The Daily COVID-19 Literature Surveillance Summary

July 15, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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

EXECUTIVE SUMMARY

Climate

- A group of interdisciplinary health professionals analyzed data on the spread of COVID-19 in 239 affected meat and poultry processing facilities and found that COVID-19 was confirmed in 16,233 workers with 86 related deaths. In the states reporting each figure, 9.1% of all workers had confirmed COVID-19 and 87% of cases occurred among racial and ethnic minority workers highlighting the need for focused preventive measures for these groups to decrease health disparities and occupational risks related to COVID-19.
- Analysis of the clinical characteristics and outcomes of 2,729 COVID-19 inpatients and outpatients at Boston Medical Center found that 44.6% were Black, 30.1% were Hispanic, and 16.4% were experiencing homelessness. Further, the hospitalization rate was higher among Hispanic patients compared to black and white patients, leading the authors to conclude that such populations would benefit from focused efforts in improving patient outcomes and reducing the burden on healthcare systems.

Understanding the Pathology

- A group of researchers utilized rapid antibody discovery to isolate 389 recombinant SARS-CoV-2-reactive human monoclonal antibodies isolated from 4 SARS-CoV-2-infected patients and 1 healthy donor. They tested antibody binding and neutralizing potency against SARS-CoV-2 and found that those recognizing the viral S glycoprotein effectively neutralized the virus. These findings suggest a target site for vaccine and antibody treatment development and identify monoclonal antibody isolates as potential biologics to prevent or treat SARS-CoV-2 infection.

Management

- A review of several randomized control trials investigating the efficacy of Remdesivir treatment for SARS-CoV-2 infection found that in comparison to a placebo, Remdesivir showed reduced mortality and improved recovery time for hospitalized patients requiring low-flow oxygen but was ineffective for patients requiring high-flow or invasive mechanical ventilation. The authors suggest these results may indicate that Remdesivir could be a key pharmacological therapy for moderately-ill hospitalized patients with COVID-19.

Adjusting Practice During COVID-19

- Anesthesiologists in Singapore provide guidelines for performing endotracheal intubation outside of a sterile operating room.
- The CDC randomly sampled pediatric practices enrolled in Vaccines for Children to examine the effects of the COVID-19 pandemic on pediatric immunization operations. Of the 1,727 practices surveyed, 72.8% were providing immunization services to all pediatric patients, 14.7% were only able to offer it to some patients, and 4.4% were unable to offer any immunizations. The authors recommend that parents and caregivers be educated about the importance of well child visits, vaccinations, and the availability of services through programs such as Vaccines for Children.

R&D: Diagnosis and Treatments

- Tulane University researchers present their CRISPR-based assay to diagnose SARS-CoV-2 infection, proposing that its benefits over traditional RT-PCR include an improved sample-to-answer time of roughly 50 minutes and that it does not require specialized laboratory reagents. They report the limit of detection of their CRISPR-based assays was 2 copies of the target RNA sequence--comparable to that of the gold-standard qPCR of 5 copies per test.

Mental Health and Resilience Needs

- A cross-sectional survey of 1242 Wuhan residents during the pandemic found that 27.5% had anxiety, 29.3% had depression, 30.0% had a sleep disorder, and 29.8% had a passive coping style as measured by validated surveys. Multivariate logistic regression showed that the risk of these problems was associated with several factors, including female gender, monthly income between 1,000-5,000 CNY, and never engaging in exercise.

TABLE OF CONTENTS

CLIMATE

A LOOK AT THE FIRST QUARANTINED COMMUNITY IN THE USA: RESPONSE OF RELIGIOUS COMMUNAL ORGANIZATIONS AND IMPLICATIONS FOR PUBLIC HEALTH DURING THE COVID-19 PANDEMIC

Weinberger-Litman SL, Litman L, Rosen Z, Rosmarin DH, Rosenzweig C.. J Relig Health. 2020 Jul 10. doi: 10.1007/s10943-020-01064-x. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

In this article, researchers used anonymous email surveys to collect quantitative and qualitative data on the experience of the first group in the United States to be quarantined on a large scale due to COVID-19, a Modern Orthodox Jewish community in New York City. The results demonstrated:
1. Significant associations between the levels of distress/anxiety seen with the extent of stigmatization experienced due to COVID-19 (Figure 1) and with feelings on the quality of public health information (Figure 2).
2. Participants considered community organizations to be the most trustworthy information sources (Figure 3).
In light of the findings, the authors argue that partnerships between public health organizations and local religious institutions and leaders can help to support community members' psychosocial well-being and to reduce the spread of COVID-19 by enabling more effective dissemination of accurate information.

ABSTRACT

The current study examined anxiety and distress among members of the first community to be quarantined in the USA due to the COVID-19 pandemic. In addition to being historically significant, the current sample was unusual in that those quarantined were all members of a Modern Orthodox Jewish community and were connected via religious institutions at which exposure may have occurred. We sought to explore the community and religious factors unique to this sample, as they relate to the psychological and public health impact of quarantine. Community organizations were trusted more than any other source of COVID-19-related information, including federal, state and other government agencies, including the CDC, WHO and media news sources. This was supported qualitatively with open-ended responses in which participants described the range of supports organized by community organizations. These included tangible needs (i.e., food delivery), social support, virtual religious services, and dissemination of COVID-19-related information. The overall levels of distress and anxiety were elevated and directly associated with what was reported to be largely inadequate and inconsistent health-related information received from local departments of health. In addition, the majority of participants felt that perception of or concern about future stigma related to a COVID-19 diagnosis or association of COVID-19 with the Jewish community was high and also significantly predicted distress and anxiety. The current study demonstrates the ways in which religious institutions can play a vital role in promoting the well-being of their constituents. During this unprecedented pandemic, public health authorities have an opportunity to form partnerships with religious institutions in the common interests of promoting health, relaying accurate information and supporting the psychosocial needs of community members, as well as protecting communities against stigma and discrimination.

FIGURES

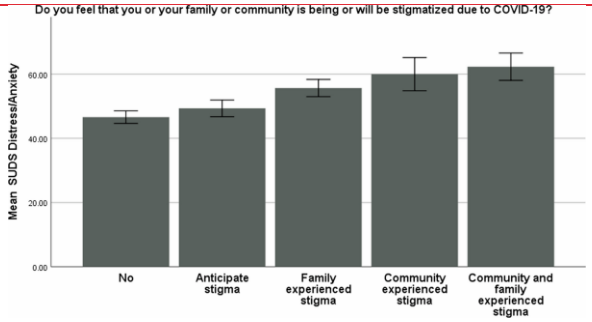


Figure 1. Association of distress as measured by the Subjective Units of Distress Scale and the extent to which one has experienced stigma.

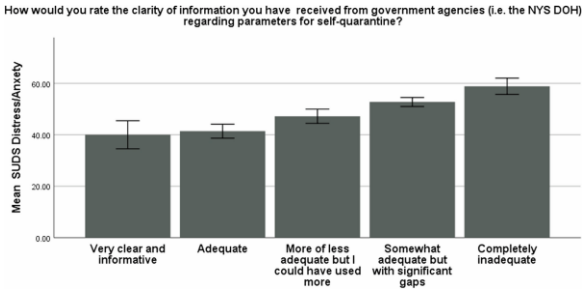


Figure 2. Association of distress as measured by the Subjective Units of Distress Scale and the clarity of health-related information.

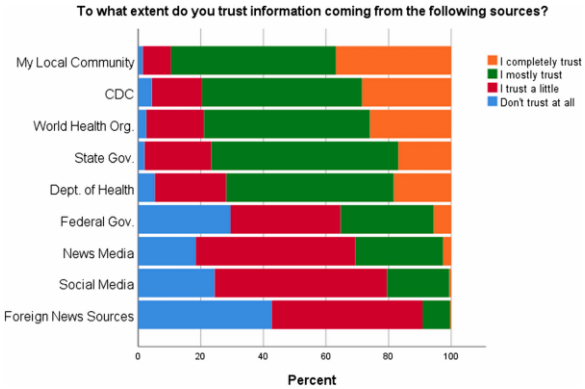


Figure 2. Association of distress as measured by the Subjective Units of Distress Scale and the clarity of health-related information.

COVID-19: ADVANCING EMPIRICAL BIOETHICS RESEARCH

Ulrich CM, Anderson EE, Walter JK.. AJOB Empir Bioeth. 2020 Jul 13:1-3. doi: 10.1080/23294515.2020.1785043. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Researchers at the University of Pennsylvania, Stritch School of Medicine, and Children's Hospital of Philadelphia discuss the directions that empirical bioethics research may take during the COVID-19 pandemic. Bioethical research is necessary to assist with developing effective and ethical policies to address the impact of the pandemic and to assess the benefits and shortcomings of such policies (summarized below). This research is vital for preparing policymakers, healthcare systems, and research institutions to address challenges that will arise during the management of the COVID-19 pandemic and future pandemics.

SUMMARY

- Currently, COVID-19 research is focused on life-saving treatments and development of a vaccine.
- Bioethics is applied to the rapidly changing circumstances to assist with developing ethical policies, such as immunity passports or new triage procedures. Empirical bioethics research is necessary to explain ethical challenges and to discuss the benefits and shortcomings of the policies enacted to address them.
- Descriptive studies, which discuss current opinions, policies, and procedures, aid in the development of future research and interventions. Such studies should include many different perspectives - e.g. from multiple different frontline workers in and out of healthcare, including those who are at risk or have family members at risk, to assess what these workers believe their professional obligations are during these times.
- Longitudinal studies on moral distress should be conducted, as frontline workers face moral dilemmas as they must care for patients in ways that they were explicitly taught not to (e.g., without proper PPE), causing them to struggle with their decisions in the future.
- Empirical research is necessary to assess whether new practices reflect ethical principles - e.g. whether new triage practices marginalize certain groups, or the benefits and risks of increased use of artificial intelligence.
- Bioethics research also seeks to address the challenges associated with using human participants to test interventions - e.g. what is an appropriate way to approach potential participants, or should participants be allowed to take on more risk than is

normally permitted for human studies?
- The pandemic has raised questions about citizen responsibilities - e.g. responsibility to become vaccinated when a vaccine becomes available, or privacy concerns which present as a result of contact tracing.

DISPARITIES

UPDATE: COVID-19 AMONG WORKERS IN MEAT AND POULTRY PROCESSING FACILITIES - UNITED STATES, APRIL-MAY 2020

Waltenburg MA, Victoroff T, Rose CE, Butterfield M, Jervis RH, Fedak KM, Gabel JA, Feldpausch A, Dunne EM, Austin C, Ahmed FS, Tubach S, Rhea C, Krueger A, Crum DA, Vostok J, Moore MJ, Turabelidze G, Stover D, Donahue M, Edge K, Gutierrez B, Kline KE, Martz N, Rajotte JC, Julian E, Diedhiou A, Radcliffe R, Clayton JL, Ortbahn D, Cummins J, Barbeau B, Murphy J, Darby B, Graff NR, Dostal TKH, Pray IW, Tillman C, Dittrich MM, Burns-Grant G, Lee S, Spieckerman A, Iqbal K, Griffing SM, Lawson A, Mainzer HM, Bealle AE, Edding E, Arnold KE, Rodriguez T, Merkle S, Pettrone K, Schlanger K, LaBar K, Hendricks K, Lasry A, Krishnasamy V, Walke HT, Rose DA, Honein MA; COVID-19 Response Team.. MMWR Morb Mortal Wkly Rep. 2020 Jul 10;69(27):887-892. doi: 10.15585/mmwr.mm6927e2.
Level of Evidence: 3 - Local non-random sample

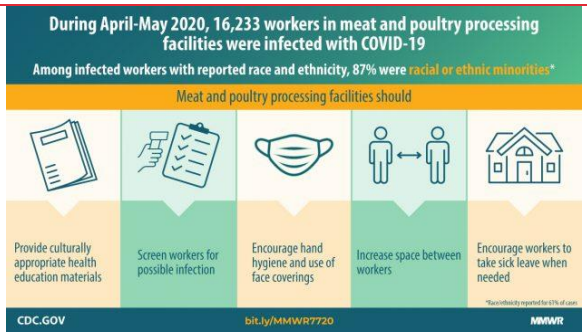
BLUF

The COVID-19 Response Team, a group of interdisciplinary health professionals, analyzed data on the spread of COVID-19 in 239 affected meat and poultry processing facilities in 23 states from April to May 2020 and found that COVID-19 was confirmed in 16,233 workers with 86 related deaths. In the states reporting each figure, 9.1% of all workers had confirmed COVID-19 (n= 112,616, 14 states) and 87% of cases occurred among racial and ethnic minority workers (n=9,919, 21 states; Figure). Based on the commonly reported interventions among facilities (Table 2), the authors highlight the need for focused preventive measures (Pictograph) for these groups to decrease health disparities and occupational risks related to COVID-19.

ABSTRACT

Meat and poultry processing facilities face distinctive challenges in the control of infectious diseases, including coronavirus disease 2019 (COVID-19) (1). COVID-19 outbreaks among meat and poultry processing facility workers can rapidly affect large numbers of persons. Assessment of COVID-19 cases among workers in 115 meat and poultry processing facilities through April 27, 2020, documented 4,913 cases and 20 deaths reported by 19 states (1). This report provides updated aggregate data from states regarding the number of meat and poultry processing facilities affected by COVID-19, the number and demographic characteristics of affected workers, and the number of COVID-19-associated deaths among workers, as well as descriptions of interventions and prevention efforts at these facilities. Aggregate data on confirmed COVID-19 cases and deaths among workers identified and reported through May 31, 2020, were obtained from 239 affected facilities (those with a laboratory-confirmed COVID-19 case in one or more workers) in 23 states.* COVID-19 was confirmed in 16,233 workers, including 86 COVID-19-related deaths. Among 14 states reporting the total number of workers in affected meat and poultry processing facilities (112,616), COVID-19 was diagnosed in 9.1% of workers. Among 9,919 (61%) cases in 21 states with reported race/ethnicity, 87% occurred among racial and ethnic minority workers. Commonly reported interventions and prevention efforts at facilities included implementing worker temperature or symptom screening and COVID-19 education, mandating face coverings, adding hand hygiene stations, and adding physical barriers between workers. Targeted workplace interventions and prevention efforts that are appropriately tailored to the groups most affected by COVID-19 are critical to reducing both COVID-19-associated occupational risk and health disparities among vulnerable populations. Implementation of these interventions and prevention efforts across meat and poultry processing facilities nationally could help protect workers in this critical infrastructure industry.

FIGURES



Pictograph

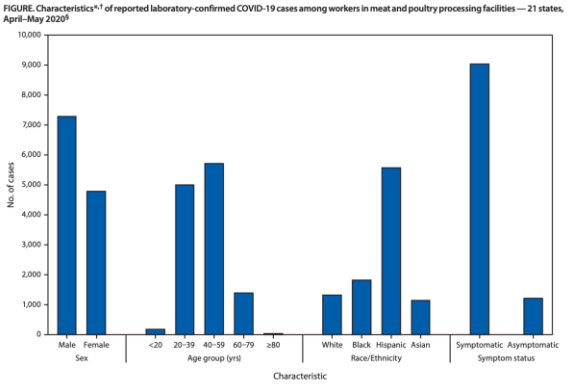


FIGURE. Characteristics[*,†] of reported laboratory-confirmed COVID-19 cases among workers in meat and poultry processing facilities — 21 states, April–May 2020[§]

Abbreviation: COVID-19 = coronavirus disease 2019.
* The analytic dataset excludes cases reported by states that were missing information on sex (n = 4,133), age group (n = 3,868), race/ethnicity (n = 6,314), and symptom status (n = 5,949). White, black, and Asian workers were non-Hispanic; Hispanic workers could be of any race.
† Testing strategies and methods for collecting symptom data varied by workplace. Symptom status was available for a single timepoint, at the time of testing or at the time of interview.
§ Data reported through May 31, 2020.

TABLE 2. Interventions and prevention efforts implemented by facilities in response to COVID-19 among workers in 111 meat and poultry processing facilities[*] —14 states, April–May 2020[†]

Intervention/Prevention effort	COVID-19–affected facilities, no. (%[§])		
	Implemented intervention	Did not implement intervention	Intervention status unknown
Worker screening on entry	89 (80)	5 (5)	17 (15)
Required universal face covering	86 (77)	5 (5)	20 (18)
Added hand hygiene stations	72 (65)	8 (7)	31 (28)
Educated employees on community spread	70 (63)	13 (12)	28 (25)
Installed physical barriers between workers	69 (62)	17 (15)	25 (23)
Staggered shifts	57 (51)	17 (15)	37 (33)
Offered SARS-CoV-2 testing to employees[¶]	41 (37)	35 (32)	35 (32)
Removed financial incentives (e.g., attendance bonuses)	33 (30)	20 (18)	58 (52)
Closed facility temporarily	24 (22)	69 (62)	18 (16)
Reduced rate of animal processing	23 (21)	14 (12)	74 (67)
Decreased crowding of transportation to worksite	17 (15)	10 (9)	84 (76)

Abbreviation: COVID-19 = coronavirus disease 2019.
* Affected facilities defined as those having one or more laboratory-confirmed COVID-19 cases among workers.
† Based on data collected through May 31, 2020.
§ Because of rounding, row percentages might not equal 100%.
¶ Testing strategies varied by facility.

RACE/ETHNICITY, UNDERLYING MEDICAL CONDITIONS, HOMELESSNESS, AND HOSPITALIZATION STATUS OF ADULT PATIENTS WITH COVID-19 AT AN URBAN SAFETY-NET MEDICAL CENTER - BOSTON, MASSACHUSETTS, 2020

Hsu HE, Ashe EM, Silverstein M, Hofman M, Lange SJ, Razzaghi H, Mishuris RG, Davidoff R, Parker EM, Penman-Aguilar A, Clarke KEN, Goldman A, James TL, Jacobson K, Lasser KE, Xuan Z, Peacock G, Dowling NF, Goodman AB.. MMWR Morb Mortal Wkly Rep. 2020 Jul 10;69(27):864-869. doi: 10.15585/mmwr.mm6927a3.
Level of Evidence: 3 - Local non-random sample

BLUF

Authors from Boston Medical Center (BMC) and Boston University describe the clinical characteristics and outcomes of 2,729 COVID-19 inpatients and outpatients at BMC from March 1 to May 18, 2020. Among these patients, 44.6% were Black, 30.1% were Hispanic, and 16.4% were experiencing homelessness (Table 1 & 2). Further, the hospitalization rate was higher among Hispanic patients (382/821, 46.5%) compared to black (481/1,218, 39.5%) and white (127/369, 34.4%) patients, and 81.6% of the total patients who died were aged ≥60 years (Figure). The authors conclude that such patient characteristics (age,

race/ethnicity, homelessness, etc.) influence COVID-19 illness and thus, may benefit from focused efforts in improving patient outcomes and reducing the burden on healthcare systems.

ABSTRACT

As of July 5, 2020, approximately 2.8 million coronavirus disease 2019 (COVID-19) cases and 130,000 COVID-19-associated deaths had been reported in the United States (1). Populations historically affected by health disparities, including certain racial and ethnic minority populations, have been disproportionally affected by and hospitalized with COVID-19 (2-4). Data also suggest a higher prevalence of infection with SARS-CoV-2, the virus that causes COVID-19, among persons experiencing homelessness (5). Safety-net hospitals, such as Boston Medical Center (BMC), which provide health care to persons regardless of their insurance status or ability to pay, treat higher proportions of these populations and might experience challenges during the COVID-19 pandemic. This report describes the characteristics and clinical outcomes of adult patients with laboratory-confirmed COVID-19 treated at BMC during March 1-May 18, 2020. During this time, 2,729 patients with SARS-CoV-2 infection were treated at BMC and categorized into one of the following mutually exclusive clinical severity designations: exclusive outpatient management (1,543; 56.5%), non-intensive care unit (ICU) hospitalization (900; 33.0%), ICU hospitalization without invasive mechanical ventilation (69; 2.5%), ICU hospitalization with mechanical ventilation (119; 4.4%), and death (98; 3.6%). The cohort comprised 44.6% non-Hispanic black (black) patients and 30.1% Hispanic or Latino (Hispanic) patients. Persons experiencing homelessness accounted for 16.4% of patients. Most patients who died were aged >=60 years (81.6%). Clinical severity differed by age, race/ethnicity, underlying medical conditions, and homelessness. A higher proportion of Hispanic patients were hospitalized (46.5%) than were black (39.5%) or non-Hispanic white (white) (34.4%) patients, a finding most pronounced among those aged <60 years. A higher proportion of non-ICU inpatients were experiencing homelessness (24.3%), compared with homeless patients who were admitted to the ICU without mechanical ventilation (15.9%), with mechanical ventilation (15.1%), or who died (15.3%). Patient characteristics associated with illness and clinical severity, such as age, race/ethnicity, homelessness, and underlying medical conditions can inform tailored strategies that might improve outcomes and mitigate strain on the health care system from COVID-19.

FIGURES

TABLE 1. Clinical characteristics of patients with COVID-19 (N = 2,729) — Boston Medical Center, March 1–May 18, 2020

		Mutually exclusive clinical severity categories				
			Inpatient hospitalization*			
Characteristic†	Total (N = 2,729)	Outpatient management (n = 1,543)	Non-ICU (n = 900)	ICU without mechanical ventilation (n = 69)	ICU with mechanical ventilation (n = 119)	Deceased§ (n = 98)
	No. (%)					
Age group (yrs)						
18–29	**309 (11.3)**	244 (15.8)	53 (5.9)	3 (4.3)	9 (7.6)	0 (—)
30–39	**472 (17.3)**	325 (21.1)	125 (13.9)	6 (8.7)	11 (9.2)	5 (5.1)
40–49	**503 (18.4)**	322 (20.9)	149 (16.6)	9 (13.0)	17 (14.3)	6 (6.1)
50–59	**517 (18.9)**	281 (18.2)	187 (20.8)	14 (20.3)	28 (23.5)	7 (7.1)
60–69	**460 (16.9)**	207 (13.4)	176 (19.6)	17 (24.6)	30 (25.2)	30 (30.6)
70–79	**258 (9.5)**	82 (5.3)	126 (14.0)	11 (15.9)	19 (16.0)	20 (20.4)
≥80	**210 (7.7)**	82 (5.3)	84 (9.3)	9 (13.0)	5 (4.2)	30 (30.6)
Sex						
Female	**1,417 (51.9)**	896 (58.1)	428 (47.6)	21 (30.4)	40 (33.6)	32 (32.7)
Male	**1,312 (48.1)**	647 (41.9)	472 (52.4)	48 (69.6)	79 (66.4)	66 (67.3)
Race/Ethnicity						
Black, non-Hispanic	**1,218 (44.6)**	689 (44.7)	399 (44.3)	32 (46.4)	50 (42.0)	48 (49.0)
Hispanic or Latino	**821 (30.1)**	421 (27.3)	320 (35.6)	19 (27.5)	43 (36.1)	18 (18.4)
White, non-Hispanic	**369 (13.5)**	221 (14.3)	101 (11.2)	10 (14.5)	16 (13.4)	21 (21.4)
Other race, non-Hispanic¶	**84 (3.1)**	60 (3.9)	17 (1.9)	2 (2.9)	2 (1.7)	3 (3.1)
Unknown/Declined	**237 (8.7)**	152 (9.9)	63 (7.0)	6 (8.7)	8 (6.7)	8 (8.2)
Underlying medical conditions**						
Asthma	**360 (13.2)**	176 (11.4)	140 (15.6)	6 (8.7)	23 (19.3)	15 (15.3)
Cancer	**195 (7.1)**	67 (4.3)	90 (10.0)	10 (14.5)	10 (8.4)	18 (18.4)
Chronic kidney disease	**332 (12.2)**	115 (7.5)	149 (16.6)	13 (18.8)	20 (16.8)	35 (35.7)
Chronic kidney disease on dialysis	**106 (3.9)**	31 (2.0)	53 (5.9)	5 (7.2)	8 (6.7)	9 (9.2)
Cirrhosis	**42 (1.5)**	17 (1.1)	16 (1.8)	2 (2.9)	3 (2.5)	4 (4.1)
Congestive heart failure	**216 (7.9)**	59 (3.8)	106 (11.8)	8 (11.6)	11 (9.2)	32 (32.7)
Chronic obstructive pulmonary disease	**146 (5.3)**	35 (2.3)	78 (8.7)	6 (8.7)	11 (9.2)	16 (16.3)
Coronary artery disease	**190 (7.0)**	71 (4.6)	73 (8.1)	6 (8.7)	10 (8.4)	30 (30.6)
Diabetes	**708 (25.9)**	274 (17.8)	317 (35.2)	24 (34.8)	47 (39.5)	46 (46.9)
HIV/AIDS	**73 (2.7)**	36 (2.3)	31 (3.4)	2 (2.9)	2 (1.7)	2 (2.0)
Hypertension	**1,248 (45.7)**	556 (36.0)	516 (57.3)	39 (56.5)	66 (55.5)	71 (72.4)
Obesity (BMI >30 kg/m²)	**1,164 (42.7)**	553 (35.8)	465 (51.7)	31 (44.9)	69 (58.0)	46 (46.9)
Serious mental illness	**219 (8.0)**	87 (5.6)	103 (11.4)	7 (10.1)	13 (10.9)	9 (9.2)
Sickle cell disease	**15 (0.5)**	5 (0.3)	8 (0.9)	0 (—)	1 (0.8)	1 (1.0)
Substance use disorder	**396 (14.5)**	161 (10.4)	178 (19.8)	14 (20.3)	24 (20.2)	19 (19.4)
≥1 of above conditions	**2,033 (74.5)**	977 (63.3)	799 (88.8)	57 (82.6)	111 (93.3)	89 (90.8)
≥2 of above conditions	**1,429 (52.4)**	606 (39.3)	613 (68.1)	44 (63.8)	89 (74.8)	77 (78.6)
Living situation††						
Homelessness	**447 (16.4)**	184 (11.9)	219 (24.3)	11 (15.9)	18 (15.1)	15 (15.3)
Residing in nursing home	**181 (6.6)**	114 (7.4)	44 (4.9)	6 (8.7)	7 (5.9)	10 (10.2)
Pregnant§§	**89 (3.3)**	42 (2.7)	42 (4.7)	1 (1.4)	4 (3.4)	0 (—)

Abbreviations: AIDS = acquired immunodeficiency syndrome; BMI = body mass index; COVID-19 = coronavirus disease 2019; HIV = human immunodeficiency virus; ICU = intensive care unit.

* Survived.

† Patient characteristics are not mutually exclusive; therefore, the counts and proportions might not sum to the totals.

§ Of the 98 patients who died, all had been hospitalized, including 27 (27.6%) who received non-ICU inpatient care, 15 (15.3%) who received ICU care without mechanical ventilation, and 56 (57.1%) who received ICU care with mechanical ventilation.

¶ Other race included persons who identified as Asian, American Indian, Middle Eastern, Native Hawaiian/Pacific Islander. These groups were consolidated due to small numbers.

** Underlying medical conditions were defined using *International Classification of Diseases, Tenth Revision* codes from patients' active condition lists or encounter diagnoses within the electronic health record. Obesity was defined by BMI ≥30 kg/m². Patients with substance use disorder were additionally identified via presence of orders for inpatient assessment of opiate or alcohol withdrawal symptoms, inpatient consult to an addiction medicine service, or encounters for previous outpatient substance use disorder treatment.

†† Homelessness was identified by a registration screening question, use of an inpatient homeless discharge planning service, or registration address listed as a known homeless shelter. Nursing home residence was identified by cross-referencing a list of known nursing home patients or matching registration address with known nursing home addresses.

§§ Patients were categorized as pregnant if a health care encounter for COVID-19 occurred before, or up to 7 days after, the end of pregnancy.

TABLE 2. Characteristics of patients with COVID-19 by race/ethnicity (N = 2,729) — Boston Medical Center, March 1–May 18, 2020

Characteristics*	Total (N = 2,729)	Race/Ethnicity: Black, non-Hispanic (n = 1,218)	Hispanic/Latino (n = 821)	White, non-Hispanic (n = 369)	Other race, non-Hispanic† (n = 84)	Unknown/Declined (n= 237)
	No. (%)					
Age group (yrs)						
18–29	**309 (11.3)**	106 (8.7)	129 (15.7)	26 (7.0)	13 (15.5)	35 (14.8)
30–39	**472 (17.3)**	198 (16.3)	152 (18.5)	67 (18.2)	13 (15.5)	42 (17.7)
40–49	**503 (18.4)**	213 (17.5)	190 (23.1)	46 (12.5)	15 (17.9)	39 (16.5)
50–59	**517 (18.9)**	223 (18.3)	165 (20.1)	66 (17.9)	15 (17.9)	48 (20.3)
60–69	**460 (16.9)**	232 (19.0)	112 (13.6)	69 (18.7)	10 (11.9)	37 (15.6)
70–79	**258 (9.5)**	137 (11.2)	46 (5.6)	47 (12.7)	8 (9.5)	20 (8.4)
≥80	**210 (7.7)**	109 (8.9)	27 (3.3)	48 (13.0)	10 (11.9)	16 (6.8)
Sex						
Female	**1,417 (51.9)**	657 (53.9)	389 (47.4)	185 (50.1)	49 (57.1)	137 (57.8)
Male	**1,312 (48.1)**	561 (46.1)	432 (52.6)	184 (49.9)	35 (41.7)	100 (42.2)
Underlying medical conditions§						
Asthma	**360 (13.2)**	188 (15.4)	102 (12.4)	43 (11.7)	6 (7.1)	21 (8.9)
Cancer	**195 (7.1)**	106 (8.7)	43 (5.2)	31 (8.4)	4 (4.8)	11 (4.6)
Chronic kidney disease	**332 (12.2)**	222 (18.2)	55 (6.7)	34 (9.2)	7 (8.3)	14 (5.9)
Chronic kidney disease on dialysis	**106 (3.9)**	64 (5.3)	22 (2.7)	10 (2.7)	3 (3.6)	7 (3.0)
Cirrhosis	**42 (1.5)**	20 (1.6)	10 (1.2)	8 (2.2)	0 (0.0)	4 (1.7)
Congestive heart failure	**216 (7.9)**	129 (10.6)	32 (3.9)	44 (11.9)	3 (3.6)	8 (3.4)
Chronic obstructive pulmonary disease	**146 (5.3)**	70 (5.7)	16 (1.9)	47 (12.7)	4 (4.8)	9 (3.8)
Coronary artery disease	**190 (7.0)**	104 (8.5)	35 (4.3)	40 (10.8)	2 (2.4)	9 (3.8)
Diabetes mellitus	**708 (25.9)**	382 (31.4)	196 (23.9)	53 (14.4)	21 (25.0)	56 (23.6)
HIV/AIDS	**73 (2.7)**	47 (3.9)	11 (1.3)	8 (2.2)	0 (0.0)	7 (3.0)
Hypertension	**1,248 (45.7)**	686 (56.3)	292 (35.6)	149 (40.4)	28 (33.3)	93 (39.2)
Obesity (BMI ≥30 kg/m^2)	**1,164 (42.7)**	576 (47.3)	388 (47.3)	102 (27.6)	11 (13.1)	87 (36.7)
Serious mental illness	**219 (8.0)**	89 (7.3)	57 (6.9)	59 (16.0)	8 (9.5)	6 (2.5)
Sickle cell disease	**15 (0.5)**	11 (0.9)	3 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Substance use disorder	**396 (14.5)**	171 (14.0)	98 (11.9)	105 (28.5)	8 (9.5)	14 (5.9)
≥1 of above conditions	**2,033 (74.5)**	983 (80.7)	602 (73.3)	258 (69.9)	43 (51.2)	147 (62.0)
≥2 of above conditions	**1,429 (52.4)**	745 (61.2)	366 (44.6)	193 (52.3)	30 (35.7)	95 (40.1)
Living situation¶						
Homelessness	**447 (16.4)**	203 (16.7)	100 (12.2)	110 (29.8)	11 (13.1)	23 (9.7)
Residing in nursing home	**181 (6.6)**	101 (8.3)	14 (1.7)	51 (13.8)	11 (13.1)	4 (1.7)
Pregnant**	**89 (3.3)**	30 (2.5)	49 (6.0)	4 (1.1)	2 (2.4)	4 (1.7)

Abbreviations: AIDS = acquired immunodeficiency syndrome; BMI = body mass index; COVID-19 = coronavirus disease 2019; HIV = human immunodeficiency virus.

* Patient characteristics are not mutually exclusive; therefore, the counts and proportions might not sum to totals.

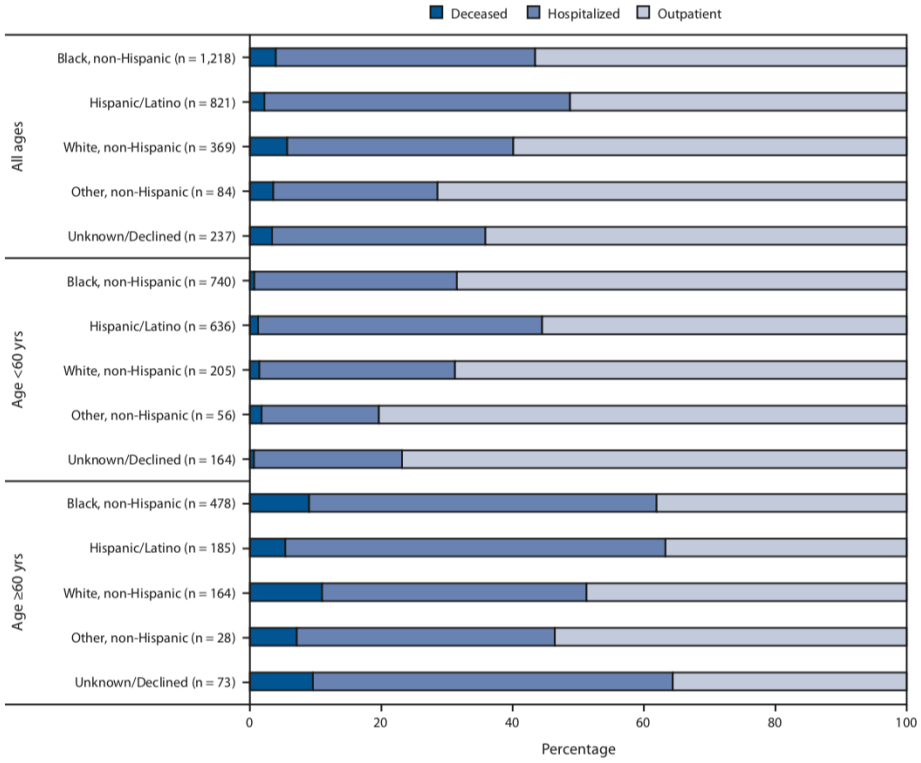
† Other race included persons who identified as Asian, American Indian, Middle Eastern, Native Hawaiian/Pacific Islander. These groups were consolidated because of small numbers.

§ Underlying medical conditions were defined using *International Classification of Diseases, Tenth Revision* codes from patients' active condition lists or encounter diagnoses within the electronic health record. Obesity was defined by BMI ≥30 kg/m^2. Patients with substance use disorder were additionally identified via presence of orders for inpatient assessment of opiate or alcohol withdrawal symptoms, inpatient consult to an addiction medicine service, or encounters for previous outpatient substance use disorder treatment.

¶ Homelessness was identified by a registration screening question, use of an inpatient homeless discharge planning service, or registration address listed as a known homeless shelter. Nursing home residence was identified by cross-referencing a list of known nursing home patients or matching registration address with known nursing home addresses.

** Patients were categorized as pregnant if a health care encounter for COVID-19 occurred before, or up to 7 days after, the end of pregnancy.

FIGURE. Clinical severity* of illness in patients with COVID-19, by age and race/ethnicity (N = 2,729) — Boston Medical Center, March 1–May 18, 2020



Abbreviation: COVID-19 = coronavirus disease 2019.

* Inpatients include surviving patients whose highest level of care included non–intensive care unit hospitalization or intensive care unit hospitalization with or without invasive mechanical ventilation.

EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

AORTIC THROMBUS IN PATIENTS WITH SEVERE COVID-19: REVIEW OF THREE CASES

de Carranza M, Salazar DE, Troya J, Alcázar R, Peña C, Aragón E, Domínguez M, Torres J, Muñoz-Rivas N.. J Thromb Thrombolysis. 2020 Jul 9. doi: 10.1007/s11239-020-02219-z. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A case series conducted in Madrid, Spain by Leonor University Hospital found that three male patients over 60 years old (Table 1) developed floating aortic thrombi, confirmed by CT angiography (Figures 1-3), suggesting that aortic thrombus is a potential complication of the procoagulant state induced by SARS-CoV-2. The authors suggest that further studies are required to determine the frequency of this finding and determine the profile of patients at risk.

SUMMARY

Case 1: 78 y/o male presented with a 4 day fever and elevated LDH, fibrinogen, and D-dimer levels. Chest X-ray demonstrated multilobar interstitial opacities. Patient was treated with "piperacillintazobactam, azithromycin, hydroxychloroquine, methylprednisolone, and enoxaparin at a dose of 60 mg daily." On day 5, CT angiography revealed three floating thrombi, pneumonia, and multisegmental pulmonary embolisms. Patient was administered LMWH.

Case 2: A 76 y/o male presented with fever, lower back pain, and asthenia. Chest X-ray revealed left lower lobe opacities. Patient was treated with "azithromycin, hydroxychloroquine, ceftriaxone, methylprednisolone, and enoxaparin 40 mg daily." CT-angiography on the 13th day after admission showed two intraluminal thrombi and occlusion of the left internal carotid artery. LMWH dosage was increased.

Case 3: A 64 y/o male presented with a 4 day history of fever, cough, and dyspnea. Chest X-ray revealed right upper lobe opacities. The patient was treated with hydroxychloroquine and azithromycin and was discharged. Ambulatory follow-up four days after admission, CT demonstrated a descending thoracic aorta floating embolism. LMWH treatment was initiated.

ABSTRACT

Coronavirus disease 2019 (COVID-19) could predispose to both venous and arterial thromboembolism, in an exaggerated immune response to the virus, especially in severe patients. Even though aortic clots are a rare entity, the pro-coagulant nature of COVID-19 is associated with thrombosis in atypical locations and should be considered in patients with severe abnormalities in coagulation parameters. We describe a series of three cases of aortic thrombi diagnosed by computerized tomography (CT) angiography in patients with confirmed SARS-CoV-2 infection.

Table 1 Main characteristics of patients with aortic trombus

	Case one	Case two	Case three
Basal characteristics			
Age	78	76	64
Sex	Male	Male	Male
Cardiovascular Risk factors	Dyslipidemia	Hypertension, Dyslipidemia Diabetes mellitus	Former smoker, Hypertension
Body mass index	23.8	27.8	31.5
Personal history	Urothelial carcinoma	Benign prostatic hyperplasia	Severe obstructive apnoea syndrome, Chronic hepatitis B
Ordinary treatment	Statin	ACE2 inhibitor Statin Metformin Protein pump inhibition	Tenofovir CPAP
Aortic thrombus			
Thrombus characteristics	Multiple (3), floating	Multiple (2), floating	Unique, floating
Trombus treatment	LMWH	LMWH	Unfractioned heparin followed by LMWH
Days to event			
From onset of symptoms	9	26	11
From admission	5	9	7
Vital signs durig event			
Blood pressure (mmhg)	160/80	129/68	106/68
Heart rate (bpm)	80	63	84
Oxygen saturation (%)	90	83	93
Analytical parameters (admission—near to event)			
Hemoglobin (g/l)	14.2–13.6	13.3–13.3	14.5–13.6
Lymphocytes(cél/µl)	600–600	700–2600	1110–700
Platelets (cél/l)	325,000–397,000	208,000–475,000	169,000–363,000
Inr	1.11–1.09	1.15–1.02	1.02–1.05
Ttpa (seg)	27.9–20.4	29.4–22.3	27.1–21.7
Fibrinogen (mg/dl)	> 500–400	> 500–425	> 500–370
D dimer (µg/l)	910–3,570	1,340–2.220	670–4640
Creatinine (mg/dl)	0.86–0.90	1.61–1.14	0.79–0.73
Ldh (u/l)	327–361	364–313	169–439
Rcp (mg/l)	86.8–38.6	133.1–4.8	81.5–10.8
Ferritin (ng/ml)	1510–1272	NA–403	NA–205
Il-6 (pg/ml)	NA–64.1	NA–81	NA–NA
Covid-19: x-ray, treatment and evolution			
Pneumonia characteristics	Severe, bilateral	Severe, bilateral	Severe, bilateral
Lmwh prophylaxis	Enoxaparin (60 mg daily)	Enoxaparin (40 mg daily)	Enoxaparin (60 mg daily)
Covid-19 treatment	Piperacilin-tazobactam Azitromicin Hydroxicloroquine Methylprednisolone Tocilizumab	Ceftriaxone Azitromicin Hydroxicloroquine Methylprednisolone Tocilizumab	Ceftriaxone Azitromicin Hydroxicloroquine Methylprednisolone Tocilizumab
Icu admission	No	No	Yes
Patient evolution	Death	Middle stay center	ICU admission

ACE angiotensin converting enzyme, *ICU* intensive care unit, *IL-6* Interleukin-6, *LDH* lactate dehydrogenase, *LMWH* low molecular weight heparin, *NA* not available *RCP* reactive C protein

Fig. 1 CT angiography of the pulmonary arteries. Axial and Sagittal MinIP reconstructions. Incidental finding of three floating thrombi, one immediately after the left subclavian artery bifurcation (12.2 mm), and two in the descending aorta immediately after the ligamentum arteriosum (8.7 mm and 10.2 mm)

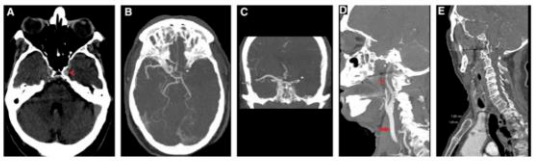


Fig. 2 **a** Unenhanced brain CT, showing a hyperdense intracranial left internal carotid artery in its petrous segment. **b** and **c** CT angiography of the cerebral arteries (arch to vertex protocol). Axial (B) and Coronal (C) MIP reconstruction showing a complete filling defect after the petrosum segment of the left carotid artery, and an absence of the left middle cerebral artery. **d** CT angiography of the cerebral arteries (arch to vertex protocol). MIP reconstruction showing the left common carotid artery (red arrow) and the internal carotid artery (red arrowhead), with a prominent carotid bulb and calcified atherosclerotic plaques with no signs of lumen narrowing or wall thickening. **e** CT angiography of the carotids and cerebral arteries MIP reconstruction. Incidental finding of two floating thrombi of around 10 mm, in the ascending aorta, just before the origin of the right brachiocephalic artery

Fig. 3 CT angiography of the pulmonary arteries. Axial and sagittal MinIP reconstructions. Incidental finding a floating thrombus in the descending aorta measuring around 12 mm

VIRAL CPG DEFICIENCY PROVIDES NO EVIDENCE THAT DOGS WERE INTERMEDIATE HOSTS FOR SARS-COV-2

Pollock DD, Castoe TA, Perry BW, Lytras S, Wade KJ, Robertson DL, Holmes EC, Boni MF, Kosakovsky Pond SL, Parry R, Carlton EJ, Wood JLN, Pennings PS, Goldstein RA.. Mol Biol Evol. 2020 Jul 13:msaa178. doi: 10.1093/molbev/msaa178. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A letter written by an international group of infectious disease researchers disputes the findings of a recent paper by a researcher from the University of Ottawa (Xia 2020) that claims that dogs were the intermediate host for SARS-CoV-2 prior to the jump to humans. This article sheds doubt on key aspects of the Xia 2020 paper, including its claim that only canine RNA viruses could account for the high levels of CpG depletion seen in SARS-CoV-2 that would not be seen with a viral origin from other animals such as bats or pangolins, when in fact the observed levels of CpG-deficiencies do not exclude bat or pangolin origins for the virus (Figures 1 and 2). This suggests that a great deal of further research and surveying of animal species for coronavirus RNA is needed before definitive determinations of the origin of SARS-CoV-2 can be made - a conclusion which has significant implications for future prevention and detection of pandemic-causing viruses.

ABSTRACT

Due to the scope and impact of the COVID-19 pandemic there exists a strong desire to understand where the SARS-CoV-2 virus came from and how it jumped species boundaries to humans. Molecular evolutionary analyses can trace viral origins by establishing relatedness and divergence times of viruses and identifying past selective pressures. However, we must uphold rigorous standards of inference and interpretation on this topic because of the ramifications of being wrong. Here, we dispute the conclusions of Xia (2020) that dogs are a likely intermediate host of a SARS-CoV-2 ancestor. We highlight major flaws in Xia's inference process and his analysis of CpG deficiencies, and conclude that there is no direct evidence for the role of dogs as intermediate hosts. Bats and pangolins currently have the greatest support as ancestral hosts of SARS-CoV-2, with the strong caveat that sampling of wildlife species for coronaviruses has been limited.

FIGURES

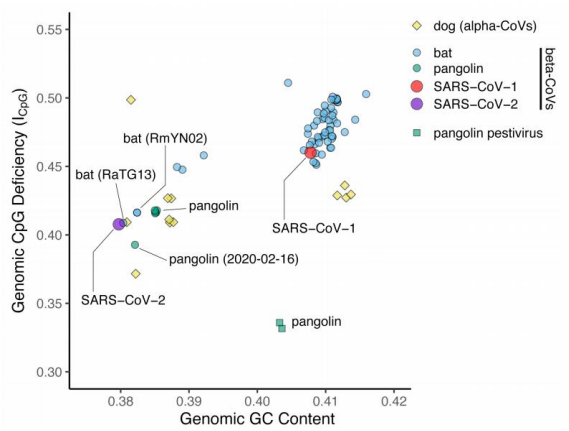


Figure 1. Coronavirus genomic CpG deficiency (ICpG) versus viral genomic GC content for select betacoronaviruses (beta-CoVs), and dog alphacoronaviruses (alpha-CoVs). Pangolin pestiviruses are also shown to illustrate variation in ICpG in a single host.

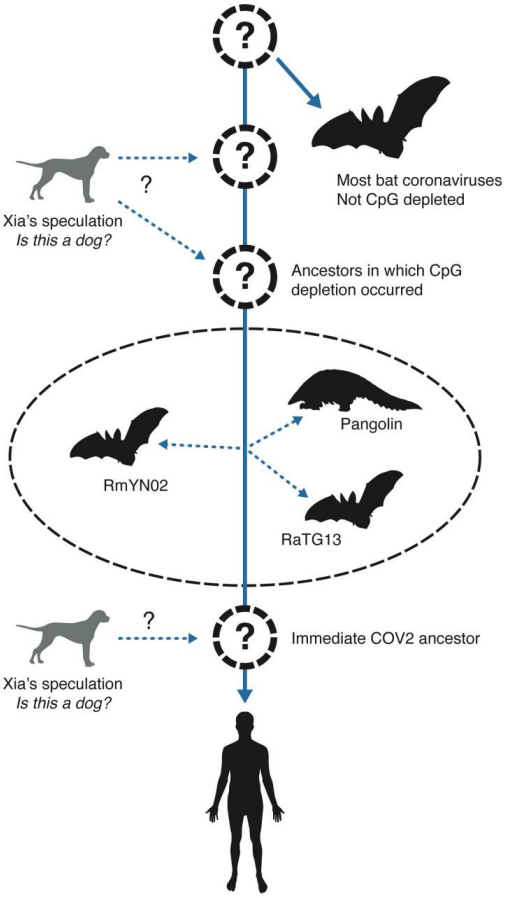


Figure 2. Prevailing origin and transmission hypotheses supported by recent literature. The organisms in black outline are host sources of viral sequences closely related to SARS-CoV-2. The dashed circles represent hosts carrying viruses on the ancestral lineage leading to SARS-Cov-2, with the large question marks indicating that despite the recurrence of bats as hosts of related viruses, the ancestral hosts are uncertain. Two ancestral hosts are indicated during the time of CpG depletion because this is a much longer timespan, and there could plausibly have been multiple hosts from divergent species during this time. Dogs are represented by grey outlines because no viruses closely related to SARS-CoV-2 have been discovered in dogs. Question mark labeled dashed arrows represent Xia's (2020) dual speculations, that dogs may have been hosts during the process of CpG depletion and during recent ancestral SARS-CoV-2 evolution.

IN VITRO

RAPID ISOLATION AND PROFILING OF A DIVERSE PANEL OF HUMAN MONOCLONAL ANTIBODIES TARGETING THE SARS-COV-2 SPIKE PROTEIN

Zost SJ, Gilchuk P, Chen RE, Case JB, Reidy JX, Trivette A, Nargi RS, Sutton RE, Suryadevara N, Chen EC, Binshtein E, Shrihari S, Ostrowski M, Chu HY, Didier JE, MacRenaris KW, Jones T, Day S, Myers L, Eun-Hyung Lee F, Nguyen DC, Sanz I, Martinez DR, Rothlauf PW, Bloyet LM, Whelan SPJ, Baric RS, Thackray LB, Diamond MS, Carnahan RH, Crowe JE Jr.. Nat Med. 2020 Jul 10. doi: 10.1038/s41591-020-0998-x. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

An interdisciplinary group of researchers conducted a study using rapid antibody discovery (Figure 1) to isolate 389 recombinant SARS-CoV-2-reactive human monoclonal antibodies (mAbs) isolated from 4 SARS-CoV-2-infected patients and 1 healthy donor. They tested mAbs binding (Figure 3) via enzyme-linked immunosorbent assay (ELISA) and neutralizing potency (Figure 5) via automated real-time cell analysis (RTCA) rapid screening assay and found mAbs recognizing multiple

epitopes on the viral S glycoprotein surface neutralized SARS-CoV-2, most of which mapped specifically to the receptor-binding domain (RBD) of S protein. These findings suggest vulnerability of SARS-CoV-2 S protein as a target site for vaccine and antibody treatment development, while potent mAb isolates could serve as potential biologics to prevent/treat SARS-CoV-2 infection.

ABSTRACT

Antibodies are a principal determinant of immunity for most RNA viruses and have promise to reduce infection or disease during major epidemics. The novel coronavirus SARS-CoV-2 has caused a global pandemic with millions of infections and hundreds of thousands of deaths to date1,2. In response, we used a rapid antibody discovery platform to isolate hundreds of human monoclonal antibodies (mAbs) against the SARS-CoV-2 spike (S) protein. We stratify these mAbs into five major classes on the basis of their reactivity to subdomains of S protein as well as their cross-reactivity to SARS-CoV. Many of these mAbs inhibit infection of authentic SARS-CoV-2 virus, with most neutralizing mAbs recognizing the receptor-binding domain (RBD) of S. This work defines sites of vulnerability on SARS-CoV-2 S and demonstrates the speed and robustness of advanced antibody discovery platforms.

FIGURES

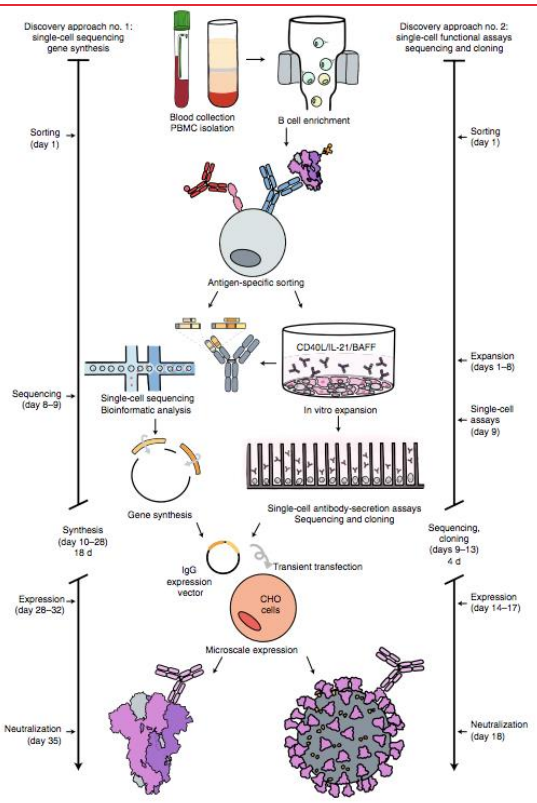


Figure 1: Workflows and timelines. a, Overview of rapid mAb discovery workflows. The overall scheme is shown, representing the several specific workflows conducted in parallel. Blood was collected and white blood cells were separated, B cells were enriched from PBMCs by negative selection using magnetic beads and antigen-specific cells were isolated by flow-cytometric sorting and then were processed for direct B cell selection and sequencing or in vitro expansion/activation. Cultured B cells were loaded on a Beacon instrument (Berkeley Lights) for functional screening or in a Chromium device (10X Genomics) followed by reverse transcription with PCR, sequence analysis, cDNA gene synthesis and cloning into an expression vector and microscale IgG expression in Chinese hamster ovary (CHO) cells by transient transfection. Recombinant IgG was tested by ELISA for binding to determine antigen reactivity and by a high-throughput neutralization screening assay (xCelligence; ACEA) with authentic virus in a biosafety-level-3 (BSL-3) laboratory for functional characterization.

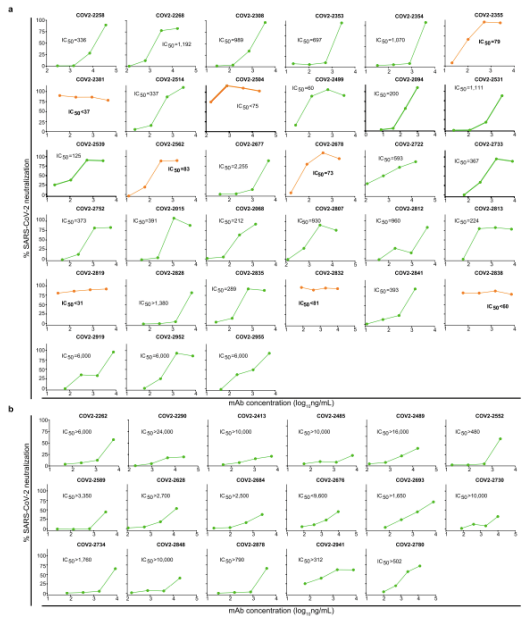
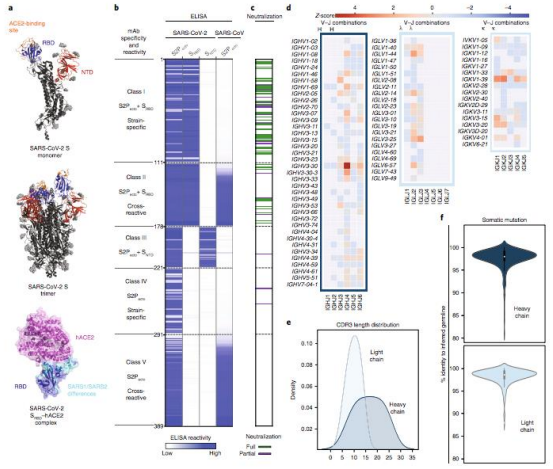


Figure 5: Real-time cell analysis assay to quantify neutralization potency. Dose-response curves showing activity of neutralizing mAbs that were identified by rapid screening using the RTCA assay. Each mAb was tested in four sequential five-fold dilutions from micro-scale purified samples in which mAbs concentrations were not normalized but quantified. Neutralization was calculated as the percent of maximal cell index in control wells without virus minus cell index in control (virus-only) wells that exhibited maximal CPE at 40 to 48 hrs after applying virus-antibody mixture to the cells. a. Representative neutralizing mAbs that fully prevented CPE at the lowest tested dilution (corresponding to the highest tested mAb concentration) are shown. IC50 values estimated from each curve are indicated. Curves for potently neutralizing mAbs (IC50 < 100 ng/mL) are shown in orange, from which mAbs COV2–2355 and COV2–2381 are genetically related. b. Representative neutralizing mAbs that partially prevented CPE at the lowest tested dilution (corresponding to the highest tested mAb concentration) are shown.



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MANAGEMENT

ACUTE CARE

THAT ESCALATED QUICKLY: REMDESIVIR'S PLACE IN THERAPY FOR COVID-19

Davis MR, McCreary EK, Pogue JM.. Infect Dis Ther. 2020 Jul 10. doi: 10.1007/s40121-020-00318-1. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

A review of several randomized control trials investigating the efficacy of Remdesivir treatment for SARS-CoV-2 infection. These studies demonstrate that in comparison to a placebo, Remdesivir showed reduced mortality (HR 0.22 [95% CI 0.08–0.58]) and improved recovery time (RR 1.47 [95% CI 1.17–1.84]) for hospitalized patients requiring low-flow oxygen but was ineffective for patients requiring high-flow or invasive mechanical ventilation (Figure 1). The authors suggest these results may indicate that Remdesivir could be a key pharmacological therapy for moderately-ill hospitalized patients with COVID-19.

ABSTRACT

Remdesivir is a nucleoside antiviral recently studied in several randomized trials for treatment of COVID-19. The available observational and prospective data are conflicting, requiring clinicians to critically evaluate and reconcile results to determine patient populations that may optimally benefit from remdesivir therapy, especially while drug supply is scarce. In this review, we analyze pertinent clinical remdesivir data for patients with COVID-19 from January 1, 2020, through May 31, 2020.

FIGURES

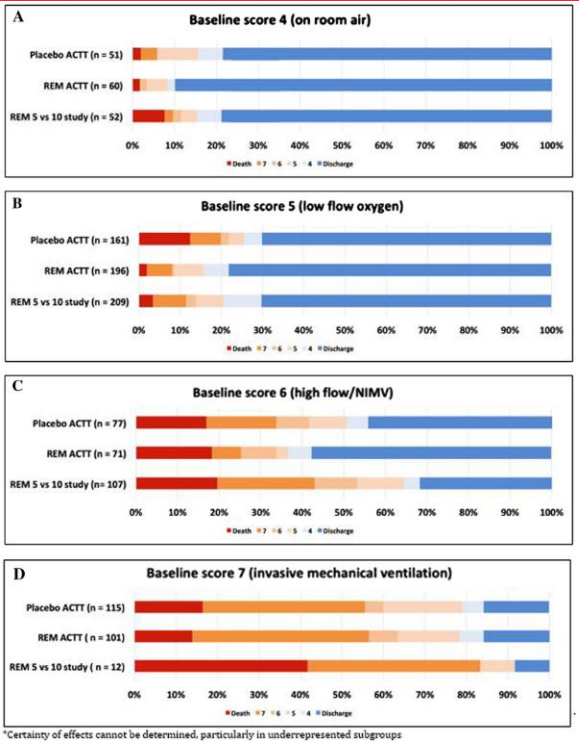

Figure 1. Clinical outcomes on day 14 or 15 by baseline clinical status

MEDICAL SUBSPECIALTIES

DERMATOLOGY

SARS-COV-2, COVID-19, SKIN AND IMMUNOLOGY - WHAT DO WE KNOW SO FAR?

Novak N, Peng WM, Naegeli MC, Galvan C, Kolm-Djamei I, Brüggen MC, Cabanillas B, Schmid-Grendelmeier P, Catala A.. Allergy. 2020 Jul 13. doi: 10.1111/all.14498. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A group of dermatologists from Europe performed a literature review of the different skin manifestations observed in COVID-19 positive patients, the possible mechanisms underlying these manifestations, and useful differential diagnostic exams. Based on their findings (Summary), the authors conclude that the cause of these skin manifestations remain largely unknown and highlight the importance of careful diagnostic evaluation in this population to better understand these skin findings in SARS-CoV-2 infection.

SUMMARY

Observed skin manifestations and possible underlying mechanisms in SARS-CoV-2 infection:

Viral rashes:
-Virus-induced maculopapular exanthema (Figure 6A) may biopsy to differentiate between viral exanthema from drug-induced exanthema.
-Virus-induced vesicular eruptions: underlying mechanisms still remain unclear; further studies are needed to evaluate if these eruptions are primarily due to SARS-CoV-2.
- Virus-induced urticarial rash: common in upper respiratory infections and may involve complement activation and serum sickness.
- Virus-induced vasculitis: may involve immune complex-mediated mechanisms, but further studies are needed to evaluate if these lesions are primarily from SARS-CoV-2.

Previous skin diseases:
-Urticaria, psoriasis, autoimmune disease, etc. might develop from SARS-CoV-2-related reactivation or aggravation of pre-existing skin diseases.
-Chilblain presents as "violaceous, infiltrated, painful and sometimes even pruritic plaques on erythematous skin with predilection to back of toes and feet" in certain COVID-19 patients and in asymptomatic or non-infected patients; its underlying mechanisms remain unclear in SARS-CoV-2 infection.

Cutaneous drug reactions:
- Cutaneous drug reactions are classified into immediate and non-immediate drug hypersensitivity reactions.
- Drug-induced urticarial rashes may be involved in direct mast cell activation, immune complex formation, and activation of complement; these could be drug-induced, induced by viral RNA, or a mixture of both.
- Drug-induced maculopapular exanthema may be a result of a type IV hypersensitivity reaction to drugs and metabolites of drugs.
- Severe cutaneous adverse drug reactions with non-specific histologic findings (Figure 9A and B), such as DRESS syndrome, have been observed in COVID-19 cases; the culprit drug must be stopped immediately after identification.

Drug-induced vasculitis:
- May be due to type III hypersensitivity reactions with changes in the vasculature or vascular pathways; 10-20% present as vasculitis, livedo racemosa, or purpura and can appear during or after drug exposure (7-14 days), depending on the drug.

ABSTRACT

The pandemic condition Coronavirus-disease (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can take asymptomatic, mild, moderate, and severe courses. COVID-19 affects primarily the respiratory airways leading to dry cough, fever, myalgia, headache, fatigue, and diarrhea and can end up in interstitial pneumonia and severe respiratory failure. Reports about the manifestation of various skin lesions and lesions of the vascular system in some subgroups of SARS-CoV-2 positive patients as such features outside the respiratory sphere, are rapidly emerging. Vesicular, urticarial and maculopapular eruptions as well as livedo, necrosis and other vasculitis forms have been reported most frequently in association with SARS-CoV-2 infection. In order to update information gained, we provide a systematic overview of the skin lesions described in COVID-19 patients, discuss potential causative factors and describe differential diagnostic evaluations. Moreover, we summarize current knowledge about immunologic, clinical and histologic features of virus- as well

as drug-induced lesions of the skin and changes to the vascular system in order to transfer this knowledge to potential mechanisms induced by SARS-CoV-2.

FIGURES

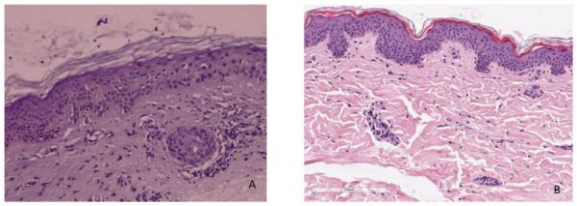

Figure 6: Histologic features of skin biopsies taken from two SARS-CoV-2 positive patients with maculopapular eruptions.
A: Skin sections showing the epidermis with mild hyperkeratosis, keratinocytes with frosted glass nuclei, with intranulcular and occasionally multinucleate inclusions,
reminiscent of cytopathic damage. Dermis without edema, perivascular inflammatory infiltrate extending focally to the basal layer, causing slight vacuolate damage and
pigmentary incontinence. No eosinophils are observed
B: Histology (H&E stain) showing an inconspicous epidermis and a very subtle perivascular lymphohistiocytic infiltrate in the upper dermis with admixture of few eosinophilic granulocytes.

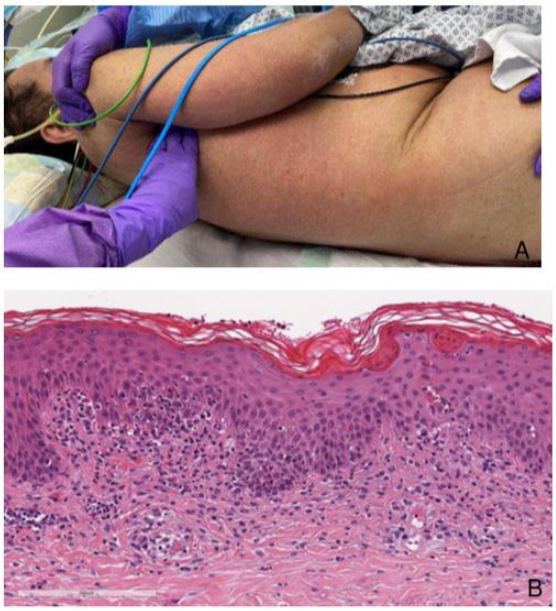

Figure 9
A:58-year old male patient diagnosed with COVID-19 and DRESS syndrome.
B: Histology (H&E stain) showing interface changes (vacuolar degeneration of the basal layer, apoptotic keratinocytes, exocytosis of lymphocytes) as well as spongiotic changes with hyperparakeratosis. Perivascular lymphohistiocytic infiltrate with admixture of few eosinophilic granulocytes. Mild extravasation of erythrocytes.

ORTHOPEDICS

IMPACT-SCOT REPORT ON COVID-19 AND HIP FRACTURES

Hall AJ, Clement ND, Farrow L; IMPACT-Scot Study Group, MacLullich AMJ, Dall GF, Scott CEH, Jenkins PJ, White TO, Duckworth AD.. Bone Joint J. 2020 Jul 7:1-10. doi: 10.1302/0301-620X.102B9.BJJ-2020-1100.R1. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

The "International Multi-Centre Project Auditing COVID-19 in Trauma & Orthopaedics" (IMPACT), a retrospective observational study, assessed data on 317 patients admitted for hip fracture who received care at six Scottish hospitals

between March 1st, 2020 and April 15th, 2020 with the goal of understanding the impact of a COVID-19 diagnosis on hip fracture outcomes and epidemiology. The results revealed that patients with a positive COVID-19 test, either on admission or during the course of hospitalization, had a statistically significant lower rate of survival than those with negative tests (Figure 1), independent of age, sex, residence, or degree of injury by Nottingham Hip Fracture Score. Secondary outcomes assessed through the study also revealed that:

1. Male gender and low platelet count (Figure 3) were independent clinical factors predictive of a positive COVID-19 status during the course of hip fracture management and
2. While social lockdown did not appear to increase or decrease the occurrence of hip fractures, after lockdown significantly fewer operations under general anesthesia were performed and hospital stays were shorter (11.3 verses 7.8 days).

ABSTRACT

AIMS: The primary aim was to assess the independent influence of coronavirus disease (COVID-19) on 30-day mortality for patients with a hip fracture. The secondary aims were to determine whether: 1) there were clinical predictors of COVID-19 status; and 2) whether social lockdown influenced the incidence and epidemiology of hip fractures. METHODS: A national multicentre retrospective study was conducted of all patients presenting to six trauma centres or units with a hip fracture over a 46-day period (23 days pre- and 23 days post-lockdown). Patient demographics, type of residence, place of injury, presentation blood tests, Nottingham Hip Fracture Score, time to surgery, operation, American Society of Anesthesiologists (ASA) grade, anaesthetic, length of stay, COVID-19 status, and 30-day mortality were recorded. RESULTS: Of 317 patients with acute hip fracture, 27 (8.5%) had a positive COVID-19 test. Only seven (26%) had suggestive symptoms on admission. COVID-19-positive patients had a significantly lower 30-day survival compared to those without COVID-19 (64.5%, 95% confidence interval (CI) 45.7 to 83.3 vs 91.7%, 95% CI 88.2 to 94.8; p < 0.001). COVID-19 was independently associated with increased 30-day mortality risk adjusting for: 1) age, sex, type of residence (hazard ratio (HR) 2.93; p = 0.008); 2) Nottingham Hip Fracture Score (HR 3.52; p = 0.001); and 3) ASA (HR 3.45; p = 0.004). Presentation platelet count predicted subsequent COVID-19 status; a value of < 217 x 109/l was associated with 68% area under the curve (95% CI 58 to 77; p = 0.002) and a sensitivity and specificity of 63%. A similar number of patients presented with hip fracture in the 23 days pre-lockdown (n = 160) and 23 days post-lockdown (n = 157) with no significant (all p >= 0.130) difference in patient demographics, residence, place of injury, Nottingham Hip Fracture Score, time to surgery, ASA, or management. CONCLUSION: COVID-19 was independently associated with an increased 30-day mortality rate for patients with a hip fracture. Notably, most patients with hip fracture and COVID-19 lacked suggestive symptoms at presentation. Platelet count was an indicator of risk of COVID-19 infection. These findings have implications for the management of hip fractures, in particular the need for COVID-19 testing.

FIGURES

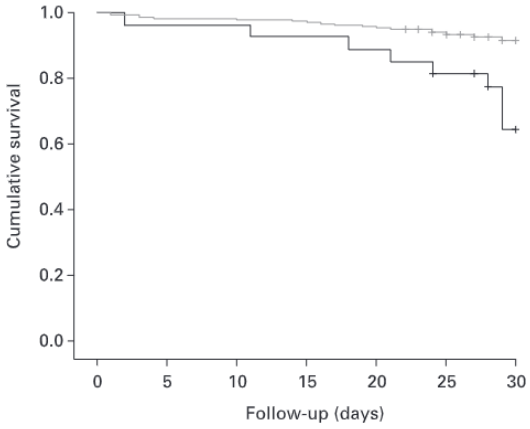

Fig. 1

Figure 1. Kaplan-Meier curve for 30 day survival according to whether a patient was COVID-19-negative (n = 290, grey) or COVID-19-positive (n = 27, black) - 91.5% vs 64.5% at 30 days; p < 0.001, log-rank.

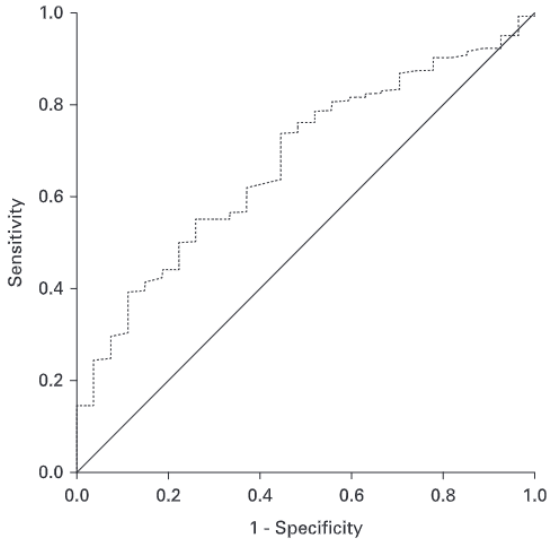

Fig. 3

Figure 3. Receiver operating characteristic curve (ROC) for platelet count as a predictor of COVID-19. Area under the curve 67.8% (95% confidence interval 58.3 to 77.3; p = 0.002, ROC curve), with a threshold platelet count value of 217 × 109/l.

ADJUSTING PRACTICE DURING COVID-19

ACUTE CARE

ANAESTHESIA

INTUBATION OUTSIDE OF THE OPERATING ROOM: NEW CHALLENGES AND OPPORTUNITIES IN COVID-19 ERA

Lee DW, Ma M, Parotto M, Wąsowicz M.. Curr Opin Anaesthesiol. 2020 Aug;33(4):608-611. doi: 10.1097/ACO.0000000000000892.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

Given that the COVID-19 pandemic poses a high-risk challenge for safe airway management, this article summarizes the important principles and guidelines for preforming endotracheal intubation (ETT) outside of a sterile operating room. The authors suggest:
1. Treating all airway interventions as high-risk procedures in the setting of the pandemic,
2. Preventing and controlling spread with negative air flow rooms and appropriate personal protective equipment (PPE),
3. Minimizing performance of procedures - such as non-invasive positive pressure ventilation and high flow nasal oxygenation - that may generate aerosols,
4. Avoiding disconnections between patients' ventilators once intubated, and
5. Utilizing high efficiency particulate air (HEPA) filters.
In order to reduce the chances of exposure and increase efficiency, the authors also suggest hospitals form Emergency Response Intubation Teams (ERITs) that are specialized in ETT.

ABSTRACT

PURPOSE OF REVIEW: Airway management in patients outside the operating room is associated with increased difficulties and risks, and the setting of the COVID-19 global pandemic adds another layer of complexity. Therefore, endotracheal intubation (ETT) of a patient who is presumptive COVID-19 or COVID-19 positive presents an additional challenge to an anesthesiologist. The aim of this review is to summarize the important principles of airway management outside of the operating room during the COVID-19 pandemic. RECENT FINDINGS: Several professional societies have formulated guidelines on airway management COVID-19 suspect and proven patients. Additionally, anesthesiologists working in hospitals treating many infected patients have developed specialized teams responsible for airway management outside the operating room. These documents and protocols focus on the importance of wearing personal protective equipment and the skills of the providers responsible for securing the airway. Staff safety is always a priority when performing ETT outside operating room. SUMMARY: The COVID-19 pandemic redefined the management of patients requiring aerosol generating procedures (droplet and airborne precautions). ETT is one of them and anesthesiologists are experts in performing airway management. Although the operating room is a highly controlled environment, airway management outside of this setting is not always the easiest task.

PEDIATRICS

PROVISION OF PEDIATRIC IMMUNIZATION SERVICES DURING THE COVID-19 PANDEMIC: AN ASSESSMENT OF CAPACITY AMONG PEDIATRIC IMMUNIZATION PROVIDERS PARTICIPATING IN THE VACCINES FOR CHILDREN PROGRAM - UNITED STATES, MAY 2020

Vogt TM, Zhang F, Banks M, Black C, Arthur B, Kang Y, Lucas P, Lamont B.. MMWR Morb Mortal Wkly Rep. 2020 Jul 10;69(27):859-863. doi: 10.15585/mmwr.mm6927a2.
Level of Evidence: 3 - Local non-random sample

BLUF

Authors from the CDC COVID-19 Emergency Response Team randomly sampled 5,144 of 37,949 pediatric practices enrolled in Vaccine for Children (VFC) on 6 May 2020 to examine the effects of the COVID-19 pandemic on pediatric immunization operations. Of the 1,727 practices who responded to follow-up survey and were operational, 1,397 (72.8%) were providing immunization services to all pediatric patients, 254 (14.7%) were only able to offer it to some patients, and 76 practices (4.4%) were unable to offer any immunizations. 32 (59.1%) of 1,933 practices surveyed reported they would be able to serve new patients for immunization services through August (Table). The authors recommend that parents and caregivers be educated about the importance of well child visits, vaccinations, and the availability of services through programs such as VFC, a federal program which provides vaccines at no cost to eligible children, especially since these have been delayed during the current pandemic.

ABSTRACT

Recent reports suggest that routine childhood immunization coverage might have decreased during the coronavirus disease 2019 (COVID-19) pandemic (1,2). To assess the capacity of pediatric health care practices to provide immunization services to children during the pandemic, a survey of practices participating in the Vaccines for Children (VFC) program was conducted during May 12-20, 2020. Data were weighted to account for the sampling design; thus, all percentages reported are weighted. Among 1,933 responding practices, 1,727 (89.8%) were currently open; 1,397 (81.1%) of these reported offering immunization services to all of their patients. When asked whether the practice would likely be able to accommodate new patients to assist with provision of immunization services through August, 1,135 (59.1%) respondents answered affirmatively. These results suggest that health care providers appear to have the capacity to deliver routinely recommended childhood vaccines, allowing children to catch up on vaccines that might have been delayed as a result of COVID-19-related effects on the provision of or demand for routine well child care. Health care providers and immunization programs should educate parents on the need to return for well-child and immunization visits or refer patients to other practices, if they are unable to provide services (3).

FIGURES

TABLE. Operational status and provision of pediatric immunization services at practices, by health care provider characteristics – Vaccines for Children Provider Survey, May 2020

Characteristic	Total, no. (%)	Urban/Rural provider practice location,* no. (weighted %)			U.S. Census region,† no. (weighted %)						
		Urban, reference	Rural	p-value§	Northeast, reference	Midwest	p-value¶	South	p-value¶	West	p-value¶
Total	**1,933 (100)**	**1,413 (73.7)**	**511 (26.3)**	—	**404 (20.7)**	**457 (23.6)**	—	**663 (34.8)**	—	**400 (20.9)**	—
Current operational status of the practice in mid-May 2020 (n = 1,933)											
Open	**1,727 (89.8)**	1,253 (89.2)	465 (91.4)	0.137	339 (85.0)	399 (87.5)	0.281	621 (93.9)	0.000	359 (90.0)	0.032
Closed	**206 (10.2)**	160 (10.9)	46 (8.6)		65 (15.0)	58 (12.5)		42 (6.2)		41 (10.0)	
Among practices that are currently open, office hours for in-person visits, relative to prepandemic hours (n = 1,727)											
Reduced	**1,063 (61.7)**	798 (63.7)	257 (55.4)	0.002	263 (77.8)	256 (64.4)	0.000	333 (53.8)	0.000	203 (56.4)	0.000
Not reduced	**664 (38.3)**	455 (36.3)	208 (44.6)		76 (22.2%)	143 (35.6)		288 (46.2)		156 (43.6)	
Among practices that are currently closed, pediatric patients have been or will be referred to a new medical home (n = 170)**											
Yes	**131 (77.2)**	101 (77.1)	30 (77.6)	0.950	35 (69.6)	36 (72.5)	0.753	25 (79.9)	0.316	35 (90.3)	0.024
No	**39 (22.8)**	30 (22.9)	9 (22.4)		16 (30.4)	13 (27.5)		6 (20.1)		4 (9.8)	
Among practices that are currently open, offering routine immunization services to pediatric patients (n = 1,727)											
All patients	**1,397 (81.1)**	1,012 (81.1)	378 (81.2)	0.013	261 (77.2)	312 (78.8)	0.177	522 (84.1)	0.014	295 (82.3)	0.238
A subset of patients	**254 (14.7)**	196 (15.5)	56 (12.3)		64 (19.0)	62 (15.3)		72 (11.6)		54 (15.1)	
No patients	**76 (4.2)**	45 (3.4)	31 (6.6)		14 (3.8)	25 (6.0)		27 (4.3)		10 (2.6)	
Practice could likely provide immunization services to additional pediatric patients through the end of August (n = 1,933)											
Yes	**1,135 (59.1)**	779 (55.5)	347 (68.4)	0.000	182 (45.5)	280 (61.0)	0.000	422 (64.1)	0.000	242 (61.2)	0.000
No††	**418 (21.3)**	334 (23.4)	84 (15.9)		128 (31.2)	85 (18.8)		121 (18.0)		84 (20.5)	
Don't know/Not sure	**380 (19.6)**	300 (21.1)	80 (15.7)		94 (23.3)	92 (20.3)		120 (17.9)		74 (18.3)	

* Classification of urban (metropolitan) or rural (nonmetropolitan) was based on county of practice location using the 2013 National Center for Health Statistics Urban–Rural Classification Scheme for Counties (https://www.cdc.gov/nchs/data/series/sr_02/sr02_166.pdf). Practices in Puerto Rico (nine) are not shown.
† https://www2.census.gov/geo/docs/maps-data/maps/reg_div.txt. Practices in Puerto Rico (nine) are not shown.
§ Chi-squared test, compared with urban location.
¶ Chi-squared test, compared with Northeast region.
** Among 206 practices reporting currently closed, those that answered "Don't know/Not sure" to their pediatric patients having been or will be referred to a new medical home (36) are not shown.
†† Includes practices that are currently open or planning to reopen but reported not likely being able to accept additional patients (400), practices permanently closed (nine), and practices not resuming immunization services for all patients (nine).

R&D: DIAGNOSIS & TREATMENTS

CHALLENGES IN EVALUATING SARS-COV-2 VACCINES DURING THE COVID-19 PANDEMIC

Abu-Raya B, Gantt S, Sadarangani M.. CMAJ. 2020 Jul 9:cmaj.201237. doi: 10.1503/cmaj.201237. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

This article discusses the unique challenges to evaluating the SARS-CoV-2 vaccine in the midst of the pandemic. The authors report that vaccine efficacy is usually influenced by baseline transmission, levels of pre-existing immunity, and susceptibility to infection in the population. These factors are affected by changing levels of COVID-19 exposure, population immunity, social distancing, and the rate by which vaccines can be developed. Authors suggest that researchers developing vaccines should consider these factors.

FIGURES

Table 1: Population-related factors affecting evaluation of vaccine efficacy in endemic versus pandemic states of infection and those unique to coronavirus disease 2019

Factors affecting demonstration of vaccine efficacy	Endemic state of infection	Pandemic state of infection	COVID-19 unique factors	Strategies
Baseline transmission of target pathogen in population (i.e., exposure) and its seasonality	Known	Rapidly changing; seasonality unknown	Social distancing and other public health interventions	Flexible trial designs to ensure adequate numbers of end points (infections or hospital admissions); determination of potential confounding by nonvaccine prevention measures
Population level of pre-existing immunity to target pathogen (i.e., susceptibility)	Known	Rapidly changing	Paucity of seroepidemiologic data; accuracy of serologic tests; unclear extent and duration of protection from natural immunity	Baseline serologic testing of participants in efficacy trials
Differential susceptibility of subpopulations to infection or disease	Known	Emerging	Numerous risk factors identified, but older adults at highest risk of severe disease; young children rarely have complications and may be less susceptible to infection; antibody-dependent enhancement	Evaluation of vaccine efficacy and end points in older adults and other high-risk groups; close monitoring and prolonged follow-up for possible antibody-dependent enhancement in all trials

Note: COVID-19 = coronavirus disease 2019.

DEVELOPMENTS IN DIAGNOSTICS

ULTRA-SENSITIVE AND HIGH-THROUGHPUT CRISPR-POWERED COVID-19 DIAGNOSIS

32553350. Ultra-sensitive and high-throughput CRISPR-p owered COVID-19 diagnosis
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Tulane University researchers present their CRISPR-based assay to diagnose SARS-CoV-2 infection, proposing that its benefits over traditional RT-PCR include an improved sample-to-answer time of roughly 50 minutes and that it does not require specialized laboratory reagents. They report the limit of detection (LOD) of their CRISPR-FDS assays was ≥2 copies of the target RNA sequence, regardless of whether it was performed with RT-PCR or RT-RPA (isothermal recombinase polymerase amplification) amplified samples. This is comparable to their measured LOD for gold-standard qPCR of 5 copies/test and suggests an improved sensitivity with the CRISPR-based assay (Figure 3).

ABSTRACT

Recent research suggests that SARS-CoV-2-infected individuals can be highly infectious while asymptomatic or pre-symptomatic, and that an infected person may infect 5.6 other individuals on average. This situation highlights the need for rapid, sensitive SARS-CoV-2 diagnostic assays capable of high-throughput operation that can preferably utilize existing equipment to facilitate broad, large-scale screening efforts. We have developed a CRISPR-based assay that can meet all these criteria. This assay utilizes a custom CRISPR Cas12a/gRNA complex and a fluorescent probe to detect target amplicons produced by standard RT-PCR or isothermal recombinase polymerase amplification (RPA), to allow sensitive detection at sites not equipped with real-time PCR systems required for qPCR diagnostics. We found this approach allowed sensitive and robust detection of SARS-CoV-2 positive samples, with a sample-to-answer time of ~50 min, and a limit of detection of 2 copies per sample. CRISPR assay diagnostic results obtained nasal swab samples of individuals with suspected COVID-19 cases were

comparable to paired results from a CDC-approved quantitative RT-PCR (RT-qPCR) assay performed in a state testing lab, and superior to those produced by same assay in a clinical lab, where the RT-qPCR assay exhibited multiple invalid or inconclusive results. Our assay also demonstrated greater analytical sensitivity and more robust diagnostic performance than other recently reported CRISPR-based assays. Based on these findings, we believe that a CRISPR-based fluorescent application has potential to improve current COVID-19 screening efforts.

FIGURES

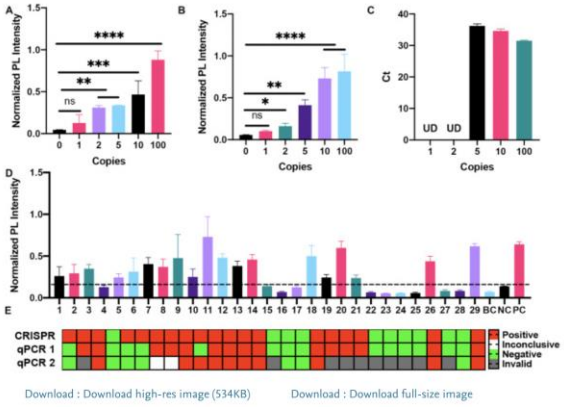

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Fig. 3. **COVID-19 CRISPR-FDS analytical and diagnostic performance.** Limit of detection (LOD) samples containing the indicated number of viral genomes after amplification by (A) RT-PCR and (B) RT-RPA for COVID-19 CRISPR-FDS analysis or by (C) RT-qPCR, indicated significant differences and undetermined (UD) results. (D) RT-PCR COVID-19 CRISPR-FDS results for a cohort of 29 individuals with suspected COVID-19 cases, run in parallel with blank (BC; nuclease free water), negative (NC; carrier RNA) and positive (PC; 10^9 target amplicon copies) control samples, where the dashed line indicates the threshold for a positive result. Results depict the mean ± SD of three experimental replicates. (E) Comparison of SARS-CoV-2 test results for matching patient samples analyzed by CRISPR-FDS, or by RT-qPCR by a state (qPCR 1) and a clinical testing laboratory (qPCR 2). (ns, $P > 0.05$; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****,$P < 0.0001$).

DEVELOPMENTS IN TREATMENTS

SELF-AMPLIFYING RNA SARS-COV-2 LIPID NANOPARTICLE VACCINE CANDIDATE INDUCES HIGH NEUTRALIZING ANTIBODY TITERS IN MICE

McKay PF, Hu K, Blakney AK, Samnuan K, Brown JC, Penn R, Zhou J, Bouton CR, Rogers P, Polra K, Lin PJC, Barbosa C, Tam YK, Barclay WS, Shattock RJ.. Nat Commun. 2020 Jul 9;11(1):3523. doi: 10.1038/s41467-020-17409-9.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Authors associated with the Imperial College London and Acuitas Therapeutics immunized mice (two injections, 1 month apart) with self-amplifying RNA (saRNA) encoding the SARS-CoV-2 spike protein within lipid nanoparticles (LNP). Their findings (detailed below) suggest that saRNA LNPs may be a hopeful target in vaccine development.

SUMMARY

Following the immunization in the mice, researchers found elevated SARS-CoV-2 specific IgG (10^5–10^6 ng mL^−1; Figure 1b), higher amounts of IgG compared to COVID-19-recovered patients, and a Th1-biased response (Figure 2). Further analyses showed saRNP LNP neutralization of both SARS-CoV-2 pseudo-virus and wild-type virus (Figure 1c, e). The neutralization was proportional to the concentration of specific IgG, and of higher magnitude when compared to COVID-19-recovered patients. Additionally, re-stimulation of saRNP LNP-injected mice with SARS-CoV-2 peptides induced high IFN-γ levels (Figure 3a).

ABSTRACT

The spread of the SARS-CoV-2 into a global pandemic within a few months of onset motivates the development of a rapidly scalable vaccine. Here, we present a self-amplifying RNA encoding the SARS-CoV-2 spike protein encapsulated within a lipid nanoparticle (LNP) as a vaccine. We observe remarkably high and dose-dependent SARS-CoV-2 specific antibody titers in mouse sera, as well as robust neutralization of both a pseudo-virus and wild-type virus. Upon further characterization we find that the neutralization is proportional to the quantity of specific IgG and of higher magnitude than recovered COVID-19

patients. saRNA LNP immunizations induce a Th1-biased response in mice, and there is no antibody-dependent enhancement (ADE) observed. Finally, we observe high cellular responses, as characterized by IFN-gamma production, upon re-stimulation with SARS-CoV-2 peptides. These data provide insight into the vaccine design and evaluation of immunogenicity to enable rapid translation to the clinic.

FIGURES

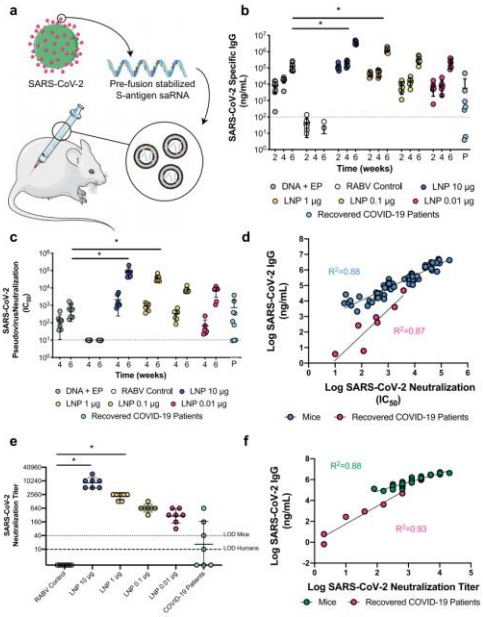

Fig. 1 Antibody quantification and neutralization of a SARS-CoV-2 saRNA vaccinated mice compared to COVID-19 recovered patients. a Schematic of vaccination of BALB/c mice with saRNA encoding pre-fusion stabilized spike protein in LNP, b SARS-CoV-2 specific IgG responses in mice vaccinated with doses of LNP-formulated saRNA ranging from 0.01–10 µg of saRNA with n = 7 biologically independent animals and COVID-19 recovered patients with n = 9 biologically independent samples, c SARS-CoV-2 pseudotyped virus neutralization of sera from BALB/c mice vaccinated with doses of LNPformulated saRNA ranging from 0.01–10 µg of saRNA with n = 7 biologically independent animals and COVID-19 recovered patients with n = 9 biologically independent samples, d Correlation between SARS-CoV-2-specific IgG and SARS-CoV-2 neutralization IC50 for vaccinated mice (n = 7 biologically independent animals) and recovered COVID-19 patients (n = 9 biologically independent samples), e SARS-CoV-2 viral neutralization of sera from BALB/c mice vaccinated with doses of LNP-formulated saRNA ranging from 0.01 to 10 µg of saRNA with n = 7 biologically independent animals, f Correlation between SARS-CoV-2-specific IgG and SARS-CoV-2 wild type viral neutralization titers for vaccinated mice (n = 7 biologically independent animals). Electroporated pDNA (DNA + EP) was used as a positive control while saRNA encoding the rabies glycoprotein (RABV) in pABOL was used as a negative control (RABV control). * indicates significance of $p < 0.05$ using a two-way ANOVA adjusted for multiple comparisons. Line and error bars indicated mean ± SD. Components of this figure were created using Servier Me

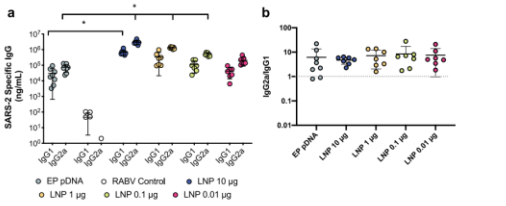

Fig. 2 Th1/Th2 skew in response to SARS-CoV-2 saRNA LNP vaccine. a IgG1 and IgG2a responses in mice vaccinated with doses of LNP-formulated saRNA ranging from 0.01–10 µg of saRNA with $n = 7$ biologically independent animals, **b** Th1/Th2 skewing responses in mice vaccinated with doses of LNP-formulated saRNA ranging from 0.01–10 µg of saRNA with $n = 7$ biologically independent animals, and 10 µg of electroporated pDNA (EP pDNA) with $n = 8$ biologically independent animals. The asterisk (*) indicates significance of $p < 0.05$ as determined by a Kruskal–Wallis test. Line and error bars indicated mean ± SD.

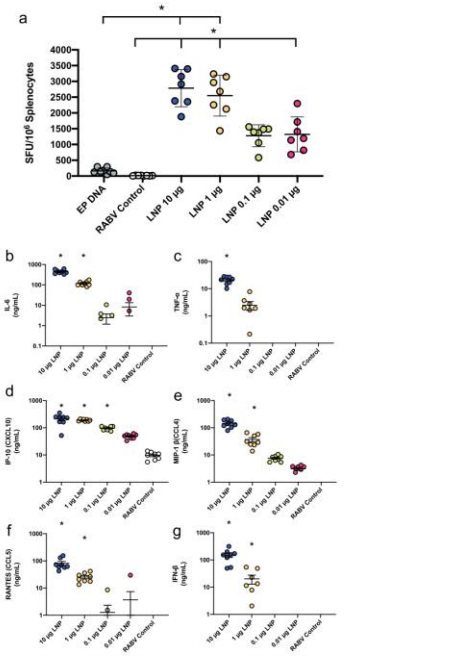

Fig. 3 Cellular and secreted cytokine responses to a SARS-CoV-2 saRNA LNP vaccine. a Quantification of IFN-γ splenocytes upon restimulation with SARS-CoV-2 peptides, expressed as spot forming units (SFU) per 10^6 cells with $n = 7$ biologically independent animals. Electroporated pDNA (EP pDNA) was used as a positive control while saRNA encoding the rabies glycoprotein (RABV) in pABOL was used as a negative control (RABV control). **b–g** Cytokine profile in sera of mice 4 h after vaccination with SARS-CoV-2 LNP vaccine with $n = 7$ biologically independent animals. Remaining cytokines can be found in Supplementary Fig. 5. The asterisk (*) indicates significance of $p < 0.05$ as determined by a Kruskal–Wallis test. Line and error bars indicated mean ± SD.

CAN INTERFERONS STOP COVID-19 BEFORE IT TAKES HOLD?

Wadman M.. Science. 2020 Jul 10;369(6500):125-126. doi: 10.1126/science.369.6500.125.
Level of Evidence: Other - Review / Literature Review

BLUF

Although results will not be published for several months, scientists studying the outcomes to interferon injections in early COVID-19 are hopeful that the robust immune response from injected interferons will halt SARS-CoV-2 entry into cells and might be a promising early-infection treatment for those at high risk of contracting the virus.

SUMMARY

This article outlines emerging clinical trials utilizing synthetic interferons to combat COVID-19. Interferons are immune molecules that trigger an immediate and intense local response when a virus invades a cell, by triggering proteins to attack the virus as well as signal additional immune cells to respond to the infection. Although interferons can be powerful at fighting viral infection, if given too late they can lead to a harmful cascade of inflammation, which is a hallmark of severe COVID-19. Therefore, this theorized treatment is time sensitive. The Stanford trial, which is one of dozens of interferon trials currently ongoing within the U.S, consists of 16 patients newly infected with COVID-19 who were given either a placebo or type III interferon. One of the patients currently in the Stanford trial is 52-year-old Valerie McCarthy (Figure 1) who tested positive for COVID-19 on April 30th. She admits she is still not back to her normal energy level, which may be a side effect from the interferon, or may be a sequela from COVID-19.

FIGURES

Figure 1. Valerie McCarthy received an injection that contained either placebo or an interferon.

PSYCHOLOGICAL HEALTH, SLEEP QUALITY, AND COPING STYLES TO STRESS FACING THE COVID-19 IN WUHAN, CHINA

Fu W, Wang C, Zou L, Guo Y, Lu Z, Yan S, Mao J.. Transl Psychiatry. 2020 Jul 9;10(1):225. doi: 10.1038/s41398-020-00913-3.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers from Huazhong University of Science and Technology, Wuhan, China conducted a cross-sectional survey of 1242 Wuhan residents from February 18th, 2020 through February 28th, 2020, assessing their psychological reaction to the COVID-19 pandemic. They found that, of individuals surveyed, 27.5% had anxiety, 29.3% had depression, 30.0% had a sleep disorder, and 29.8% had a passive coping style as measured by validated surveys. Multivariate logistic regression showed that the risk of these problems, compared to pre-pandemic norms, was associated with several factors, including female gender, monthly income between 1,000-5,000 CNY, and never engaging in exercise (Tables 3 and 4). The authors indicate these results suggest public health officials and clinicians should be aware of risk factors for poor psychological health during the pandemic and help patients engage in healthy behaviors to reduce the prevalence of unhealthy psychological states.

ABSTRACT

To understand Wuhan residents' psychological reactions to the COVID-19 epidemic and offer a reference point for interventions, an online questionnaire survey was conducted. It included the Disorder 7-Item Scale (GAD-7), the Patient Health Questionnaire 9-Item Scale (PHQ-9), Athens Insomnia Scale, and Simplified Coping Style Questionnaire. Categorical data were reported as numbers and percentages. Multivariate logistic regression models were used to evaluate the association between demographic factors and anxiety, depression, sleep disorder, and passive coping style. A total of 1242 Wuhan residents investigated, 27.5% had anxiety, 29.3% had depression, 30.0% had a sleep disorder, and 29.8% had a passive response to COVID-19. Being female was the risk factor for anxiety (OR = 1.62) and sleep disorder (OR = 1.36); being married was associated with anxiety (OR = 1.75); having a monthly income between 1000 and 5000 CNY (OR = 1.44, OR = 1.83, OR = 2.61) or >5000 CNY (OR = 1.47, OR = 1.45, OR = 2.14) was a risk factor for anxiety, depression, and sleep disorder; not exercising (OR = 1.45, OR = 1.71, OR = 1. 85, OR = 1.71) was a common risk factor for anxiety, depression, sleep disorder, and passive coping style; and having a higher education level (bachelor's degree and above) (OR = 1.40) was associated with having a sleep disorder. Wuhan residents' psychological status and sleep quality were relatively poorer than they were before the COVID-19 epidemic; however, the rate of passive coping to stress was relatively higher.

FIGURES

Table 3 Multivariate logistic regression of anxiety and depression.

Variables	β	SE	Wald	P	OR	95% CI
Anxiety						
Constant	−1.896	0.197	92.446	0.000		
Female (Ref:Male)	0.480	0.149	10.397	0.001	1.62	1.21–2.16
Married (Ref:Unmarried)	0.560	0.163	11.819	0.001	1.75	1.27–2.41
Monthly income (CNY) 1000–5000 (Ref:Monthly income <1000)	0.362	0.172	4.438	0.035	1.44	1.03–2.01
Monthly income (CNY) > 5000 (Ref:Monthly income <1000)	0.373	0.189	4.715	0.046	1.47	1.16–2.07
No exercise (Ref:Regular exercise)	0.368	0.148	6.183	0.013	1.45	1.08–1.93
Depression						
Constant	−1.997	0.224	79.566	0.000		
Monthly income (CNY) 1000–5000 (Ref:Monthly income <1000)	0.603	0.15	16.082	0.000	1.83	1.36–2.45
Monthly income (CNY) > 5000 (Ref:Monthly income <1000)	0.368	0.166	4.891	0.027	1.45	1.04–2.01
Network communication <2 times a day (Ref:No communication)	0.384	0.181	4.528	0.033	1.47	1.03–2.09
Network communication ≥2 times a day (Ref:No communication)	0.520	0.177	8.682	0.003	1.68	1.19–2.38
No exercise (Ref:Regular exercise)	0.538	0.148	13.164	0.000	1.71	1.28–2.29

SE standard error, *OR* odds ratio, *CI* confidential interval, *Ref.* reference.

Table 3. Multivariate logistic regression of anxiety and depression.

Table 4 Multivariate logistic regression of sleep disorder and passive coping style.

Variables	*β*	*SE*	*Wald*	*P*	*OR*	95% CI
Sleep disorder						
Constant	−2.233	0.208	114.76	0.000		
Female (Ref:Male)	0.305	0.142	4.597	0.032	1.36	1.03–1.79
Education (bachelor's degree and above) (Ref:College and below)	0.334	0.145	5.268	0.022	1.40	1.05–1.86
Monthly income (CNY) 1000–5000 (Ref:Monthly income <1000)	0.958	0.15	40.578	0.000	2.61	1.94–3.50
Monthly income (CNY) > 5000 (Ref:Monthly income <1000)	0.760	0.165	21.301	0.000	2.14	1.55–2.95
No exercise (Ref:Regular exercise)	0.613	0.148	17.167	0.000	1.85	1.38–2.47
Passive coping style						
Constant	−0.672	0.18	13.898	0.000		
Urban (Ref:Rural)	−0.287	0.139	4.282	0.039	0.75	0.57–0.99
Education (bachelor's degree and above) (Ref:College and below)	−0.624	0.138	20.545	0.000	0.54	0.41–0.70
No exercise (Ref:Regular exercise)	0.537	0.145	13.756	0.000	1.71	1.29–2.27

SE standard error, *OR* odds ratio, *CI* confidential interval, *Ref.* reference.

Table 4. Multivariate logistic regression of sleep disorder and passive coping style.

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