1 and April 30, 2020, 30 of whom lived in a household with an infected adult. Four children from a household cluster (4/30 [13.3%]) were co-infected with picornaviruses (n=3), hMPV (n=1), and/or HCoV-NL63 (n=1) while no adult household contacts (0/41) had a co-infection. The frequency of circulating respiratory viruses in all children was lower than in the same period in 2019 (73.0% [27/37] vs 11.7 [6/51] in 2020; p<0.001). Authors suggest COVID-19 lockdown measures have reduced circulation of other respiratory viruses, but children remain more vulnerable to respiratory viruses than the adults with the same community-level exposure.

Understanding the Pathology

- The Clinical Research in Intensive Care, Sepsis Trial Group from Strasbourg, France evaluated the viral loads and outcomes of 287 patients hospitalized with SARS-CoV-2 between March 3 and April 5, 2020. They found a median viral load of 4.76 log 10 copies/reaction on the initial upper respiratory swab at admission, with no difference between survivors and non-survivors (p=0.332). Respiratory viral load measurement was not predictive of in-hospital mortality (AOR=1.05, 95%CI: 0.85-1.31 [p=0.637]) or disease severity (AOR=0.88, 95%CI: 0.73-1.06 [p=0.167]). Authors conclude there is no correlation between viral load and disease severity, and suggest individual co-morbidities and immune responses to the virus contribute more to outcomes.

Transmission & Prevention

- Statisticians from the National Chiao Tung University in Taiwan used the Johns Hopkins Coronavirus Resource Center data dashboard to evaluate the relationship between COVID-19 prevalence and mortality from COVID-19 in 36 countries. They found a positive correlation between the number of cases and COVID-19 mortality (Spearman R: 0.8304, P<.001), with a mortality increase of 1.29268% per every 1 in 1000 increase in prevalence, though there was significant heterogeneity between countries. The authors suggest a mortality-prevalence ratio can help detect undocumented infections, and emphasize the importance of infection prevention practices to minimize mortality from COVID-19.

- A virologist from the Laboratory of Retrovirology at The Rockefeller University in New York argues against withholding second doses of SARS-CoV-2 vaccines. He suggests there is not enough evidence that single dose vaccination provides long-term immunity, citing data showing 50-fold higher neutralizing antibody titers after the second dose of mRNA vaccination. The author also raises concerns that insufficient immunity after a single vaccine dose could drive antigenic drift leading to antibody resistant variants.

- Scientists associated with BioNTech, Pfizer and TRON gGmBH assessed the ability of the BioNTech-Pfizer mRNA vaccine BNT162b2 to induce a neutralizing response against the new B.1.1.7 lineage of the SARS-CoV-2 virus. They found antibodies from individuals previously vaccinated with BNT162b2 (n=40) neutralized the B.1.1.7 strain with a slightly reduced response compared to their action against the native Wuhan strain based on the 50% neutralization geometric mean titer (GMT). The authors suggest BNT162b2 appears to offer sustained neutralization of new variants of the SARS-

CoV-2 virus.

- An interdisciplinary group of researchers from the USA, Canada, and Brazil developed a model of SARS-CoV-2 transmission in the United States assuming 40% vaccination coverage in 284 days. With healthcare workers and high-risk individuals prioritized and no vaccine given to those under 18, vaccination reduced the overall attack rate (9.0% to 4.6%) and adverse outcomes (non-ICU hospitalizations, ICU hospitalizations, and mortality decreased by 63.5%, 65.6%, and 69.3%, respectively). The authors suggest even low rates of vaccination could reduce the burden of COVID-19 in the United Sates if non-pharmaceutical public health interventions such as masking and handwashing continue.

Management

- A prospective cohort study conducted by cardiologists in Bologna, Italy found a significant correlation between major adverse events (MAEs) and abnormal EKG findings in patients hospitalized with COVID-19. EKG abnormalities were associated with increased MAEs when present both at hospital admission ($p=0.04$) and on hospital day #7 ($p=0.001$), with MAEs defined as mortality, ICU admission, invasive mechanical ventilation, and renal replacement therapy. The results of this study highlight the potential role of EKGs in triaging and prognosticating patients with COVID-19.

R&D: Diagnosis & Treatments

- Microbiologists from Columbia, Venezuela, and the United States assessed whether the Berlin-Charité protocol for RT-PCR assays could detect the new SARS-CoV-2 B.1.1.7 lineage from the United Kingdom. Using 3,296 full genome sequences, they found the primer and probes detected 98% of the RdRp, N, and E genes targeted in the protocol, though several sequences were missed. The authors suggest that while the Berlin-Charité protocol can detect most SARS-CoV-2 B.1.1.7 variants, future variants may evade detection and incorporating different regions of the viral genome into existing testing could build redundancies that increase the likelihood of their detection.

- A scoping review conducted by medical institutions and laboratories in New Delhi, India in June 2020 identified 17 articles finding saliva-based molecular diagnostics as a simpler, time-conscious, and less technical alternative to nasopharyngeal swab collection for detection of SARS-CoV-2 based on parameters of gene targets, viral load, sensitivity, and point-of-care testing for initial screening in community and hospital-based settings. Salivary testing also allows for simpler self-collection, which decreases the amount of medical staff and personal protective equipment needed for screening settings. This article suggests more robust studies be performed to further assess salivary testing in asymptomatic cases, oral symptoms of infection, and accounting for age, sex, and other comorbidities.

- A review article from medical institutions in Manipal, India discusses that saliva, tears, and breath samples may offer more readily available, reliable, and faster techniques for rapid detection of SARS-CoV-2. Their findings support use of these methods and indicate they may be more suitable for large-scale screening compared to the current gold standard of nasopharyngeal testing.

- A literature review conducted at Carlsbad, California during 2021 by Active Motif Inc. found epigenetic pathways may serve as invaluable targets for future therapeutic targets designed to reduce the spread and pathogenesis of COVID-19 infections.

TABLE OF CONTENTS

ETHICS OF EMERGING INFECTIOUS DISEASE OUTBREAK RESPONSES: USING EBOLA VIRUS DISEASE AS A CASE STUDY OF LIMITED RESOURCE ALLOCATION

Nichol AA, Antierens A.. PLoS One. 2021 Feb 2;16(2):e0246320. doi: 10.1371/journal.pone.0246320. eCollection 2021.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

A biomedical ethicist from Stanford and a physician from Médecins Sans Frontières conducted semi-structured interviews with 16 senior healthcare personnel from organizations engaged in the 2013–2016 Ebola Virus Disease (EVD) response in West Africa to explore the ethical challenges faced when mounting a new infectious disease outbreak response in resource-limited settings. Interviewees emphasized the importance of local community engagement, transparency, and adapting a guiding ethical framework for international responses (Table 1). The authors suggest that the lessons learned during the EVD response can also be applied to the current response COVID-19 in resource-limited areas.

FIGURES

Community Engagement	■ Promote collaboration and open dialogue by creating streams of bi-lateral information between all stakeholders (e.g. medical response coordinators, researchers, local frontline responders, community members)
	■ Incorporate community insights into decision-making processes by consultation of the community leaders, community members, and local clinical expertise
	■ Reflect the context-specific cultural values and norms
	■ Encourage transparency on the part of responders to ensure the legitimacy of the response
	■ Build trust and foster relationships between communities and responders for potential responses in the future
	■ Reduce rumors that result in infected persons hiding out and not receiving medical care by actively working to alleviate fear in communities
Experimental Therapeutic Interventions	■ Provide therapeutics to beneficiaries in monitored settings
	■ Minimize harms from potential side-effects
	■ Offer MEURI to vulnerable populations excluded from clinical research trial eligibility criteria (e.g. pregnant women, children under 5 years of age)
	■ Prioritize frontline healthcare workers
	■ Do not prioritize expatriated healthcare workers over local frontline responders
Clinical Trial Designs	■ Prioritize establishment of clinical trials
	■ Offer MEURI prior to the start of clinical trials and through post-trial access
	■ Consider the possibility of alternative trial designs to the standard randomized controlled trial (RCT)
	■ Include stoppage rules to minimize potential harm
	■ Employ interim analysis to promote on-going evaluation and reflection
Informed Consent	■ Respect individual autonomy
	■ Minimize coercion and undue influence
	■ Protect vulnerable populations
	■ Foster understanding of clinical trials and reduce therapeutic misconception
	■ Utilize appropriate medical terms, matching the level of fluency in scientific vocabulary
	■ Create culturally meaningful consent and consider alternatives to written forms based on community feedback and local expertise

Table 1. Proposed framework of guiding principles for preparedness and implementation by international response organizations for EID outbreaks.

BLOOD GROUP A EPITOPES DO NOT FACILITATE ENTRY OF SARS-COV-2

Schetelig J, Baldauf H, Wendler S, Heidenreich F, Real R, Kolditz M, Rosner A, Dalpke A, de With K, Lange V, Markert J, Barth R, Bunzel C, Endert D, Hofmann JA, Sauter J, Bernas SN, Schmidt AH.. J Intern Med. 2021 Jan 27. doi: 10.1111/joim.13256. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A multidisciplinary team of researchers from various hospitals use a stem cell donor registry in Dresden, Germany to conduct a cross-sectional study among 6257 COVID-positive patients found blood group A was a risk factor for contracting SARS-CoV-2 compared to blood group O (See Table 1). The data also demonstrated blood group B was associated with higher risk of severe respiratory tract infection and respiratory hospitalizations compared to blood group O (See Table 1). These findings provide insight into the association between genetic variance in ABO blood type genes and risk for COVID-19 infection and associated severe disease complications.

ABSTRACT

Information on the impact of ABO blood group (BG) on SARS-CoV-2 infections is conflicting (1-4). To identify risk factors for severe COVID-19 courses we performed a cross-sectional study in volunteers between 18 and 61 years of age registered with DKMS for stem cell donation approved by the Institutional Review Board of the Technische Universitat Dresden. All participants provided explicit consent that COVID-19 specific data were linked to genotype data in the donor registry file.

FIGURES

Geno-type	Contracting SARS-CoV-2				Evaluable* infections	Severe respiratory tract infections			Respiratory hospitalizations			
	Tests (%)	Cases	OR (95%-CI)	p	N	N	OR (95%-CI)	p	N	OR (95%-CI)		p
$O+O$	40,975 (40.0)	1,916	1		1,653	398	1		55	1		
$B+O$	10,997 (10.7)	533	1.05 (0.94-1.16)	0.392	443	138	1.45 (1.14-1.83)	0.002	30	2.16	(1.36-3.45)	0.001
$B+B$	869 (0.8)	37	0.95 (0.68-1.34)	0.784	33	6	0.71 (0.29-1.77)	0.467	1	0.79	(0.10-6.07)	0.817
$B+A_1$	4,072 (4.0)	215	1.17 (1.01-1.36)	0.042	186	53	1.29 (0.92-1.83)	0.140	6	1.01	(0.42-2.39)	0.987
$B+A_2$	1,298 (1.3)	70	1.29 (1.00-1.66)	0.052	59	17	1.30 (0.73-2.33)	0.377	0	-	-	-
A_1+O	27,251 (26.6)	1,462	1.15 (1.07-1.23)	<.001	1229	316	1.09 (0.92-1.30)	0.311	36	0.89	(0.58-1.37)	0.589
A_1+A_1	4,612 (4.5)	214	0.99 (0.85-1.15)	0.860	187	54	1.26 (0.90-1.77)	0.180	5	0.78	(0.31-1.99)	0.604
A_1+A_2	3,031 (3.0)	169	1.22 (1.03-1.44)	0.023	150	35	0.90 (0.60-1.34)	0.611	5	0.99	(0.39-2.55)	0.990
A_2+O	8,714 (8.5)	470	1.16 (1.04-1.29)	0.008	407	112	1.23 (0.96-1.58)	0.101	12	0.92	(0.48-1.74)	0.785
A_2+A_2	523 (0.5)	30	1.32 (0.90-1.95)	0.157	28	10	1.93 (0.87-4.27)	0.107	0	-	-	-

Legend: N, number of cases, OR, odds ratio; CI, confidence interval; p, p value. Odds ratios were calculated in a multivariable logistic regression model containing information on age, sex, BMI, diabetes mellitus, arterial hypertension, smoking status and month of testing.

* Infections reported for the months January to July, excluding August and September.

Table 1. Impact of ABO genotypes and phenotypes.

ARE COLLEGE CAMPUSES SUPERSPREADERS? A DATA-DRIVEN MODELING STUDY

Lu H, Weintz C, Pace J, Indana D, Linka K, Kuhl E.. Comput Methods Biomech Biomed Engin. 2021 Jan 13:1-11. doi: 10.1080/10255842.2020.1869221. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

Researchers from Stanford University utilize data-driven modeling from data reported by 30 colleges (Figure 1) during Fall of 2020 to assess COVID-19 transmission associated with reopening campuses. Results demonstrated a spike in infections during the first 2 weeks of in-person or hybrid instruction in nearly half of the institutions (14/30), with peak seven-day instances well above 1,000 per 100,000 (Figure 4). They also found that while all colleges were able to quickly reduce transmission on campus, many failed to control the spread of the virus into the surrounding communities. These results suggest that the first 2 weeks of college reopenings are an especially high risk time period, with potential to cause superspreader events. The authors call for better control of viral spreading when reopening campuses, implementing limitation of the number of students during the initial weeks, regulation of testing, stressing the importance of isolation and quarantine, and continued rapid response regarding outbreaks.

ABSTRACT

The COVID-19 pandemic continues to present enormous challenges for colleges and universities and strategies for save reopening remain a topic of ongoing debate. Many institutions that reopened cautiously in the fall experienced a massive wave of infections and colleges were soon declared as the new hotspots of the pandemic. However, the precise effects of college outbreaks on their immediate neighborhood remain largely unknown. Here we show that the first two weeks of instruction present a high-risk period for campus outbreaks and that these outbreaks tend to spread into the neighboring communities. By integrating a classical mathematical epidemiology model and Bayesian learning, we learned the dynamic reproduction number for 30 colleges from their daily case reports. Of these 30 institutions, 14 displayed a spike of infections within the first two weeks of class, with peak seven-day incidences well above 1,000 per 100,000, an order of magnitude larger than the nation-wide peaks of 70 and 150 during the first and second waves of the pandemic. While most colleges were able to rapidly reduce the number of new infections, many failed to control the spread of the virus beyond their own campus: Within only two weeks, 17 campus outbreaks translated directly into peaks of infection within their home counties. These findings suggests that college campuses are at risk to develop an extreme incidence of COVID-19 and become superspreaders for neighboring communities. We anticipate that tight test-trace-quarantine strategies, flexible transition to online instruction, and-most importantly-compliance with local regulations will be critical to ensure a safe campus reopening after the winter break.

FIGURES

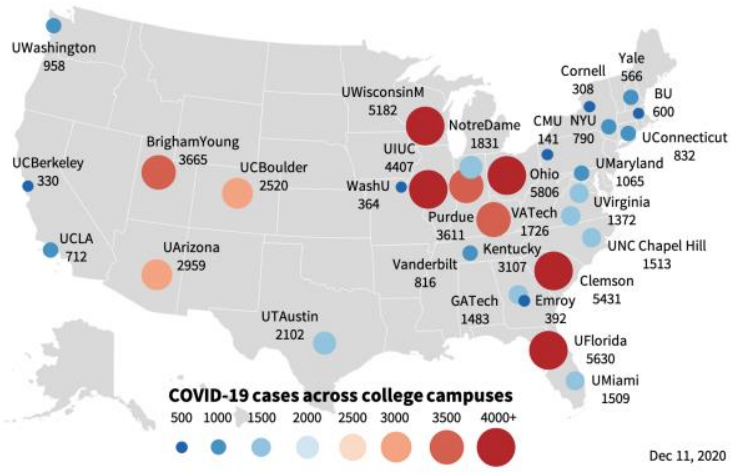


Figure 1. COVID-19 cases across 30 college campuses. Reported cases for ten high case number, public, and private institutions across the United States since the outbreak of the pandemic.

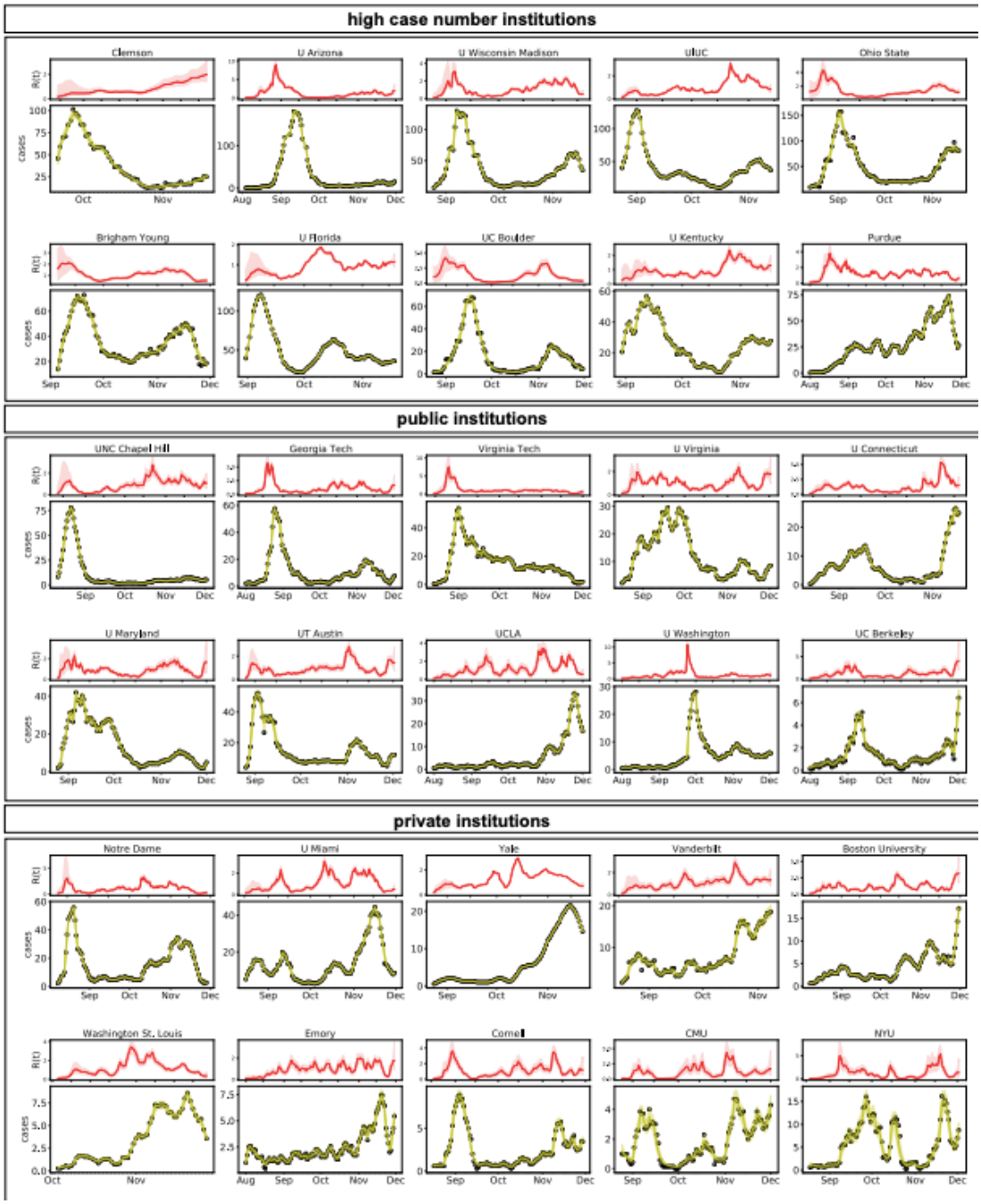


Figure 4. COVID-19 dynamic reproduction number of for 30 college campuses. Dynamic reproduction number, reported cases, and new infectious population for ten high case number, public, and private institutions across the United States throughout the fall of 2020. Circles mark the reported daily campus cases; red and yellow curves highlight the learnt Gaussian random walk based dynamic reproduction number and new infectious population, both with confidence intervals.

VIRAL CO-INFECTIONS AMONG SARS-COV-2-INFECTED CHILDREN AND INFECTED ADULT HOUSEHOLD CONTACTS

Pigny F, Wagner N, Rohr M, Mamin A, Cherpillod P, Posfay-Barbe KM, Kaiser L, Eckerle I, L'Huillier AG; Geneva Pediatric COVID Group.. Eur J Pediatr. 2021 Jan 27. doi: 10.1007/s00431-021-03947-x. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

The Geneva Pediatric COVID Group characterized viral co-infections in 51 children infected with SARS-CoV-2 between March 1 and April 30, 2020, 30 of whom lived in a household with an infected adult. Four children from a household cluster (4/30 [13.3%]) were co-infected with picornaviruses (n=3), hMPV (n=1), and/or HCoV-NL63 (n=1) while no adult household contacts (0/41) had a co-infection. The frequency of circulating respiratory viruses in all children was lower than in the same period in 2019 (73.0% [27/37] vs 11.7 [6/51] in 2020; p<0.001). Authors suggest COVID-19 lockdown measures have reduced circulation of other respiratory viruses, but children remain more vulnerable to respiratory viruses than the adults with the same community-level exposure.

ABSTRACT

We evaluated the rates of viral respiratory co-infections among SARS-CoV-2-infected children. Twelve percent of SARS-CoV-2-infected children had viral co-infection with one or more common respiratory viruses. This was significantly more frequent than among their SARS-CoV-2-infected adult household contacts (0%; p=0.028). Compared to the same period the previous year, common respiratory viruses were less frequently detected (12% vs 73%, p<0.001).Conclusion: Despite partial lockdown with school and daycare closure, and consequently similar exposure to common viruses between children and adults, SARS-CoV-2-infected children had more frequent viral respiratory co-infections than their SARS-CoV-2-infected adult household contacts. Circulation of common respiratory viruses was less frequent during the SARS-CoV-2 outbreak when compared to the same period last year, showing the impact of partial lockdown on the circulation of common viruses. What is Known: Viral respiratory co-infections are frequent in children. SARS-CoV-2 can be identified alongside other respiratory viruses, but data comparing children and adults are lacking. What is New: Children infected with SARS-CoV-2 are more likely to have viral respiratory co-infections than their SARS-CoV-2-infected adult household contacts, which is surprising in the context of partial lockdown with schools and daycare closed. When compared to data collected during the same period last year, our study also showed that partial lockdown reduced circulation of common respiratory viruses.

SARS-COV-2 VIRAL LOAD IN NASOPHARYNGEAL SWABS IN THE ED DOES NOT PREDICT COVID-19 SEVERITY AND MORTALITY

Le Borgne P, Solis M, Severac F, Merdji H, Ruch Y, Alamé K, Bayle E, Hansmann Y, Bilbault P, Fafi-Kremer S, Meziani F; CRICS TRIGGERSEP Group (Clinical Research in Intensive Care, Sepsis Trial Group for Global Evaluation, Research in Sepsis)..
Acad Emerg Med. 2021 Jan 22. doi: 10.1111/acem.14217. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

The Clinical Research in Intensive Care, Sepsis Trial Group from Strasbourg, France evaluated the viral loads and outcomes of 287 patients hospitalized with SARS-CoV-2 between March 3 and April 5, 2020. They found a median viral load of 4.76 log 10 copies/reaction on the initial upper respiratory swab at admission, with no difference between survivors and non-survivors (p=0.332). Respiratory viral load measurement was not predictive of in-hospital mortality (AOR=1.05, 95%CI: 0.85-1.31 [p=0.637]) or disease severity (AOR=0.88, 95%CI: 0.73-1.06 [p=0.167])(Table 2). Authors conclude there is no correlation between viral load and disease severity, and suggest individual co-morbidities and immune responses to the virus contribute more to outcomes.

ABSTRACT

INTRODUCTION: The ongoing COVID-19 pandemic has led to devastating repercussions on healthcare systems worldwide. This viral infection has a broad clinical spectrum broad (ranging from influenza-like disease, viral pneumonia, hypoxemia to ARDS requiring prolonged ICU stays). The prognostic impact of measuring viral load on nasopharyngeal swab specimens (by RT-PCR) is yet to be elucidated. METHODS: Between March 3rd and April 5th , 2020, we conducted a retrospective study on a cohort of COVID-19 patients (mild or severe disease) who were hospitalized after presenting to the emergency department (ED) and had at least one positive nasopharyngeal swab during their hospital stay. We led our study at the University Hospitals of Strasbourg, in the Greater East region of France, one of the pandemic's epicenters in Europe. RESULTS: We have collected samples from a cohort of 287 patients with a confirmed diagnosis of COVID-19 who were included in our study. Nearly half of them (50.5%) presented a mild form of the disease, while the other half (49.5%) presented a severe form, requiring mechanical ventilation. Median viral load on the initial upper respiratory swab at admission was 4.76 (3.29-6.06) log10 copies/reaction. When comparing survivors and non-survivors, this viral load measurement did not differ according to subgroups (p=0.332). Additionally, we have found that respiratory viral load measurement was predictive of neither in-hospital mortality (AOR=1.05, 95%CI: 0.85-1.31, p=0.637) nor disease severity (AOR=0.88, 95%CI: 0.73-1.06, p=0.167). CONCLUSION: Respiratory viral load measurement on the first nasopharyngeal swab (by RT-PCR) during initial ED management is neither a predictor of severity nor mortality in SARS-CoV-2 infection. Host response to this viral infection along with the extent of pre-existing co-morbidities might be more foretelling of disease severity than the virus itself.

Table 2: Multivariable analysis of factors associated with in-hospital mortality

General characteristics	Adjusted Odds Ratio	95%CI	p value
Age <50	1	-	-
Age 50-65 years	1.56	0.39-6.27	0.532
Age >65 years	4.70	1.29-17.07	**0.019**
Obesity (BMI>30)	1.25	0.52-3.04	0.618
Men	0.99	0.42-2.38	0.993
Comorbidities			
Hypertension	0.79	0.33-1.89	0.590
Cardiovascular Dis	1.14	0.39-3.36	0.809
Diabetes mellitus	1.26	0.50-3.19	0.626
Renal insufficiency	0.67	0.15-2.98	0.596
Dialysis	14.43	1.38-151.14	**0.027**
COPD	3.14	0.63-15.66	0.164
Malignencies	2.81	0.60-13.23	0.194
Corticosteroids	1.50	0.22-9.99	0.678
Immunotherapy	1.73	0.13-22.38	0.676
Laboratory findings			
CRP (>100mg/L)	1.32	0.51-3.40	0.567
Creatinine (>90 µmol/L)	2.15	0.83-5.61	0.118
Anemia (<10g/dL)	5.14	1.19-22.19	**0.032**
Platelets (>400x10^9/L)	0.26	0.02-4.09	0.339
Lymphopenia (<1500/mm^3)	2.95	0.56-15.68	0.209
Viral load (log_{10} copies/reaction)	1.05	0.85-1.31	0.637

UNIQUE INFLAMMATORY PROFILE IS ASSOCIATED WITH HIGHER SARS-COV-2 ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) MORTALITY

Balnis J, Adam AP, Chopra A, Chieng HC, Drake LA, Martino N, Bossardi Ramos R, Feustel PJ, Overmyer KA, Shishkova E, Coon JJ, Singer HA, Judson MA, Jaitovich A.. Am J Physiol Regul Integr Comp Physiol. 2021 Jan 12. doi: 10.1152/ajpregu.00324.2020. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

A prospective cohort study conducted by the Albany Medical Center evaluated the cytokine expression profiles (summary) in 41 COVID-19 patients with acute respiratory distress syndrome (ARDS) on mechanical ventilation and found that RANTES, EGF, IL1a, and IL5 were associated with lower mortality ($p<0.05$) while IL8, IL1RA, and CCL19 were associated with greater mortality ($p<0.05$) (Figure 1). These findings provide insight into the inflammatory profile associated with COVID-19 ARDS and may potentially guide future therapeutics.

SUMMARY

Cytokine measurements were obtained from the ELISA assay on plasma samples, while leukocyte mRNA expression was determined through qPCR analysis.

ABSTRACT

The COVID19 pandemic has caused more than a million of deaths worldwide, primarily due to complications from COVID19-associated acute respiratory distress syndrome (ARDS). Controversy surrounds the circulating cytokine/chemokine profile of COVID19-associated ARDS, with some groups suggesting that it is similar to non-COVID19 ARDS patients and others observing substantial differences. Moreover, while a hyperinflammatory phenotype associates with higher mortality in non-COVID19 ARDS, there is little information on the inflammatory landscape's association with mortality in COVID19 ARDS patients. Even though the circulating leukocytes' transcriptomic signature has been associated with distinct phenotypes and outcomes in critical illness including ARDS, it is unclear whether the mortality-associated inflammatory mediators from COVID19 patients are transcriptionally regulated in the leukocyte compartment. Here, we conducted a prospective cohort study of 41 mechanically ventilated patients with COVID19 infection using highly calibrated methods to define the levels of plasma cytokines/chemokines and their gene expressions in circulating leukocytes. Plasma IL1RA and IL8 were found positively associated with mortality while RANTES and EGF negatively associated with that outcome. However, the leukocyte gene expression of these proteins had no statistically significant correlation with mortality. These data suggest a unique inflammatory signature associated with severe COVID19.

Figure 1

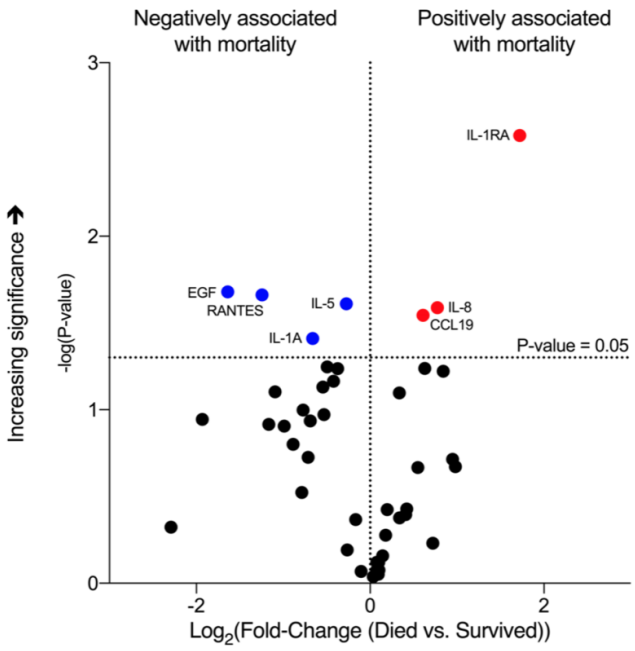


Figure 1. Cytokine determinations at the time of enrollment and association with mortality based on multiplex system determination. Volcano plot showing cytokines/chemokines significantly associated with mortality: blue dots, negatively associated; red dots, positively associated. Black dots identify entities not statistically significantly associated with mortality. Threshold of significance was established at a p value of 0.05 before adjustment for false discovery rate.

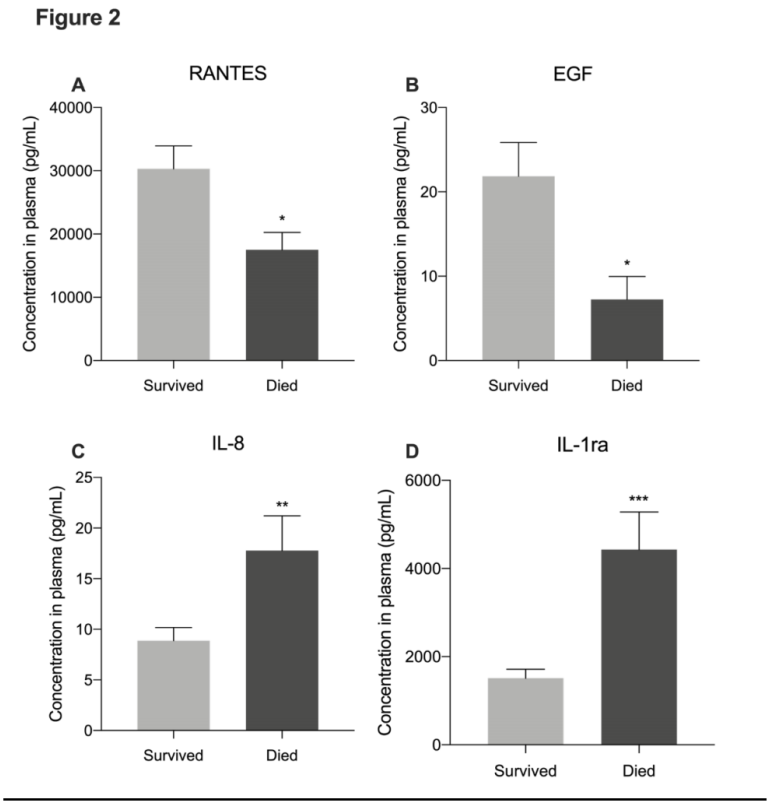


Figure 2. Cytokines associated with mortality based on ELISA tests performed individually. Bar graphs showing the cytokines/chemokines that were found associated with mortality by ELISA testing. *p<0.05; **p<0.01; ***p<0.001.

STRUCTURAL SIMILARITY-BASED PREDICTION OF HOST FACTORS ASSOCIATED WITH SARS-COV-2 INFECTION AND PATHOGENESIS

Tiwari R, Mishra AR, Gupta A, Nayak D.. J Biomol Struct Dyn. 2021 Jan 28:1-12. doi: 10.1080/07391102.2021.1874532. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

Molecular biologists from the Indian Institute of Technology Indore used a structural based computational approach to create an interactome profile of structural components and pathway mediated processes involved in the pathogenesis of SARS-COV-2. They identified the key events of and proteins involved in the SARS-CoV-2 life cycle (see summary) based on the strength and number of interactions depicted in their models (Figures 3, 4, 5). Authors suggest isolating these key pathways in SARS-CoV-2 pathogenesis is crucial for identifying new therapeutic targets.

SUMMARY

The authors propose the following life cycle for SARS-CoV-2:
1. "SARS-CoV-2 enters through clathrin-mediated endocytosis"
2. "[T]he genome is trafficked to the early endosomes in a RAB5-dependent manner"
3. The genome "replicate[s] in a double-membrane vesicle (DMV) composed of the endoplasmic reticulum, autophagosome, and ERAD machinery"
4. "SARS-CoV-2 down-regulates host translational machinery by interacting with protein kinase R, PKR-like endoplasmic reticulum kinase, and heme-regulated inhibitor and can phosphorylate eIF2a"
5. "virion assembly occurs in the ER-Golgi intermediate compartment (ERGIC) organized by the spike and matrix protein"

They propose "axon guidance, membrane trafficking, vesicle-mediated transport, apoptosis, clathrin-mediated endocytosis, Vpu mediated degradation of CD4 T cell, and interferon-gamma signaling" are critical to this process. IRF1/9/7, TP53, CASP3, UBA52, and UBC are crucial proteins for interferon-gamma signaling.

ABSTRACT

The current pandemic resulted from SARS-CoV-2 still remains as the major public health concern globally. The precise mechanism of viral pathogenesis is not fully understood, which remains a major hurdle for medical intervention. Here we generated an interactome profile of protein-protein interactions based on host and viral protein structural similarities information. Further computational biological study combined with Gene enrichment analysis predicted key enriched pathways associated with viral pathogenesis. The results show that axon guidance, membrane trafficking, vesicle-mediated transport, apoptosis, clathrin-mediated endocytosis, Vpu mediated degradation of CD4 T cell, and interferon-gamma signaling are key events associated in SARS-CoV-2 life cycle. Further, degree centrality analysis reveals that IRF1/9/7, TP53, and CASP3, UBA52, and UBC are vital proteins for IFN-gamma-mediated signaling, apoptosis, and proteasomal degradation of CD4, respectively. We crafted chronological events of the virus life cycle. The SARS-CoV-2 enters through clathrin-mediated endocytosis, and the genome is trafficked to the early endosomes in a RAB5-dependent manner. It is predicted to replicate in a double-membrane vesicle (DMV) composed of the endoplasmic reticulum, autophagosome, and ERAD machinery. The SARS-CoV-2 down-regulates host translational machinery by interacting with protein kinase R, PKR-like endoplasmic reticulum kinase, and heme-regulated inhibitor and can phosphorylate eIF2a. The virion assembly occurs in the ER-Golgi intermediate compartment (ERGIC) organized by the spike and matrix protein. Collectively, we have established a spatial link between viral entry, RNA synthesis, assembly, pathogenesis, and their associated diverse host factors, those could pave the way for therapeutic intervention.

FIGURES

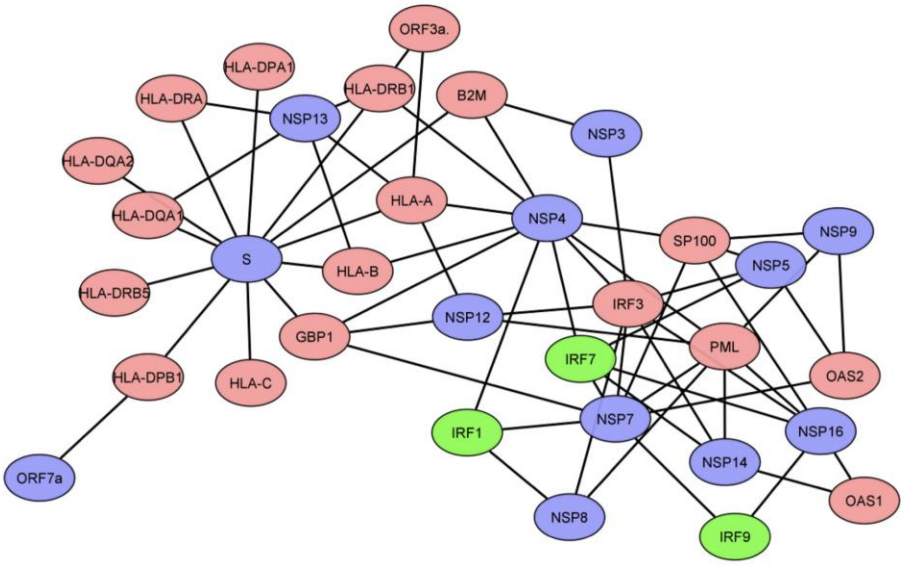


Figure 3. A predicted interaction map of the top 20 IFN-γ associated human proteins and their interacting SARS-CoV-2 protein. Blue color represents the virus proteins, and brown color represents the human interactor proteins. Twelve SARS-CoV-2 proteins interact with human proteins related to IFN-γ signaling pathway. IRF1, IRF7, and IRF9 (represented in green color) are highly weighted proteins and may regulate IFN-γ signaling cascade. (Interaction map was created using Cytoscape.)

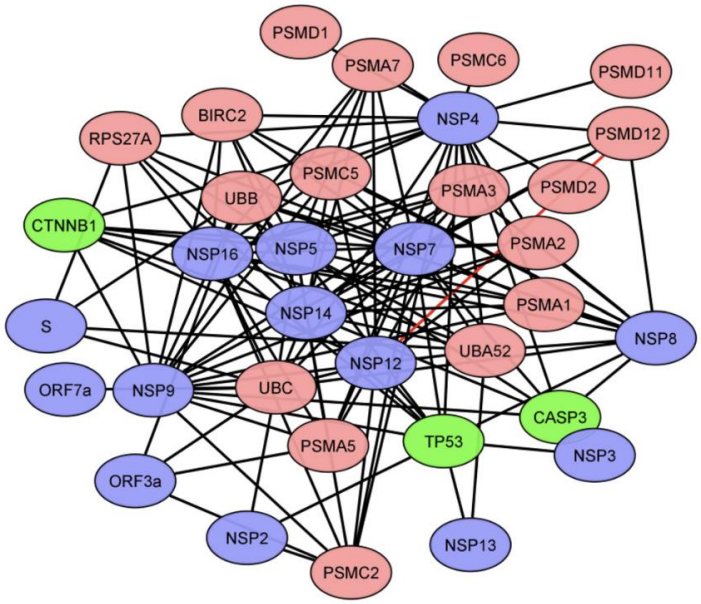


Figure 4. A predicted interaction map of the top 20 apoptosis associated human proteins and their interacting SARS-CoV-2 protein. Blue color represents the virus proteins, and brown color represents the human interactor proteins. Fourteen SARS-CoV-2 proteins interact with human proteins connected with apoptosis. Degree centrality analysis revels that TP53, CASP3, and CTNNB1 (represented in green color) are the principal players in the SARS-CoV-2 mediated apoptosis. (Interaction map was created using Cytoscape.)

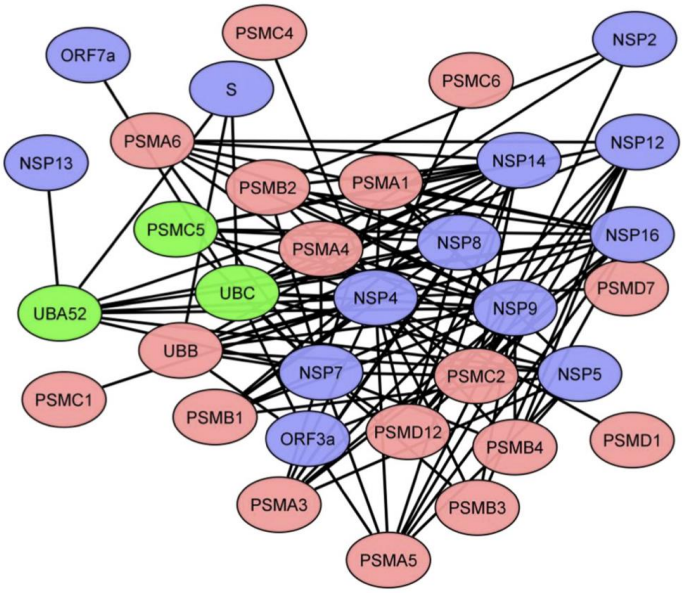


Figure 5. A predicted interaction map of the top 20 proteasomal degradation of CD4 associated human proteins and their interacting SARS-CoV-2 protein. Blue color represents the viral proteins, and brown color represents the human interactor proteins. Thirteen SARS-CoV-2 proteins interact with human proteins connected with proteasomal degradation of CD4 T cells. Degree centrality analysis revels that UBA52, UBC, and PSMC5 (represented in green color) are the key player in the process of proteasomal degradation of CD4 T cells. (Interaction map was created using Cytoscape.)

ANTIBODIES, EPICENTER OF SARS-COV-2 IMMUNOLOGY

Pecetta S, Pizza M, Sala C, Andreano E, Pileri P, Troisi M, Pantano E, Manganaro N, Rappuoli R.. Cell Death Differ. 2021 Jan 26. doi: 10.1038/s41418-020-00711-w. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Scientists involved in research and development at GlaxoSmithKline and the Monoclonal Antibody Discovery (MAD) Lab at Fondazione Toscana Life Sciences in Italy discuss the role of antibodies in the immune response to SARS-CoV-2. They review the body's natural antibody response, the potential benefits of using monoclonal antibodies for treatment, and the response to vaccination. The authors conclude it will be critical to characterize how neutralizing antibody titers correlate to degree of protection as the world begins mass vaccination.

USING THE NOVEL MORTALITY-PREVALENCE RATIO TO EVALUATE POTENTIALLY UNDOCUMENTED SARS-COV-2 INFECTION: CORRELATIONAL STUDY

Lin SH, Fu SC, Kao CM.. JMIR Public Health Surveill. 2021 Jan 27;7(1):e23034. doi: 10.2196/23034.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

Statisticians from the National Chiao Tung University in Taiwan used the Johns Hopkins Coronavirus Resource Center data dashboard to evaluate the relationship between COVID-19 prevalence and mortality from COVID-19 in 36 countries. They found a positive correlation between the number of cases and COVID-19 mortality (Spearman R: 0.8304, P<.001), with a mortality increase of 1.29268% per every 1 in 1000 increase in prevalence (Figures 1, 2), though there was significant heterogeneity between countries. The authors suggest a mortality-prevalence ratio can help detect undocumented infections, and emphasize the importance of infection prevention practices to minimize mortality from COVID-19.

ABSTRACT

BACKGROUND: The prevalence of COVID-19 has caused 200 thousand death-cases since early 2020. The corresponding mortality rate among different countries and time varies. OBJECTIVE: This study aims to investigate the relationship between mortality rate and the prevalence of COVID-19 within a country. METHODS: We collected data from Johns Hopkins Coronavirus Resource Center, which included daily cumulative death count, recovered count, and confirmed count for each country. This study focuses on a total of 36 countries with over 10,000 confirmed cases. Mortality is the main outcome and dependent variable, which is computed as the number of COVID-19 deaths divided by the number of confirmed cases. RESULTS: The result of global panel regression showed that there was a highly significant correlation between prevalence and mortality (Spearmans^' correlation=0.8304). We found that every increment of one confirmed case in a thousand individuals leaded to 1.29268% increment in mortality after controlling country-specific baseline mortality and time-fixed effects. Over 70% of excess mortality could be explained by prevalence, and the heterogeneity among countries' mortality to prevalence (MP) ratio was significant. We further showed that China had an abnormally high and significant MP ratio compared to other countries. This unusual deviation of MP ratio disappeared with the removal of data from China collected after February 17th. It is worth noting that the prevalence of a disease relies on accurate diagnosis and comprehensive surveillance, which could be difficult to achieve due to practical or political concerns. CONCLUSIONS: The mortality-prevalence association was observed and being quantified as MP ratio. Our results highlight the significance of constraining disease transmission on decreasing mortality. Comparison of MP ratio among countries can be powerful in detecting or even quantifying the proportion of undocumented infected individuals. CLINICALTRIAL:

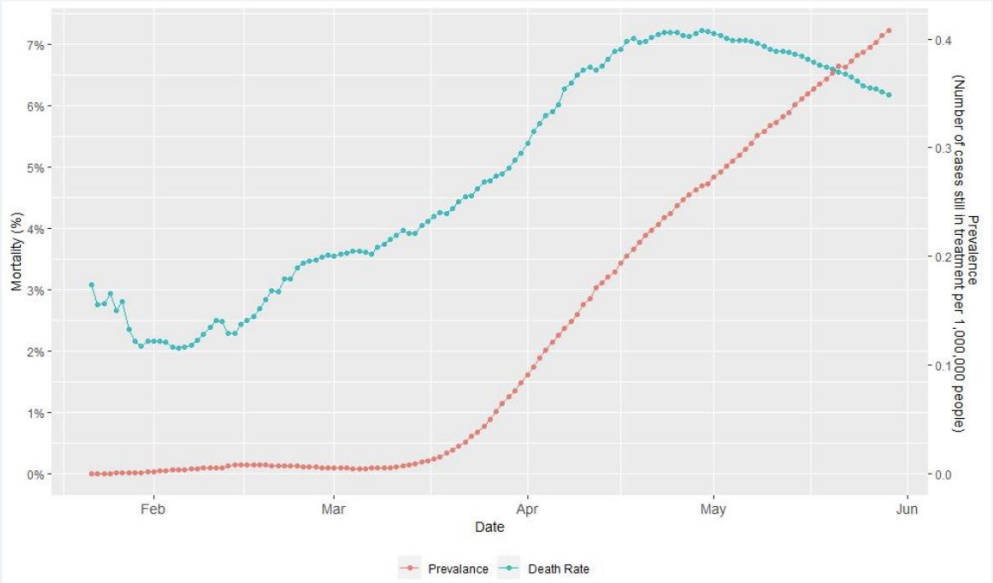
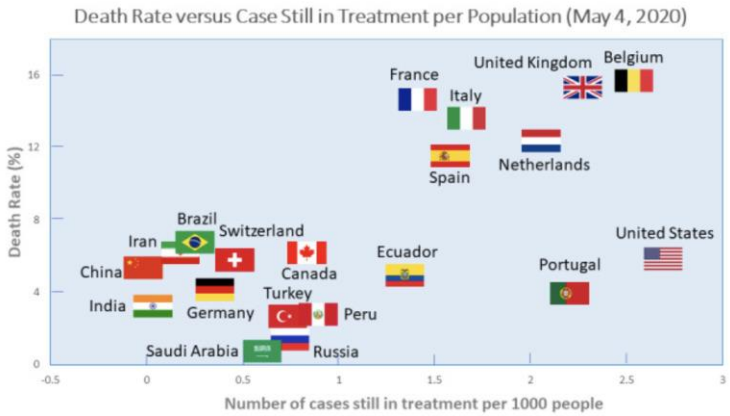


Figure 2. Trends of global COVID-19 mortality and prevalence over time.

Figure 1



COVID-19 mortality and prevalence of all countries (ρ=0.8304; *P*<.001). Only the top 20 countries with the highest prevalence are shown.

DELETION OF THE NKG2C RECEPTOR ENCODING KLRC2 GENE AND HLA-E VARIANTS ARE RISK FACTORS FOR SEVERE COVID-19

Vietzen H, Zoufaly A, Traugott M, Aberle J, Aberle SW, Puchhammer-Stöckl E.. Genet Med. 2021 Jan 26. doi: 10.1038/s41436-020-01077-7. Online ahead of print.
Level of Evidence: 4 - Local non-random sample

BLUF

Virologists from the Medical University of Vienna and the Kaiser Franz Josef Hospital investigated the association between genetic variants (KLRC2 deletion and HLA-E*0101/0103 allelic variants) and COVID-19 (Table 1) in 361 patients hospitalized between February 17 and April 17, 2020. They found both variants were more likely in hospitalized non-ICU patients (OR 2.6 [p=0.0006] for KLRC2 deletion and OR 2.1 [p = 0.01] for HLA-E*0101/0103) and those requiring intensive care (OR 7.1 [p < 0.0001] and OR 2.7 [p = 0.01]) than non-hospitalized patients (Figure 1, Summary). The authors concluded that these genetic variants are correlated with increased risk of severe COVID-19, and suggest their presence can be used to identify patients at higher risk.

SUMMARY

The patient cohort was stratified as follows:
1. Nonhospitalized: "patients showed only minor symptoms and stayed in home quarantine" (92/361 [25.5%])
2. Hospitalized non-ICU: "hospitalized with severe COVID-19 symptoms but never required intensive care" (190/361 [52.6%])
3. Hospitalized ICU: "severely affected and needed intensive care" (79/361 [21.9%])

ABSTRACT

PURPOSE: Host genetic variants may contribute to severity of COVID-19. NKG2C+ NK cells are potent antiviral effector cells, potentially limiting the extent of SARS-CoV-2 infections. NKG2C is an activating NK cell receptor encoded by the KLRC2 gene, which binds to HLA-E on infected cells leading to NK cell activation. Heterozygous or homozygous KLRC2 deletion (KLRC2del) may naturally occur and is associated with a significantly lower or absent NKG2C expression level. In addition, HLA-E*0101/0103 genetic variants occur, caused by a single-nucleotide polymorphism. We therefore investigated whether the severity of COVID-19 is associated with these genetic variants. METHODS: We investigated the distribution of KLRC2 deletion and HLA-E*0101/0103 allelic variants in a study cohort of 361 patients with either mild (N = 92) or severe (N = 269) COVID-19. RESULTS: Especially the KLRC2del, and at a lower degree the HLA-E*0101, allele were significantly overrepresented in hospitalized patients (p = 0.0006 and p = 0.01), particularly in patients requiring intensive care (p < 0.0001 and p = 0.01), compared with patients with mild symptoms. Both genetic variants were independent risk factors for severe COVID-19. CONCLUSION: Our data show that these genetic variants in the NKG2C/HLA-E axis have a significant impact on the development of severe SARS-CoV-2 infections, and may help to identify patients at high-risk for severe COVID-19.

FIGURES

Table 1 Characteristics of the study cohort.

From: Deletion of the NKG2C receptor encoding *KLRC2* gene and HLA-E variants are risk factors for severe COVID-19

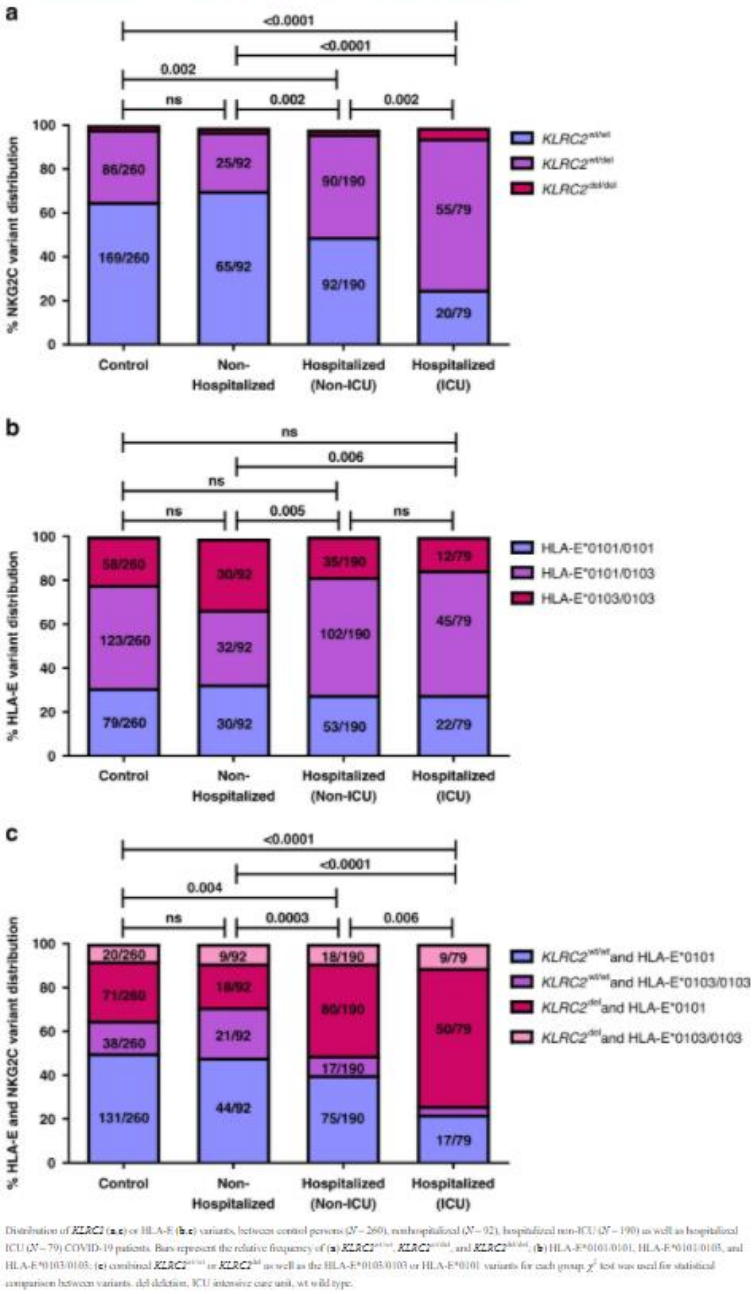
	Nonhospitalized *N* = 92	Hospitalized (non-ICU) *N* = 190	Hospitalized (ICU) *N* = 79	*p* value[a]
Female gender (%)	*N* = 54 (58%)	*N* = 78 (41%)	*N* = 31 (39%)	*P* = 0.02 Nonhospitalized vs. hospitalized: *p* = 0.007 Nonhospitalized vs. ICU: *p* = 0.01 Hospitalized vs. ICU: *p* = 0.79
Median age (years, min–max)	45 (18–93)	74.4 (18–99)	78.3 (20–97)	*P* < 0.0001 Nonhospitalized vs. hospitalized: *P* < 0.0001 Nonhospitalized vs. ICU: *P* < 0.0001 Hospitalized vs. ICU: *P* < 0.0001
Comorbidities Obesity (%) Hypertension (%) COPD (%) CAD (%) None (%)	 *N* = 5 (5.4%) *N* = 1 (1.1%) *N* = 1 (1.1%) *N* = 0 (0%) *N* = 85 (91.3%)	 *N* = 20 (10.5%) *N* = 85 (44.7%) *N* = 44 (23.1%) *N* = 31 (16.3%) *N* = 15 (7.9%)	 *N* = 12 (15.2%) *N* = 36 (45.6%) *N* = 21 (26.5%) *N* = 13 (16.4%) *N* = 12 (15.2%)	*P* < 0.0001 Nonhospitalized vs. hospitalized: *P* < 0.0001 Nonhospitalized vs. ICU: *P* < 0.0001 Hospitalized vs. ICU: *p* = 0.61

CAD coronary artery disease, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit.

[a]Differences were assessed with the χ^2 (gender and comorbidities) and analysis of variance (ANOVA) and Dunn post test (age).

Fig. 1: Distribution of *KLRC2* and HLA-E variants in patients with different disease severities of COVID-19.

From: Deletion of the NKG2C receptor encoding *KLRC2* gene and HLA-E variants are risk factors for severe COVID-19



Distribution of *KLRC2* (**a**,**c**) or HLA-E (**b**,**c**) variants, between control persons ($N = 260$), nonhospitalized ($N = 92$), hospitalized non-ICU ($N = 190$) as well as hospitalized ICU ($N = 79$) COVID-19 patients. Bars represent the relative frequency of (**a**) $KLRC2^{wt/wt}$, $KLRC2^{wt/del}$, and $KLRC2^{del/del}$, (**b**) HLA-E*0101/0101, HLA-E*0101/0103, and HLA-E*0103/0103, (**c**) combined $KLRC2^{wt/wt}$ or $KLRC2^{del}$ as well as the HLA-E*0103/0103 or HLA-E*0101 variants for each group. χ^2 test was used for statistical comparison between variants. del deletion, ICU intensive care unit, wt wild type.

THE CASE AGAINST DELAYING SARS-COV-2 MRNA VACCINE BOOSTING DOSES

Bieniasz P.. Clin Infect Dis. 2021 Jan 27:ciab070. doi: 10.1093/cid/ciab070. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

A virologist from the Laboratory of Retrovirology at The Rockefeller University in New York argues against withholding second doses of SARS-CoV-2 vaccines. He suggests there is not enough evidence that single dose vaccination provides long-term immunity, citing data showing 50-fold higher neutralizing antibody titers after the second dose of mRNA vaccination. The author also raises concerns that insufficient immunity after a single vaccine dose could drive antigenic drift leading to antibody resistant variants.

CHANGES IN THE HUMORAL IMMUNITY RESPONSE IN SARS-COV-2 CONVALESCENT PATIENTS OVER 8 MONTHS

Peng P, Hu J, Deng HJ, Liu BZ, Fang L, Wang K, Tang N, Huang AL.. Cell Mol Immunol. 2021 Jan 8. doi: 10.1038/s41423-020-00605-4. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A cohort study conducted at Chongqing Medical University by the Key Laboratory of Molecular Biology for Infectious Diseases from February - October, 2020 found patients previously infected with COVID-19 had significant reductions in IgG levels, suggesting that those patients may lose protective capacity enough to risk reinfection (Figure 1).

SUMMARY

This study compared the antibody (Ab) levels of 20 patients previously hospitalized with COVID-19 infections at re-evaluation 25 days post-infection, and 230 days post-infection. In all 20, a decrease was observed in OD450, or optical density observed with a 450-nm filter microplate, from 1.78 to 0.38 over 8 months. At a level below 0.26, 5 patients were measured and classified as seronegative in the 230-day measure. A similar decline was observed in the Neutralization Assay, from 50% infectious dose (ID50) of 836.55 to 170.30. 5 participants also were deemed as having antibody levels unsuitable to neutralize a COVID-19 infection based on a pseudovirus-based neutralization assay. The study may provide insights into the mechanisms by which post-infectious patients may have an impaired immune response. More data regarding the longevity of humoral immunity is necessary to determine long-term effects on immunity.

FIGURES

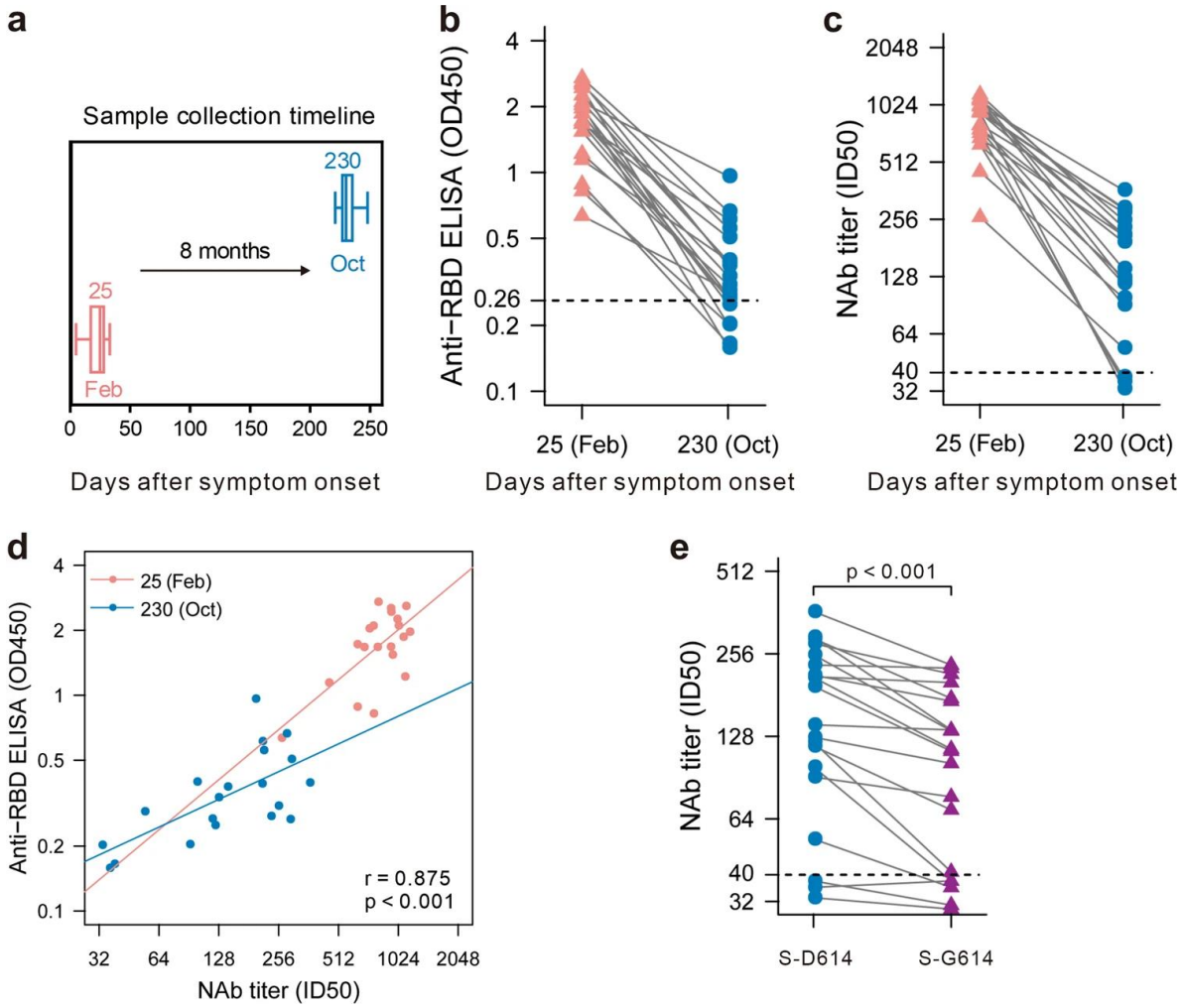


Figure 1. Maintenance of the humoral response to SARS-CoV-2 in convalescent patients over 8 months. a Blood samples were collected in February and October. Enzyme-linked immunosorbent assays (ELISAs) (b) and pseudovirus-based neutralizing assays (c) were performed to detect IgG levels and neutralizing antibody (NAb) titers against SARS-CoV-2. The thresholds of detection were 0.26 for the OD450 value and 1:40 for the ID50. d Correlation of IgG and NAb levels. e Neutralizing activities of convalescent plasma against SARS-CoV-2 S-D614 or S-G614 mutant at 8 months after symptom onset

NEUTRALIZATION OF SARS-COV-2 LINEAGE B.1.1.7 PSEUDOVIRUS BY BNT162B2 VACCINE-ELICITED HUMAN SERA

Muik A, Wallisch AK, Sänger B, Swanson KA, Mühl J, Chen W, Cai H, Maurus D, Sarkar R, Türeci Ö, Dormitzer PR, Şahin U.. Science. 2021 Jan 29:eabg6105. doi: 10.1126/science.abg6105. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Scientists associated with BioNTech, Pfizer and TRON gGmBH assessed the ability of the BioNTech-Pfizer mRNA vaccine BNT162b2 to induce a neutralizing response against the new B.1.1.7 lineage of the SARS-CoV-2 virus. They found antibodies from individuals previously vaccinated with BNT162b2 (n=40) neutralized the B.1.1.7 strain with a slightly reduced response compared to their action against the native Wuhan strain based on the 50% neutralization geometric mean titer (GMT) (Figures 1,2). The authors suggest BNT162b2 appears to offer sustained neutralization of new variants of the SARS-CoV-2 virus.

ABSTRACT

Recently, a new SARS-CoV-2 lineage called B.1.1.7 (variant of concern: VOC 202012/01) emerged in the United Kingdom that was reported to spread more efficiently and faster than other strains. This variant has an unusually large number of mutations with 10 amino acid changes in the spike protein, raising concerns that its recognition by neutralizing antibodies may be affected. Here, we tested SARS-CoV-2-S pseudoviruses bearing either the Wuhan reference strain or the B.1.1.7 lineage spike protein with sera of 40 participants who were vaccinated in a previously reported trial with the mRNA-based COVID-19 vaccine BNT162b2. The immune sera had slightly reduced but overall largely preserved neutralizing titers against the B.1.1.7 lineage pseudovirus. These data indicate that the B.1.1.7 lineage will not escape BNT162b2-mediated protection.

FIGURES

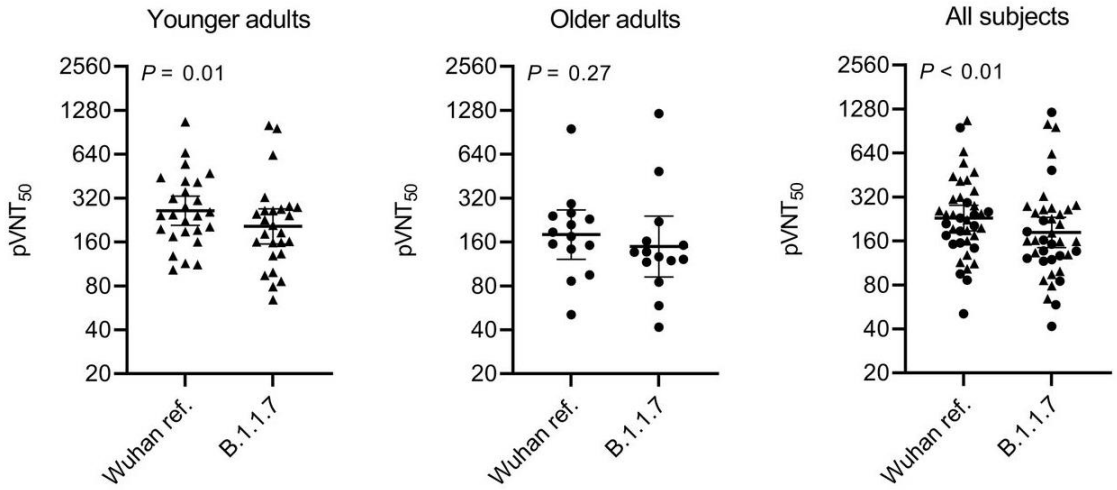


Fig. 1 50% pseudovirus neutralization titers (pVNT50) of 40 sera from BNT162b2 vaccine recipients against VSV-SARS-CoV-2-S pseudovirus bearing the Wuhan or lineage B.1.1.7 spike protein.

N = 26 sera from younger adults (aged 23 to 55 yrs; indicated by triangles) and n = 14 sera from older adults (aged 57 to 73 yrs; indicated by circles) drawn at either day 29 or day 43 (7 or 21 days after dose 2) were tested. Statistical significance of the difference between the neutralization of the VSV-SARS-CoV-2-S pseudovirus bearing the Wuhan or lineage B.1.1.7 spike protein was calculated by a Wilcoxon matched-pairs signed rank test. Two-tailed p-values are reported. Geometric mean titer (GMT) and 95% confidence intervals are indicated.

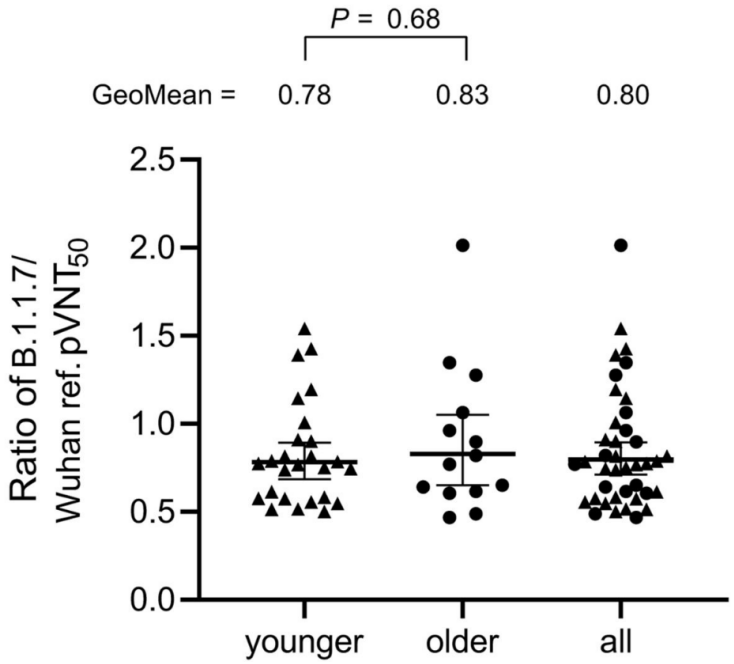


Fig. 2 Ratio of pVNT50 between SARS-CoV-2 lineage B.1.1.7 and Wuhan reference strain spike-pseudotyped VSV.

Triangles represent sera from younger adults (aged 23 to 55 yrs), and circles represent sera from older adults (aged 56 to 73 yrs). Sera were drawn either on day 29 or day 43 (7 or 21 days after dose 2). The geometric mean ratio of pVNT50 between SARS-CoV-2 lineage B.1.1.7 and Wuhan reference strain spike-pseudotyped VSV and 95% confidence intervals are indicated. The difference in distribution of titer ratios between younger and older adults was tested for statistical significance with a two-tailed Mann-Whitney-U test.

THE IMPACT OF VACCINATION ON COVID-19 OUTBREAKS IN THE UNITED STATES

Moghadas SM, Vilches TN, Zhang K, Wells CR, Shoukat A, Singer BH, Meyers LA, Neuzil KM, Langley JM, Fitzpatrick MC, Galvani AP.. Clin Infect Dis. 2021 Jan 30:ciab079. doi: 10.1093/cid/ciab079. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

An interdisciplinary group of researchers from the USA, Canada, and Brazil developed a model of SARS-CoV-2 transmission in the United States assuming 40% vaccination coverage in 284 days (Table 1). With healthcare workers and high-risk individuals prioritized and no vaccine given to those under 18, vaccination reduced the overall attack rate (9.0% to 4.6%) and adverse outcomes (non-ICU hospitalizations, ICU hospitalizations, and mortality decreased by 63.5%, 65.6%, and 69.3%, respectively) (Figure 2, Figure 4). The authors suggest even low rates of vaccination could reduce the burden of COVID-19 in the United Sates if non-pharmaceutical public health interventions such as masking and handwashing continue.

ABSTRACT

BACKGROUND: Global vaccine development efforts have been accelerated in response to the devastating COVID-19 pandemic. We evaluated the impact of a 2-dose COVID-19 vaccination campaign on reducing incidence, hospitalizations, and deaths in the United States (US). METHODS: We developed an agent-based model of SARS-CoV-2 transmission and parameterized it with US demographics and age-specific COVID-19 outcomes. Healthcare workers and high-risk individuals were prioritized for vaccination, while children under 18 years of age were not vaccinated. We considered a vaccine efficacy of 95% against disease following 2 doses administered 21 days apart achieving 40% vaccine coverage of the overall population within 284 days. We varied vaccine efficacy against infection, and specified 10% pre-existing population immunity for the base-case scenario. The model was calibrated to an effective reproduction number of 1.2, accounting for current non-pharmaceutical interventions in the US. RESULTS: Vaccination reduced the overall attack rate to 4.6% (95% CrI: 4.3% - 5.0%) from 9.0% (95% CrI: 8.4% - 9.4%) without vaccination, over 300 days. The highest relative reduction (54-62%) was observed among individuals aged 65 and older. Vaccination markedly reduced adverse outcomes, with non-ICU hospitalizations, ICU hospitalizations, and deaths decreasing by 63.5% (95% CrI: 60.3% - 66.7%), 65.6% (95% CrI: 62.2% - 68.6%), and 69.3% (95% CrI: 65.5% - 73.1%), respectively, across the same period. CONCLUSIONS: Our results indicate that vaccination can have a substantial impact on mitigating COVID-19 outbreaks, even with limited protection against infection. However, continued compliance with non-pharmaceutical interventions is essential to achieve this impact.

Table 1. Description of model parameters and their estimates.

Description	0–4	5–19	20–49	50–64	65–79	80+	Source
Transmission probability per contact during pre-symptomatic stage	Depending on the level of herd immunity 0.0395, 0.042, 0.0465						Calibrated to R=1.2 [48]
Incubation period (days)	LogNormal(shape: 1.434, scale: 0.661)						[32]
Asymptomatic period (days)	Gamma(shape: 5, scale: 1)						Derived from [34,35]
Pre-symptomatic period (days)	Gamma(shape: 1.058, scale: 2.174)						Derived from [30,33]
Infectious period from onset of symptoms (days)	Gamma(shape: 2.768, scale: 1.1563)						Derived from [34]
Proportion of infections that are asymptomatic	0.30	0.38	0.33	0.33	0.19	0.19	[54–56]
Proportion of symptomatic cases that exhibit mild symptoms	0.95	0.90	0.85	0.60	0.20	0.20	[26,37]
Proportion of cases hospitalized with one or more comorbidities	37.6%						[16,17]
Non-ICU	67%						
ICU	33%						
Proportion of cases hospitalized without any comorbidities	9%						[16,17]
Non-ICU	75%						
ICU	25%						
Length of non-ICU stay (days)	Gamma(shape: 4.5, scale: 2.75)						Derived from [38,39]
Length of ICU stay (days)	Gamma(shape: 4.5, scale: 2.75) + 2						Derived from [38,39]

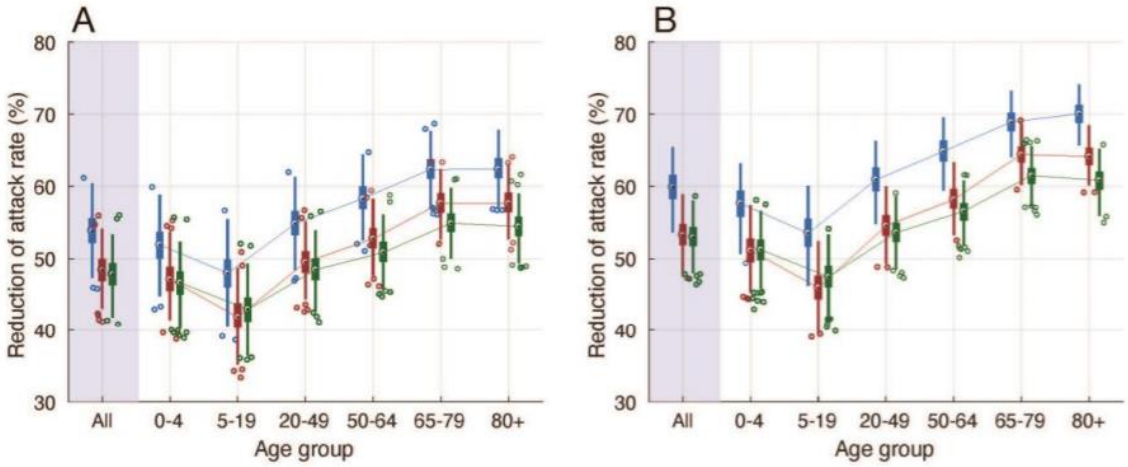


Figure 2. Overall and age-specific relative reduction of mean attack rates with vaccination, as compared to the outbreak scenario in the absence of vaccination, with 5% (blue), 10% (red), and 20% (green) levels of pre-existing immunity over 300 days. Panels (A) and (B) correspond, respectively, to scenarios with and without reduction of vaccine efficacy in comorbid individuals and the elderly.

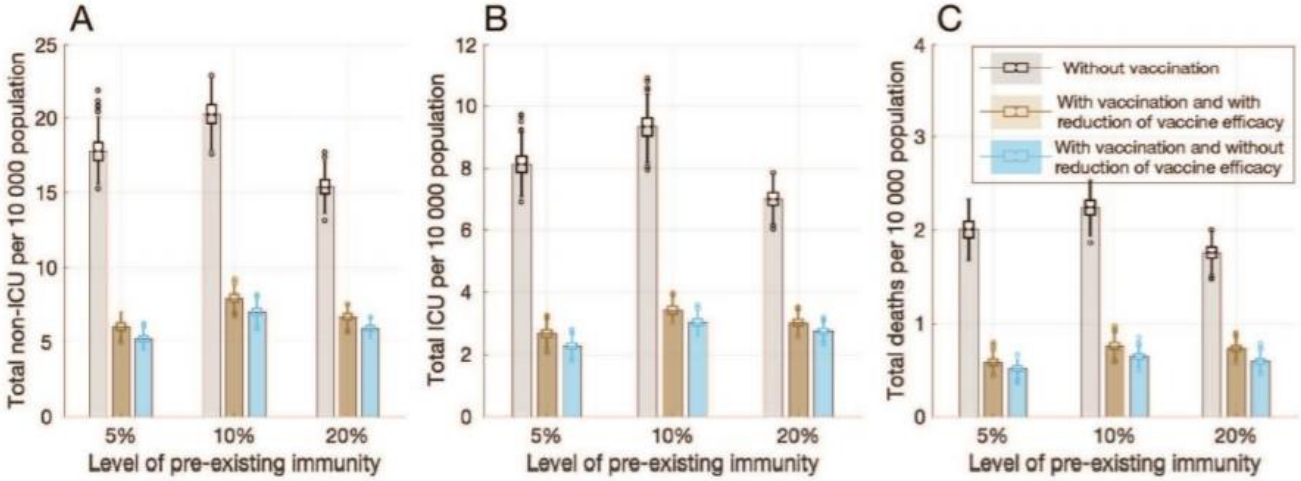


Figure 4. Projected total number of non-ICU hospitalizations (A), ICU hospitalizations (B), and deaths (C) per 10,000 populations with 5%, 10%, and 20% levels of pre-existing immunity over 300 days. Colored bars with vaccination correspond, respectively, to scenarios with (brown) and without (blue) reduction of vaccine efficacy in comorbid individuals and the elderly.

FACTORS THAT AFFECT THE DURATION OF WEARING DISPOSABLE PERSONAL PROTECTIVE EQUIPMENT BY HEALTHCARE PROFESSIONALS IN WUHAN DURING TREATMENT OF COVID-19 PATIENTS: AN EPIDEMIOLOGICAL STUDY

Li F, Jiang T, Shi T, Liu Y, Liu X, Xu G, Liu Y, Shi Y.. Nurs Health Sci. 2021 Jan 13. doi: 10.1111/nhs.12814. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A cross-sectional study of 139 front-line healthcare workers at LeiShenShan Hospital in Wuhan, China between March 16, 2020 to April 1, 2020 investigated factors that affect the duration of personal protective equipment (PPE) usage in order to identify the optimal duration and safety limits of re-use. The study found the mean duration of PPE usage during a single work shift to be 194.17 minutes with many factors including the level of discomfort in wearing PPE to be significantly associated with the duration its usage (Table 4). Additionally, none of the examined healthcare workers developed COVID-19 symptoms during the study period, indicating the duration of PPE usage to be within the safe range.

SUMMARY

Factors affecting the duration of PPE usage:

1. The presence of a chronic disease: Healthcare workers with chronic disease tended to wear PPE for longer periods of time as compare workers without chronic disease (p=0.008).

2. Working hours when felling discomfort: Those that felt discomfort soon after wearing PPE used it for a shorter duration (p=0.001).

3. Amount of patient cooperation: Lack of patient cooperation affected the psychological status of healthcare professionals which led to psychological pressure in the healthcare worker, essentially reducing the duration of PPE usage. This psychological pressure was negatively associated with duration of PPE use (p=0.003)

4. A long continuous time of wearing PPE: Workers with longer working hours wore PPE for longer (p=0.018).

5. Feeling anxious about physical strength: Medical professionals who experienced anxiety were more likely to wear PPE for a shorter duration (p=0.015).

6. The presence of fatigue when wearing PPE: Healthcare workers who developed symptoms of fatigue wore their PPE longer than those who did not (p=0.024).

ABSTRACT

The purpose of this study of healthcare workers who cared for COVID-19 patients was to identify factors that affected the duration of wearing personal protective equipment (PPE). The results of this study will provide initial guidance to practicing clinicians and a foundation for further research on this topic. This cross-sectional study examined 139 frontline healthcare professionals who worked at a single hospital in Wuhan, China from March 16 to April 1, 2020. General and demographic data, physical and mental status, use of PPE, type of hospital work, and duration of wearing PPE were recorded. The mean duration of wearing PPE was 194.17 min (standard deviation: 3.71). Multiple linear regression analysis indicated that the duration of wearing PPE was significantly associated with the presence of a chronic disease, working hours when feeling discomfort, lack of patient cooperation and subsequent psychological pressure, prolonged continuous wearing of PPE, feeling anxious about physical strength, and the presence of fatigue when wearing PPE. These factors should be considered by practicing healthcare professionals and in future studies that examine the optimal duration of wearing PPE.

Label	*B*	*SE*	*β*	*t*	*p*
Constant	151.526	14.447	-	10.488	<0.001
Do you have a chronic disease(hypertension, diabetes, etc.)?(yes or no)	18.843	6.961	0.209	2.707	0.008
The hours working when feeling discomfort wearing PPE	0.170	0.051	0.254	3.326	0.001
Did lack of patient cooperation lead to psychological pressure? (yes or no)	-21.196	6.950	-0.233	-3.050	0.003
The maximum working hours when continuously wearing PPE	0.075	0.031	0.186	2.395	0.018
Did you feel anxious when your physical strength reached a limit? (yes or no)	-16.992	6.883	-0.189	-2.469	0.015
Did you have fatigue when wearing PPE? (yes or no)	16.802	7.368	0.174	2.280	0.024

Note: R=0.503, R^2=0.253, adjusted R^2=0.219, F=7.346, p<0.001

Table 4. Multiple linear regression analysis of the association of different variables with the duration of wearing PPE (n = 139).

CARDIOLOGY

THE VALUE OF ECG CHANGES IN RISK STRATIFICATION OF COVID-19 PATIENTS

Bergamaschi L, D'Angelo EC, Paolisso P, Toniolo S, Fabrizio M, Angeli F, Donati F, Magnani I, Rinaldi A, Bartoli L, Chiti C, Biffi M, Pizzi C, Viale P, Galié N.. Ann Noninvasive Electrocardiol. 2021 Jan 29:e12815. doi: 10.1111/anec.12815. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A prospective cohort study conducted by cardiologists in Bologna, Italy found a significant correlation between major adverse events (MAEs) and abnormal EKG findings in patients hospitalized with COVID-19. EKG abnormalities (Tables 1, 2) were associated with increased MAEs when present both at hospital admission (p=0.04) and on hospital day #7 (p=0.001), with MAEs defined as mortality, ICU admission, invasive mechanical ventilation, and renal replacement therapy. The results of this study highlight the potential role of EKGs in triaging and prognosticating patients with COVID-19.

ABSTRACT

BACKGROUND: There is growing evidence of cardiac injury in COVID-19. Our purpose was to assess the prognostic value of serial electrocardiograms in COVID-19 patients. METHODS: We evaluated 269 consecutive patients admitted to our center with confirmed SARS-CoV-2 infection. ECGs available at admission and after 1 week from hospitalization were assessed. We evaluated the correlation between ECGs findings and major adverse events (MAE) as the composite of intra-hospital all-cause mortality or need for invasive mechanical ventilation. Abnormal ECGs were defined if primary ST-T segment alterations, left ventricular hypertrophy, tachy or bradyarrhythmias and any new AV, bundle blocks or significant morphology alterations (e.g., new Q pathological waves) were present. RESULTS: Abnormal ECG at admission (106/216) and elevated baseline troponin values were more common in patients who developed MAE (p = .04 and p = .02, respectively). Concerning ECGs recorded after 7 days (159), abnormal findings were reported in 53.5% of patients and they were more frequent in those with MAE (p = .001). Among abnormal ECGs, ischemic alterations and left ventricular hypertrophy were significantly associated with a higher MAE rate. The multivariable analysis showed that the presence of abnormal ECG at 7 days of hospitalization was an independent predictor of MAE (HR 3.2; 95% CI 1.2-8.7; p = .02). Furthermore, patients with abnormal ECG at 7 days more often required transfer to the intensive care unit (p = .01) or renal replacement therapy (p = .04). CONCLUSIONS: Patients with COVID-19 should receive ECG at admission but also during their hospital stay. Indeed, electrocardiographic alterations during hospitalization are associated with MAE and infection severity.

TABLE 1 Electrocardiogram findings and outcomes of COVID-19 patients at admission

	Total $N = 216$	No major events $N = 162$	Major events $N = 54$	p-valu e
ECG evaluation				
Sinus rhythm	194 (89.8%)	143 (88.3%)	51 (94.4%)	.2
Atrial fibrillation	20 (9.3%)	17 (10.5%)	3 (5.6%)	.3
HR, bpm	78 (69–89)	77 (69–88)	81 (70–96)	.3
First-degree AV block	12 (5.5%)	9 (5.5%)	3 (5.8%)	.9
QRS complex, msec	93 (85–105)	92 (85–104)	95.5 (87–105)	.
Peripheral low voltage	12 (5.6%)	8 (4.9%)	4 (7.4%)	.5
LAFB	19 (8.8%)	11 (6.8%)	8 (14.8%)	.07
RBBB	15 (6.9%)	9 (5.6%)	6 (11.1%)	.1
LBBB	6 (2.8%)	4 (2.5%)	2 (3.7%)	.6
QT, msec	395 (360–428)	395 (360–428)	400 (360–428)	.8
QTc, msec	440 (422–465)	439 (420–460)	460 (430–473)	.05
Normal ECG	110 (50.9%)	89 (54.9%)	21 (38.9%)	.04
Abnormal ECG	106 (49.1%)	73 (45.1%)	33 (61.1%)	
Primary ST-T segment alterations	12 (5.6%)	5 (3.1%)	7 (13.0%)	.006
Left ventricular hypertrophy	16 (7.4%)	6 (3.7%)	10 (18.5%)	<.001
Other ECG findings	78 (36.1%)	61 (37.7%)	17 (31.5%)	.4
Elevated hs-Tn I	26/60 (43.3%)	10 (30.3%)	16 (59.3%)	.02

Note: Continuous variables are presented as median (IQR) while categorical ones as n (%) or n/N (%), where N is the total number of patients with available data.

Abbreviations: AV, atrioventricular; ECG, electrocardiogram; HR, heart rate; hs – Tn I, high-sensitivity cardiac Troponin I; LAFB, left anterior fascicular block; LBBB, left bundle branch block; RBBB, right bundle branch block.

Other findings = new tachy or bradyarrhythmias and any new AV, bundle blocks or significant morphology alterations (e.g., new Q pathological wave)

TABLE 2 Electrocardiogram findings and outcomes of COVID-19 patients at 7 days of hospitalization

	Total $N = 159$	No major events $N = 111$	Major events $N = 48$	p-valu e
ECG evaluation				
Sinus rhythm	140 (88.1%)	96 (86.5%)	44 (91.7%)	.3
Atrial fibrillation	17 (10.7%)	13 (11.7%)	4 (8.3%)	.5
HR, bpm (IQR)	76 (65–84)	74 (65–80)	82 (73–95)	.001
First-degree AV block	7 (4.4%)	4 (3.6%)	3 (6.3%)	.4
QRS complex, msec	94 (87–104)	92 (86–104)	96 (90–103)	.
Peripheral low voltage	8 (5.0%)	3 (2.7%)	5 (10.4%)	.04
LAFB	12 (7.5%)	8 (7.2%)	4 (8.3%)	.8
RBBB	11 (6.9%)	7 (6.3%)	4 (8.3%)	.6
LBBB	5 (3.1%)	3 (2.7%)	2 (4.2%)	.6
QT, msec	410 (380–440)	417 (385–440)	398 (366–440)	.09
QTc, msec	452 (432–475)	450 (433–474)	458 (431–484)	.4
Normal ECG	74 (46.5%)	61 (55.0%)	13 (27.1%)	.001
Abnormal ECG	85 (53.5%)	50 (45.0%)	35 (72.9%)	
Primary ST-T segment alterations	13 (8.2%)	5 (4.5%)	8 (16.7%)	.01
Left ventricular hypertrophy	14 (8.8%)	6 (5.4%)	8 (16.7%)	.02
Other ECG findings	58 (36.5%)	39 (35.1%)	19 (39.6%)	.6
Delta HR ≥20%[a]	17/149 (11.4%)	7 (6.3%)	10 (26.3%)	.001
Wide QRS acquired[b]	6/146 (4.1%)	1 (1%)	5 (11.6%)	.003

Note: Continuous variables are presented as median (IQR) while categorical ones as n (%) or n/N (%), where N is the total number of patients with available data.

Abbreviations: AV, atrioventricular; ECG, electrocardiogram; HR, heart rate; LAFB, Left anterior fascicular block; LBBB, Left bundle branch block; RBBB, right bundle branch block.

Other findings, new tachy or bradyarrhythmias and any new AV, bundle blocks or significant morphology alterations (e.g., new Q pathological wave).

[a]Respect to admission heart rate.

[b]Respect to admission QRS duration.

TABLE 3 All-cause intra-hospital mortality or orotracheal intubation and other outcomes according to ECG findings at 7 days of hospitalization

	Total $N = 159$	Normal ECG $N = 74$	Abnormal ECG $N = 85$	p-valu e
All-cause mortality/OTI	48 (30.2%)	13 (17.6%)	35 (41.2%	.001
All-cause mortality	26/152[a] (17.1%)	5 (7.0%)	21 (25.9%)	.002
Admission to ICU	33 (20.8%)	9 (12.2%)	24 (28.2%)	.01
CVVH	5 (3.1%)	1 (1.3%)	7 (8.2%)	.04
ECMO	4 (2.5%)	1 (1.4%)	3 (3.5%)	.4

Note: Categorical variables are presented as n (%) or n/N (%), where N is the total number of patients with available data.

Abbreviations: CVVH, renal failure requiring continuous veno-venous hemofiltration; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; OTI, orotracheal intubation.

[a]7 patients were still hospitalized.

AMBIENT NOISE LEVELS AND WIRELESS HEADSETS FOR COMMUNICATION IN AEROSOLIZING OTOLARYNGOLOGY SURGERY DURING COVID-19

Levin M, Zhou K, Sommer EC, McHugh T, Sommer DD.. Otolaryngol Head Neck Surg. 2021 Jan 12:194599820986584. doi: 10.1177/0194599820986584. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

An observational survey study conducted in Toronto, Canada, examined the effect of noise-cancelling headphones on operating room (OR) communication in OR procedures involving COVID-19 patients requiring the use of devices such as powered air-purifying respirators (PAPR) which increase OR noise level. Survey questions included: "Was OR noise problematic?"; "Did OR noise cause issues with communication?"; "What was the biggest contributor to noise?"; and finally, "What was their experience using the PAPR/N95s?" The researchers found improvement in OR communication when using the headsets, as evidenced by study participants indicating a significantly smaller likelihood of encountering communication problems when wearing headphones, compared to non-headphone wearers (93% vs. 31%, P < .001). Authors believe the results of this study offer a potential solution to improve operating room communication during this pandemic.

SUMMARY

This study included a list of benefits as well as potential drawbacks for the use of different headphone models (figure 1). The headsets themselves were connected via the WhatsAPP application for communication.

ABSTRACT

The objective of this short scientific communication is to describe and test a strategy to overcome communication barriers in coronavirus disease 2019 (COVID-19) era otolaryngology operating rooms. Thirteen endoscopic sinus surgeries, 4 skull base surgeries, and 1 tracheotomy were performed with powered air-purifying respirators. During these surgeries, surgical team members donned headsets with microphones linked via conference call. Noise measurements and survey responses were obtained and compared to pre-COVID-19 data. Noise was problematic and caused miscommunication as per 93% and 76% of respondents, respectively. Noise in COVID-19 era operating rooms was significantly higher compared to pre-COVID-19 era data (73.8 vs 70.2 decibels, P = .04). Implementation of this headset strategy significantly improved communication. Respondents with headsets were less likely to encounter communication problems (31% vs 93%, P < .001). Intraoperative measures to protect surgical team members during aerosolizing surgeries may impair communication. Linking team members via a conference call is a solution to improve communication.

FIGURES

Table 2. Summary of the Different In-Ear Wireless Headsets Used in This Study.

Headset type	Benefits	Potential drawbacks
Apple EarPods	Adequate voice broadcasting	Wired, may limit motion of wearer
Apple AirPod Pro	Adequate voice broadcasting Wireless	May interfere with brainstem auditory evoked responses and other neuromonitoring if not worn as single-ear headset
AfterShokz Air bone conduction wireless model	Does not cover wearer's ears so does not interfere with outside call communication Has behind-head strap to ensure it is secured on wearer's head	Sound quality is different compared with non–bone conduction headphones
SOUNDPEATS Truecapsule Bluetooth earphones	Adequate voice broadcasting Wireless	May interfere with brainstem auditory evoked responses and other neuromonitoring if not worn as single-ear headset
Jabra elite sport earbuds	Wireless	Had voice broadcasting/microphone issues and may interfere with brainstem auditory evoked responses and other neuromonitoring if not worn as single-ear headset
Anker Soundcore Life P2 True Wireless Earbuds	Wireless	May interfere with brainstem auditory evoked responses and other neuromonitoring if not worn as single-ear headset

Figure 1. Summary of Different In-Ear Wireless Headphones Used in the Study.

ASSESSMENT OF MATERNAL AND NEONATAL CORD BLOOD SARS-COV-2 ANTIBODIES AND PLACENTAL TRANSFER RATIOS

Flannery DD, Gouma S, Dhudasia MB, Mukhopadhyay S, Pfeifer MR, Woodford EC, Triebwasser JE, Gerber JS, Morris JS, Weirick ME, McAllister CM, Bolton MJ, Arevalo CP, Anderson EM, Goodwin EC, Hensley SE, Puopolo KM.. JAMA Pediatr. 2021 Jan 29. doi: 10.1001/jamapediatrics.2021.0038. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A multicenter cohort study from Philadelphia analyzed blood samples from 1471 mother/newborn dyads for evidence of IgM and IgG antibodies to SARS-CoV-2. They found antibody positivity in 83 mothers (Table 1, Figure 2), while 72 of the 83 newborns also had IgG antibodies present but none with IgM (Table 3). These results support the theory of maternal-fetal IgG transfer and protection from SARS-CoV-2 during the neonatal period. More data is necessary to determine if these antibodies are protective to help guide maternal vaccination strategies.

ABSTRACT

Importance: Maternally derived antibodies are a key element of neonatal immunity. Understanding the dynamics of maternal antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy and subsequent transplacental antibody transfer can inform neonatal management as well as maternal vaccination strategies. Objective: To assess the association between maternal and neonatal SARS-CoV-2-specific antibody concentrations. Design, Setting, and Participants: This cohort study took place at Pennsylvania Hospital in Philadelphia, Pennsylvania. A total of 1714 women delivered at the study site between April 9 and August 8, 2020. Maternal and cord blood sera were available for antibody measurement for 1471 mother/newborn dyads. Exposures: SARS-CoV-2. Main Outcomes and Measures: IgG and IgM antibodies to the receptor-binding domain of the SARS-CoV-2 spike protein were measured by enzyme-linked immunosorbent assay. Antibody concentrations and transplacental transfer ratios were analyzed in combination with demographic and clinical data. Results: The study cohort consisted of 1714 parturient women, with median (interquartile range) age of 32 (28-35) years, of whom 450 (26.3%) identified as Black/non-Hispanic, 879 (51.3%) as White/non-Hispanic, 203 (11.8%) as Hispanic, 126 (7.3%) as Asian, and 56 (3.3%) as other race/ethnicity. Among 1471 mother/newborn dyads for which matched sera were available, SARS-CoV-2 IgG and/or IgM antibodies were detected in 83 of 1471 women (6%; 95% CI, 5%-7%) at the time of delivery, and IgG was detected in cord blood from 72 of 83 newborns (87%; 95% CI, 78%-93%). IgM was not detected in any cord blood specimen, and antibodies were not detected in any infant born to a seronegative mother. Eleven infants born to seropositive mothers were seronegative: 5 of 11 (45%) were born to mothers with IgM antibody only, and 6 of 11 (55%) were born to mothers with significantly lower IgG concentrations compared with those found among mothers of seropositive infants. Cord blood IgG concentrations were positively correlated with maternal IgG concentrations ($r = 0.886$; $P < .001$). Placental transfer ratios more than 1.0 were observed among women with asymptomatic SARS-CoV-2 infections as well as those with mild, moderate, and severe coronavirus disease 2019. Transfer ratios increased with increasing time between onset of maternal infection and delivery. Conclusions and Relevance: In this cohort study, maternal IgG antibodies to SARS-CoV-2 were transferred across the placenta after asymptomatic as well as symptomatic infection during pregnancy. Cord blood antibody concentrations correlated with maternal antibody concentrations and with duration between onset of infection and delivery. Our findings demonstrate the potential for maternally derived SARS-CoV-2 specific antibodies to provide neonatal protection from coronavirus disease 2019.

Characteristic	All (N = 83)	Disease			P value
		Asymptomatic (n = 50)	Mild (n = 25)[a]	Moderate to critical (n = 8)	
NP-PCR tested (mother), No. (%)[b]	82 (99)	49 (98)	25 (100)	8 (100)	>.99
NP-PCR ever positive	44 (54)	15 (31)	21 (84)	8 (100)	<.001
Reason for NP-PCR testing					
Routine admission screening	52 (63)	47 (96)	5 (20)	0	<.001
Symptoms	27 (33)	0	19 (76)	8 (100)	
Other[c]	3 (4)	2 (4)	1 (4)	0	
Time between NP-PCR test and delivery, median (IQR), d	1 (0-27)	1 (0-1)	27 (10-73)	53 (44-73)	<.001
Maternal IgM >0.48 arbitrary U/mL, No. (%)	48 (58)	28 (56)	13 (52)	7 (88)	.21
Maternal IgM concentration, geometric mean (95% CI)[d]	1.85 (1.43-2.39)	1.39 (1.03-1.89)	2.50 (1.42-4.39)	3.33 (1.60-6.93)	.77
Maternal IgG >0.48 arbitrary U/mL, No. (%)	78 (94)	46 (92)	24 (96)	8 (100)	.80
Maternal IgG concentration, geometric mean (95% CI)[d]	4.69 (3.57-6.14)	3.92 (2.82-5.46)	4.44 (2.67-7.38)	15.27 (5.82-40.09)	.91
Cord IgG >0.48 arbitrary U/mL[e]	72 (92)	44 (96)	20 (83)	8 (100)	.26
Cord IgG concentration, geometric mean (95% CI)[e,f]	4.23 (3.06-5.84)	4.01 (2.77-5.83)	3.09 (1.59-6.01)	14.58 (4.26-49.84)	.44
Transfer ratio, geometric mean (95% CI), %[e,f]	0.90 (0.76-1.07)	1.02 (0.85-1.23)	0.70 (0.48-1.01)	0.95 (0.45-2.01)	.34

Table 1. Maternal Illness Severity and Results of NP-PCR Testing and Antibody Concentrations
Abbreviations: IQR, interquartile range; NP-PCR, nasopharyngeal polymerase chain reaction; U, units.
a Mild disease in 21 of 25 cases was defined by symptoms reported in conjunction with NP-PCR testing. In the remaining 4 cases, women reported coronavirus disease 2019–consistent symptoms to obstetric caregivers prior to delivery, but testing was not done. In each case, routine NP-PCR screening results at the time of admission to labor floor were negative.
b One asymptomatic woman declined routine admission NP-PCR screening.
c Tested due to contact.
d Only values >0.48 arbitrary U/mL included in the calculation of geometric mean.
e Only includes infants born to IgG-seropositive mothers (maternal IgG >0.48 arbitrary U/mL).
f Six of 78 infants born to IgG-seropositive mothers were seronegative (cord IgG 0.48 arbitrary U/mL); cord IgG concentration was set at 0.24 arbitrary U/mL for these 6 infants.

Characteristic	No. (%)					
		Transfer ratio[a]				
	No transfer (n = 6)	<0.50 (n = 8)	0.50-<1.00 (n = 24)	1.00-<1.50 (n = 19)	1.50-<2.00 (n = 14)	≥2.00 (n = 7)
Preterm delivery at GA <37 wk	1 (17)	2 (25)	2 (8)	3 (16)	0	0
Concentration, geometric mean (95% CI)						
Maternal IgG	1.27 (0.57-2.82)	7.11 (3.52-14.33)	7.74 (4.45-13.48)	3.43 (1.83-6.44)	4.11 (2.74-6.15)	4.82 (1.82-12.75)
Maternal IgM[b]	0.44 (0.16-1.18)	1.73 (1.13-2.66)	1.44 (0.78-2.64)	0.57 (0.33-0.99)	0.38 (0.25-0.57)	0.53 (0.19-1.51)
NP-PCR tested during pregnancy	6 (100)	8 (100)	23 (96)	19 (100)	14 (100)	7 (100)
NP-PCR positive[b]	5 (83)	8 (100)	11 (48)	11 (58)	5 (36)	3 (43)
Time between positive NP-PCR test and delivery, median (IQR), d	10 (0-12)	4 (0-26)	27 (2-66)	72 (27-85)	50 (0-98)	55 (1-102)

Table 3. Characteristics Across Transfer Ratio Categories Among IgG-SeropositiveWomen (n = 78)
Abbreviations: GA, gestational age; NP-PCR, nasopharyngeal polymerase chain reaction; IQR, interquartile range.
a Transfer ratio calculated as (cord IgG concentration)/(maternal IgG concentration).
b After excluding 6 infants with no transfer, there was a significant difference between the transfer ratio categories for geometric mean maternal IgM concentration (P = .01) and number of NP-PCR–positive women (P = .04); all other characteristics were not significantly different (P > .05) between the transfer ratio categories.

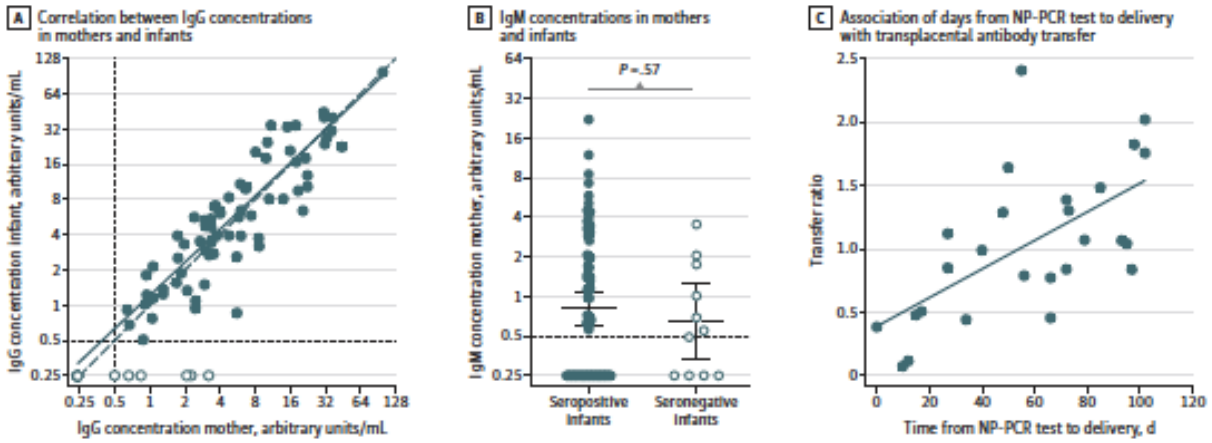


Figure 2. Correlation Between Maternal and Neonatal Cord Sera Severe Acute Respiratory Syndrome Coronavirus 2–Specific Antibody Concentrations

A, Correlation between IgG concentrations in sera from seropositive women and matched cord blood from seropositive (n = 72; filled circles) and seronegative (n = 11; open circles) infants. IgG concentrations in cord blood positively correlate with maternal IgG concentrations (r = 0.886; P < .001). B, IgMconcentrations in sera from seropositive women with seropositive (n = 72; filled circles) and seronegative (n = 11; open circle) infants. Horizontal lines represent geometric mean titers and error bars indicate the 95%CI (P = .57 using an unpaired t test on log2-transformed IgM concentrations). In panels A and B, the horizontal dashed line indicates 0.48 arbitrary units/mL, which was the cutoff used to distinguish positive vs negative samples. Samples that were below this cutoff were assigned an antibody concentration of 0.24 arbitrary units/mL. C, Association of duration in days from nasopharyngeal polymerase chain reaction (NP-PCR) test to delivery with transplacental antibody transfer. Transfer ratio of IgG antibodies from mother to infant (n = 26 matched mother-infant dyads) is positively correlated with days from NP-PCR test to delivery (r = 0.620; P < .001).

WILL THE EMERGENT SARS-COV2 B.1.1.7 LINEAGE AFFECT MOLECULAR DIAGNOSIS OF COVID19?

Ramírez JD, Muñoz M, Patiño LH, Ballesteros N, Paniz-Mondolfi A.. J Med Virol. 2021 Jan 28. doi: 10.1002/jmv.26823. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

Microbiologists from Columbia, Venezuela, and the United States assessed whether the Berlin-Charité protocol for RT-PCR assays could detect the new SARS-CoV-2 B.1.1.7 lineage from the United Kingdom. Using 3,296 full genome sequences, they found the primer and probes detected 98% of the RdRp, N, and E genes targeted in the protocol, though several sequences were missed. The authors suggest that while the Berlin-Charité protocol can detect most SARS-CoV-2 B.1.1.7 variants, future variants may evade detection and incorporating different regions of the viral genome into existing testing could build redundancies that increase the likelihood of their detection.

ABSTRACT

As the COVID19 pandemic keep tackling global public health systems worldwide. The SARS-CoV2 genome keeps mutating. In that regard, the recent emergence of the B.1.1.7 lineage in the United Kingdom has called the attention of global authorities. One point of concern is that if this lineage can be detected by traditional molecular schemes for SARS-CoV2 detection. Herein, we showed that this lineage does not affect the Berlin-Charite protocol but can challenge the available commercial kits directed to the Spike (S) gene. All efforts should be made to continue to monitor SARS-CoV-2 genomes for potential variants that can impair diagnostic testing and lead to false negative results. This article is protected by copyright. All rights reserved.

EXPLORING SALIVARY DIAGNOSTICS IN COVID-19: A SCOPING REVIEW AND RESEARCH SUGGESTIONS

Kapoor P, Chowdhry A, Kharbanda OP, Bablani Popli D, Gautam K, Saini V.. BDJ Open. 2021 Jan 26;7(1):8. doi: 10.1038/s41405-021-00064-7.
Level of Evidence: 5 - Review / Literature Review

BLUF

A scoping review conducted by medical institutions and laboratories in New Delhi, India in June 2020 identified 17 articles (See Figure 2) finding saliva-based molecular diagnostics as a simpler, time-conscious, and less technical alternative to nasopharyngeal swab collection for detection of SARS-CoV-2 based on parameters of gene targets, viral load, sensitivity, and point-of-care testing (See Table 2) for initial screening in community and hospital-based settings. Salivary testing also allows for simpler self-collection, which decreases the amount of medical staff and personal protective equipment needed for screening settings. This article suggests more robust studies be performed to further assess salivary testing in asymptomatic cases, oral symptoms of infection, and accounting for age, sex, and other comorbidities.

ABSTRACT

INTRODUCTION: Molecular diagnostics for SARS-CoV-2 infection characteristically involves the sampling of the throat or nasopharyngeal swab (NPS). However, these procedures are invasive, require necessary skills for sample collection, cause patient discomfort, and are non-conducive for extensive scale testing. Saliva is increasingly being suggested as an alternate diagnostic sample in SARS-CoV-2 infection. OBJECTIVES: This scoping review was done with the objective of exploring the evidence on the role of saliva as an alternate diagnostic sample in SARS-CoV-2 condition. METHODS: Thorough search of the literature in major databases was undertaken in June 2020 using free text and MESH terms, followed by PRISMA to identify 17 studies for data extraction. RESULTS AND CONCLUSIONS: Evidence was summarised for study characteristics, salivary sampling characteristics, viral load, and longevity of virus in saliva. The literature supports that saliva offers a simple sample collection method compared to technique-sensitive NPS and has the advantage of point-of-care testing for initial screening in community or hospital-based set-up. The additional highlights of this review are heterogeneity in the current literature and the gaps in methodology. Therefore, a robust study design to generate higher levels of evidence has been proposed.

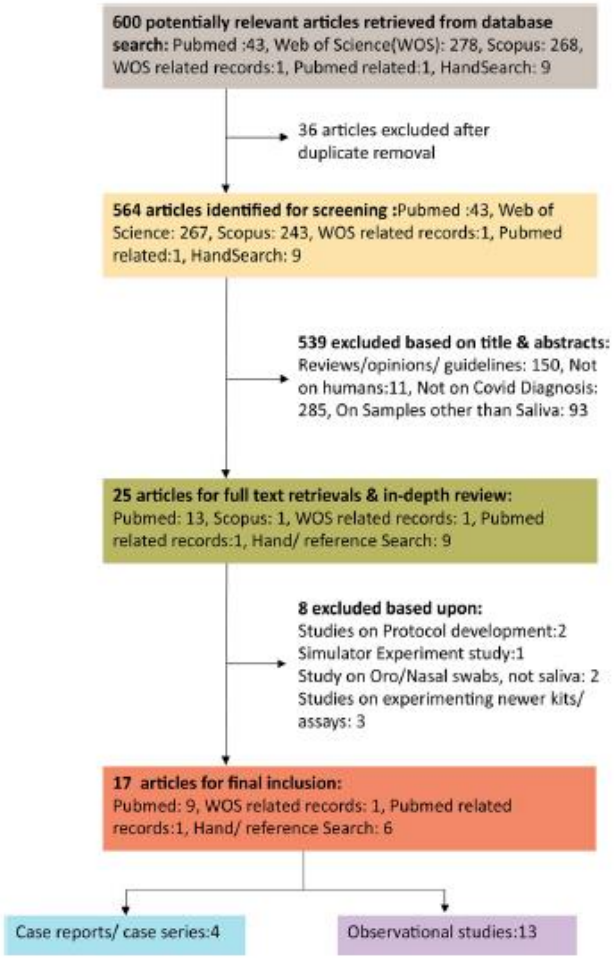


Fig. 2 Search strategy. Preferred reporting Items for systematic reviews and meta-analysis (PRISMA) was employed to search the literature from different sources.

Table 2. Comparison of parameters in saliva and nasopharyngeal swabs.

Parameters	Specific characteristics	Results
Gene targets	E and N2 gene targets	Earlier median Ct value in NPS than in saliva, statistically significant in one study—$p = 0.0002$,[32] non-significant in other[26]
	ORF1ab and N genes	Lower median Ct value (32.0 and 30.5), in NPS than in saliva (32.7 and 31.8), for ORF1ab and N genes, respectively, though non-significant[24]
		Detection of ORF1ab and nCoV-N in NPS > saliva[21]
Mean viral titre	Salivary viral load > NPS	SARS-CoV-2 RNA copies in saliva (mean $\log_{10}$ 5.58) greater than NPS (mean $\log_{10}$ 4.93)[16]
		Viral load higher (5.9×10^6 copies/mL) in saliva than pooled NPS and throat swabs (3.3×10^6 copies/mL) in 1 patient out of 42 confirmed cases[22]
	Salivary viral load <NPS	Study on neonate: a steep difference in viral load level in NPS than in saliva in early stages of the disease[20]
		Significantly high viral titres with significantly low Ct values in NPS than in saliva at all time points[28]
Viral sensitivity	Positive results in saliva and not in NPS on same day collection	Multiple studies reported the finding in paired NPS and salivary samples: ($n = 1$),[25,29] ($n = 2$),[17,24] ($n = 3$)[22]
	Sensitivity in NPS > saliva	Saliva positive in 4 out of the 13 subjects tested positive by NPS[21]
		COVID-19 screening clinic: 39 out of 622 NPS samples tested PCR-positive (6.3%; 95% CI, 4.6–8.5%), and out of these 39 patients, 33 salivary samples tested SARS-CoV-2 positive (84.6%; 95% CI, 70.0–93.1%)[29]
		A single case report of two male patients: >60 years, showed positive salivary sample on day 10 and 26 after hospital admission, whereas 2 consecutive NPS samples came negative[21]
POCT	Viability of saliva for POCT	Two studies, one study showed high +ve percent agreement b/w NPS and saliva (96%, 47/49 positive samples)[23] and high −ve percent agreement (99%, 1 sample +ve for saliva out of 106 samples −ve for NPS),[23] the second study showed +ve testing of virus in both saliva and NPS (49/58), greater in NPS only [10.3% (6/58)] compared to saliva only [5.2% (3/58)][32]

The parameters of gene targets, mean viral load, and sensitivity have been compared between saliva and NPS.
+ve positive, −ve negative, b/w between, *CI* confidence interval, *Ct* cycle threshold, *NPS* nasopharyngeal swab, *PCR* polymerase chain reaction, *POCT* point-of-care testing.

Table 2. Comparison of parameters in saliva and nasopharyngeal swabs.

SELF-COLLECTED SALINE GARGLE SAMPLES AS AN ALTERNATIVE TO HEALTHCARE WORKER COLLECTED NASOPHARYNGEAL SWABS FOR COVID-19 DIAGNOSIS IN OUTPATIENTS

Goldfarb DM, Tilley P, Al-Rawahi GN, Srigley JA, Ford G, Pedersen H, Pabbi A, Hannam-Clark S, Charles M, Dittrick M, Gadkar VJ, Pernica JM, Hoang LMN.. J Clin Microbiol. 2021 Jan 29:JCM.02427-20. doi: 10.1128/JCM.02427-20. Online ahead of print.

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

BLUF

Microbiologists and laboratory scientists from British Columbia, Canada investigated the reliability of saliva samples for SARS-CoV-2 PCR in 40 patients (adult and pediatric) with SARS-CoV-2. They found Nasopharyngeal (NP) swab PCR had a sensitivity of 95%, while PCR of mouth rinse/gargle samples had a sensitivity of 98% and saliva a sensitivity of 79% (Table 1, with true positive defined as any test positivity). Patients rated both the mouth rinse/gargle and saliva collection methods more favorably than NP swab (Table 2). Authors suggest collecting mouth rinse/gargle and saliva samples for SARS-CoV-2 PCR is an effective patient-friendly testing modality that could have great utility as testing becomes an integral part of daily life in a pandemic.

ABSTRACT

Background: We assessed the performance, stability, and user acceptability of swab-independent self-collected saliva and saline mouth rinse/gargle sample types for the molecular detection of SARS-CoV-2 in adults and school-aged children. Methods: Outpatients who had recently been diagnosed with COVID-19 or were presenting with suspected COVID-19 were asked to have a nasopharyngeal swab collected and provide at least one self-collected sample type. Participants were also asked about sample acceptability using a five point Likert scale. For those previously diagnosed with COVID-19, all samples underwent real-time PCR testing using a lab-developed assay, and the majority were also tested using an FDA-authorized assay. For those presenting with suspect COVID-19, only those with a positive nasopharyngeal swab sample went on to have other samples tested. Saline mouth rinse/gargle and saliva samples were tested daily at time zero, day one, and day 2 to assess nucleic acid stability at room temperature. Results: 50 participants (aged 4 to 71 years) were included; of these, 40 had at least one positive sample and were included in the primary sample yield analysis. Saline mouth rinse/gargle samples had a sensitivity of 98% (39/40) while saliva samples had a sensitivity of 79% (26/33). Both saline mouth rinse/gargle and saliva samples showed stable viral RNA detection after 2 days of room temperature storage. Mouth rinse/gargle samples had the highest (mean 4.9) and HCW-collected NP swabs had the lowest acceptability scores (mean 3.1). Conclusion: Saline mouth rinse/gargle samples demonstrated the highest combined user acceptability ratings and analytical performance when compared with saliva and HCW collected NP swabs. This sample type is a promising swab-independent option, particularly for outpatient self-collection in adults and school aged children.

Table 1. Performance of sample types in 40 COVID-19 positive participants

Study ID	NP Swab (LDT)	NP Swab (Gx)	Gargle (LDT)	Gargle (Gx)	Saliva (LDT)
1	P	P	P	P	P
2	P	P	P	P	N
3	N	PP	P	NT	N
4	P	P	P	PP	N
5	P	P	P	P	P
6	NT	NT	P	P	P
7	P	P	P	P	P
8	P	P	P	P	P
9	P	P	P	P	P
10	P	P	P	P	N
11	P	P	P	P	P
12	P	P	P	P	P
13	P	P	P	P	P
14	P	P	P	P	P
15	P	P	P	P	P
16	P	P	P	P	P
17	P	P	P	P	P
18	P	P	P	P	P
19	P	P	P	P	P
20	NT	NT	P	P	P
21	NT	NT	P	P	P
22	P	P	P	P	P
23	P	P	P	P	P
24	P	P	P	P	N
25	P	P	P	P	P
26	P	P	P	P	P
27	P	P	P	P	P
28	N	N	P	P	P
29	P	P	P	P	P
30	P	P	P	N	P
31	P	P	N	P	N
32	P	P	P	P	N
33	P	P	P	P	P
34	P	NT	P	P	NT
35	P	NT	P	P	NT
36	P	NT	P	P	NT
37	P	NT	P	P	NT
38	P	NT	P	P	NT
39	P	NT	P	P	NT
40	P	NT	P	P	NT
N=40	35/37	29/30	39/40	38/39	26/33
Sensitivity	NA	NA	97.5%	97.4%	78.8%
95% CI	NA	NA	86.8, 99.9	86.5, 99.9	61.0, 91.0

NP = nasopharyngeal, LDT = laboratory developed test, Gx = genexpert assay, NA = not applicable, P = positive test, N = negative test, PP = presumptive positive, NT = not tested, CI = confidence interval

Table 2. Acceptability of sample types as rated on a 5 point Likert scale (1= lowest acceptability and 5 = highest acceptability)

Sample	Mean acceptability	Acceptability difference		95%CI of difference	Tukey p of difference
Mouth Rinse/Gargle	4.95	vs: saliva NPFS	 0.50 1.78	 0.0074 to 0.99 1.28 to 2.27	 0.046 <0.001
Saliva	4.45	vs: NPFS	 1.28	 0.78 to 1.77	 <0.001
NPFS	3.17				

NPFS = nasopharyngeal flocked swab, CI = confidence interval

A REVIEW ON HUMAN BODY FLUIDS FOR THE DIAGNOSIS OF VIRAL INFECTIONS: SCOPE FOR RAPID DETECTION OF COVID-19

Adigal SS, Rayaroth NV, John RV, Pai KM, Bhandari S, Mohapatra AK, Lukose J, Patil A, Bankapur A, Chidangil S.. Expert Rev Mol Diagn. 2021 Feb 1:1-12. doi: 10.1080/14737159.2021.1874355. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A review article from medical institutions in Manipal, India discusses that saliva, tears, and breath samples may offer more readily available, reliable, and faster techniques for rapid detection of SARS-CoV-2. Their findings (summarized in Table 1 and specific details summarized below) support use of these methods and indicate they may be more suitable for large-scale screening compared to the current gold standard of nasopharyngeal testing.

SUMMARY

The techniques described in the review require the use of highly sensitive optical techniques, such as high-performance liquid chromatography coupled with laser-induced fluorescence (HPLC-LIF) for saliva and tears (Figure 1) and photo-acoustic absorption spectroscopy (Figure 7) and E-nose based technology for breath samples extrapolated to include rapid detection of SARS-CoV-2.

ABSTRACT

Introduction: The unprecedented outbreaks of corona virus disease of 2019 (COVID-19) have highlighted the necessity of readily available, reliable, precise, and faster techniques for its detection. Nasopharyngeal swab has been the gold standard for the diagnosis of COVID-19. However, it is not an ideal screening procedure for massive screening as it implicates the patient's stay in the hospital or at home until diagnosis, thus causing crowding of the specimen at the diagnostic centers. Present study deal with the exploration of potential application of different body fluids using certain highly objective techniques (Optical and e-Nose) for faster detection of molecular markers thereby diagnosing viral infections. Areas covered: This report presents an evaluation of different body fluids, and their advantages for the rapid detection of COVID-19, coupled with highly sensitive optical techniques for the detection of molecular biomarkers. Expert opinion: Tears, saliva, and breath samples can provide valuable information about viral infections. Our brief review strongly recommends the application of saliva/tears and exhaled breath as clinical samples using technics such as high-performance liquid chromatography-laser-induced fluorescence, photoacoustic spectroscopy, and e-Nose, respectively, for the fast diagnosis of viral infections.

FIGURES

Table 1. Biosafety guidelines for collection, transportation, storage, and detection rate of COVID-19 based on different body fluids.

Specimens	Sites	Collection and procedure	Temperature maintained during transportation	Storage (no. of days (d)) and temperature until analysis	Detection rate in %
Throat/pharyngeal/oropharyngeal swab	Upper respiratory Tract	Using polyester flocked swabs	2°C–8°C	≤5 d, 2°C–8°C > 5 d, −70°C (dry ice)	32% [15]
Nasopharyngeal swabs	Nose	Using sterile container	2°C–8°C	≤5 d, 2°C–8°C > 5 d, −70°C (dry ice)	63% [82]
Saliva	Oral cavity	Coughing out- Self collection, saliva swabs, and directly from salivary gland duct	-	-	-
Bronchoalveolar lavages, Deep sputum	Lower respiratory tract	Using sterile container	2°C–8°C	≤48 h, 2°C–8°C > 48 h, −70°C (dry ice)	72% [15]
Induced sputum	Respiratory tract	10 mL of 3% hypertonic saline was inhaled through a mask with oxygen at a flow rate of 6 L/min for 20 min or until the sputum is produced [81]	-	-	76.9% [82]
Tissue from biopsy or autopsy	-	Using sterile container with saline	2°C–8°C	≤24 h, 2°C–8°C > 24 h, −70°C (dry ice)	-
Whole blood	Veins	Using collection tubes	2°C–8°C	≤5 d, 2°C–8°C > 5 d, −70°C (dry ice)	1% [15]
Serum	-	Serum separator tubes (adults, collect 3–5 mL whole blood)	2°C–8°C	≤5 d, 2°C–8°C >5 d, −70°C (dry ice)	
Stool/Feces	Lower gastrointestinal tract	Stool container -Self-collection	2°C–8°C	≤5 d, 2°C–8°C > 5 d, −70°C (dry ice)	29% [15]
Urine	Urinary bladder	Using urine collection container – Self-collection	2°C–8°C	≤5 d, 2°C–8°C >5 d, −70°C (dry ice)	73.6% [83]
Tears	Eyes	Using Schirmer strips or capillary tube from the lower lateral tear meniscus [84].	-	-	2.5% [85]
Breath condensate/VOC	Upper gastrointestinal tract and Respiratory tract	Using Tedlar bag/Mylar bag from mouth or nose- Self collection [86]	-	-	-

Table 1. Biosafety guidelines for collection, transportation, storage, and detection rate of COVID-19 based on different body fluids.

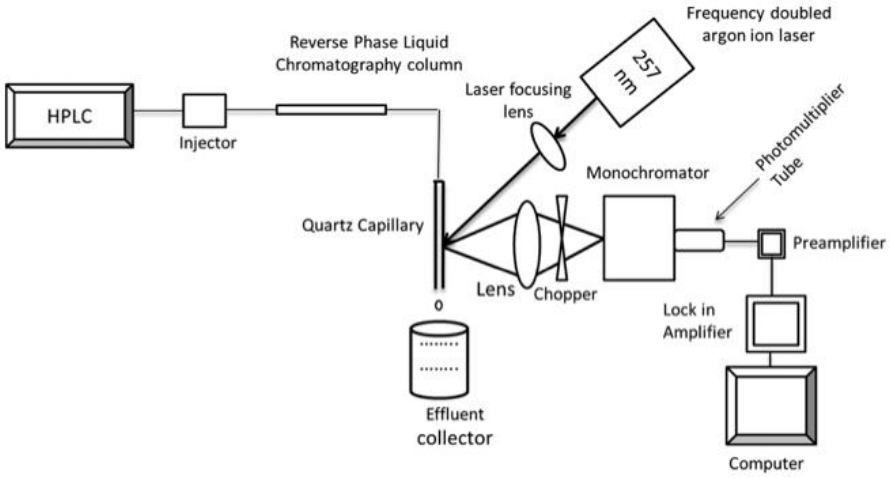


Figure 1. Schematic diagram of HPLC-LIF set up.

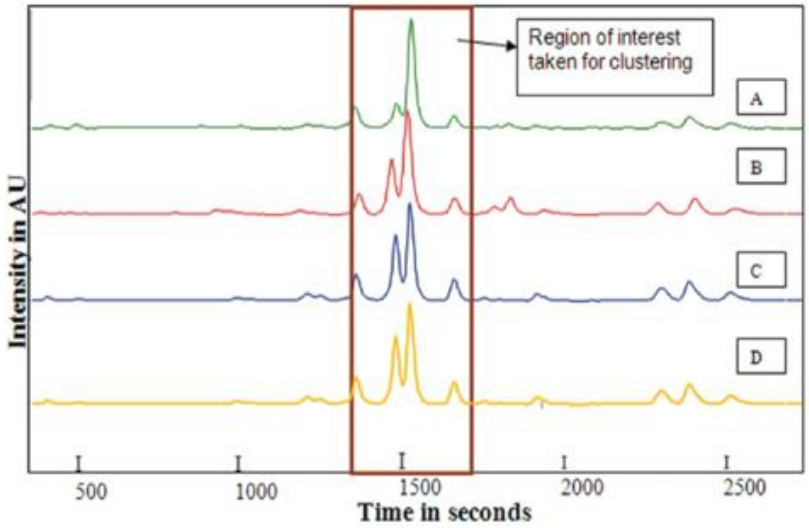


Figure 3. A. normal B. Cervical cancer C. Oral cancer D. Ovarian cancer tissue protein profiles using proposed HPLC-LIF system. Adapted from IEEE proceedings [98].

RETRAINED GENERIC ANTIBODIES CAN RECOGNIZE SARS-COV-2

Han Y, McReynolds KD, Král P.. J Phys Chem Lett. 2021 Feb 1:1438-1442. doi: 10.1021/acs.jpclett.0c03615. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

A simulation study conducted by chemistry doctorates at the University of Illinois at Chicago evaluates the potential use of double-faced peptide-based boosters to retrain preexisting antibodies to recognize SARS-CoV-2. The three boosters evaluated have faces that bind the receptor binding domain (RBD) of the SARS-CoV-2 spike protein and the antibody fragment (AF) of Hepatitis B antibodies (Figure 1). Molecular dynamics simulations were run to evaluate the free energy of binding and Root-Mean-Square Deviation (RMSD) for each booster, finding that Booster 1 had the best binding for both the RBD and AF sites and Booster 3 had the weakest (Figures 2, S4). This study suggests that these boosters could be utilized to provide efficient immunization against SARS-CoV-2 using preexisting antibodies.

ABSTRACT

The dramatic impact novel viruses can have on humans could be more quickly mitigated if generic antibodies already present in one's system are temporarily retrained to recognize these viruses. This type of intervention can be administered during the early stages of infection, while a specific immune response is being developed. With this idea in mind, double-faced peptide-based boosters were computationally designed to allow recognition of SARS-CoV-2 by Hepatitis B antibodies. One booster face is made of ACE2-mimic peptides that can bind to the receptor binding domain (RBD) of SARS-CoV-2. The other booster face is composed of a Hepatitis B core-antigen, targeting the Hepatitis B antibody fragment. Molecular dynamics simulations revealed that the designed boosters have a highly specific and stable binding to both the RBD and the antibody fragment (AF). This approach can provide a cheap and efficient neutralization of emerging pathogens.

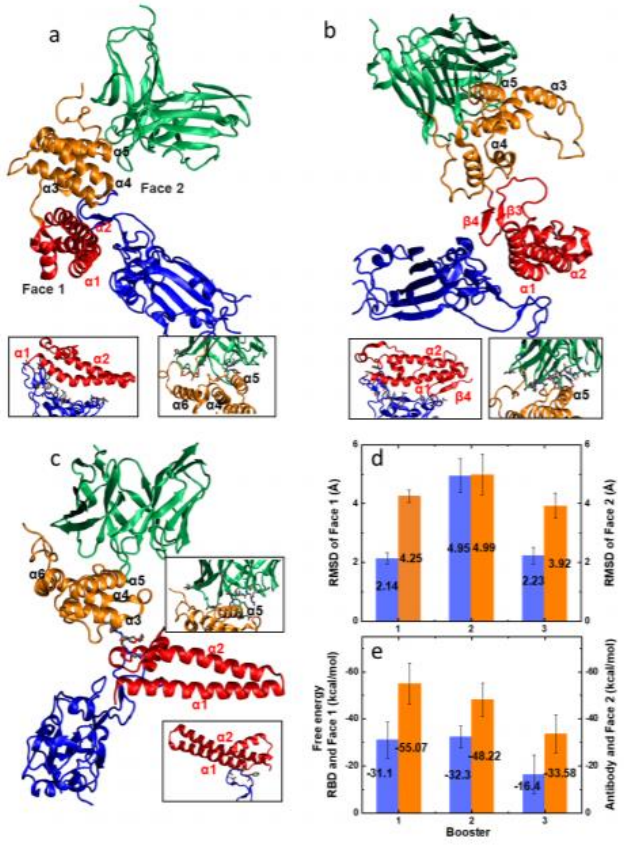
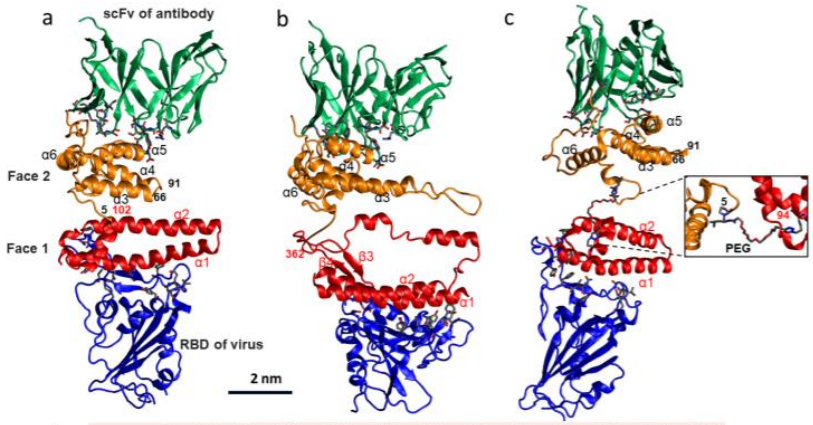


FIG. 2: Simulated booster, RBD and AF complexes. (a-c) Final conformations of Booster 1-3 systems at 100 ns. (d) Averaged RMSD for Face 1 (ACE2-mimic) and Face 2 (antigen); (e) Averaged free energy of binding of RBD with Face 1 and antibody with Face 2.



d

Residue	34	94	95	96	155	156	157	158	159	180	181	182	183
	R	D	T	S	I	D	L	S	S	Y	G	G	S
	184	186	198	199	200	201	207	226	228	229	230	231	
	I	Y	S	K	T	S	K	S	G	D	G	Y	

e

Residue	417	446	449	453	455	456	473	475	476	486	487	489	493	496	498	500	501	502	505
	K	G	Y	Y	L	F	Y	A	G	F	N	Y	Q	G	Q	T	N	G	Y

FIG. 1: The structure of double-faced boosters bound to the Spike RBD and AF. (a) Booster 1 is composed of Face 1 (ACE2-mimic, 19 – 102 amino acids [13]) and the Hepatitis B antigen (without residues between 66 – 91 [14]); (b) Booster 2 is composed of inhibitor 3 from the previous work [2] as Face 1 and the Hepatitis B antigen [14] as Face 2; (c) Booster 3 is composed of the same faces as Booster 1 but with a PEG linker in between (inset); (d) the initial amino acids of antibody which interact with Face 2; (e) the initial amino acids of RBD which interact with Face 1. Color scale: green-antibody, orange-antigen, red-ACE2-mimic, blue-RBD, gray-C atom, red-O atom, blue-N atom. ACE2: Angiotensin-converting enzyme 2, which is the cellular receptor of SARS-CoV-2.

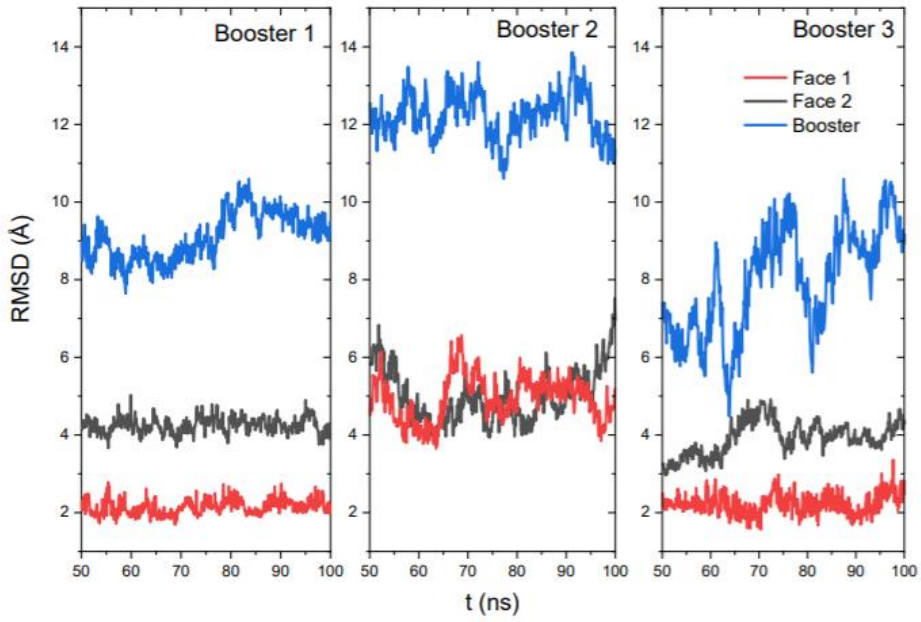


Figure S4. RMSD of the components in the three booster systems.

EPIGENETIC MECHANISMS INFLUENCING COVID-19

Sen R, Garbati MR, Bryant K, Lu Y.. Genome. 2021 Jan 4. doi: 10.1139/gen-2020-0135. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A literature review conducted at Carlsbad, California during 2021 by Active Motif Inc. found epigenetic pathways may serve as invaluable targets for future therapeutic targets designed to reduce the spread and pathogenesis of COVID-19 infections.

SUMMARY

Introduction

The goal of the article is to provide an overview of how epigenetic modifications influence COVID-19 infections, and if any points provide potential therapeutic targets. Because epigenetic mechanisms both reduce, and enhance the replication and spread of viruses, the pathways ought to be analyzed at the chemical level to discern points of clinical application.

Overview of the SARS-CoV-2 Life Cycle

COVID-19's RNA genome, which resembles the host cell, self-replicates and transcribes enzymes, which are subsequently translated by the host cell. Some potential targets for viral entry are the interaction of the viral spike protein with the ACE2 receptor, as well as inhibiting the transmembrane serine protease 2, which allows the S protein to fuse with cells for viral entry.

Immune Response to SARS-COV-2 Infection: Inflammation & Cytokine Storm

Current trials are examining how to target the abnormal acute elevation of several proinflammatory cytokines. One pathway in particular, the JAK-STAT pathway, as influenced by IL-6, may be targeted by currently available therapeutics to mitigate the damage to host cells.

DNA Methylation and it's Effects on ACE2 expression levels

Methylation differences in ACE2 are analyzed across differences in sex as well as chromosomes loci. Higher expression of the receptor correlates with higher disease severity, and cancer has been observed to be positively correlated with expression of ACE2, via hypomethylation.

X-Chromosome Inactivation and COVID-19 Severity

A sex-related analysis of a large sample size of patients found COVID-19 infectiousness to be higher in females than in males. This may be partly explained by the fact that the gene for ACE2 may escape X-inactivation, meaning it is expressed, on average, higher in females than in males.

Epigenetic-Based Therapies & Clinical Trials

Two current clinical trials are analyzing the role of epigenetic mechanisms in COVID-19 infection. The first trial explores methylation patterns relationship to current immune profiles, smoking, and the effect on gene activity. The second study analyzes how the severity of infections relates to epigenetic markers.

ABSTRACT

The COVID-19 pandemic is one of the most significant public health threats in recent history and has impacted the lives of almost everyone worldwide. Epigenetic mechanisms contribute to many aspects of the SARS-CoV-2 replication cycle, including expression levels of viral receptor ACE2, expression of cytokine genes as part of the host immune response, and the implication of various histone modifications in several aspects of COVID-19. SARS-CoV-2 proteins physically associate with many different host proteins over the course of infection, and notably there are several interactions between viral proteins and epigenetic enzymes such as HDACs and bromodomain-containing proteins as shown by correlation-based studies. The many contributions of epigenetic mechanisms to the viral life cycle and the host immune response to infection have resulted in epigenetic factors being identified as emerging biomarkers for COVID-19, and project epigenetic modifiers as promising therapeutic targets to combat COVID-19. This review article highlights the major epigenetic pathways at play during COVID-19 disease and discusses ongoing clinical trials that will hopefully contribute to slowing the spread of SARS-CoV-2.

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