The Daily COVID-19 Literature Surveillance Summary

July 13, 2020

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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

Climate:

- Researchers at Washington University mapped current trends in COVID-19 transmission in the US using geographical mapping software and county-level data on reported infections between January 22 and May 13, 2020. They found cases had decreased in the Northeastern states (down 16.6% per week) but had consistently increased in the Midwest, South, and Western states (up 13.2%, 5.6%, and 5.7% per week, respectively). Additionally, the incidence of COVID-19 has been consistently increasing in rural counties and counties with majority-minority populations, raising concern because these communities have less healthcare resources to mitigate a surge.
- Authors highlight the vulnerabilities faced by people who use drugs (PWUD) during the COVID-19 pandemic because of their increased risk for homelessness, interactions with the criminal justice system, and need for in-person substance use treatment. To address these vulnerabilities, they recommend international stakeholders create policies and programs to invest in public health infrastructure, prioritize decriminalization, and increase access to harm reduction programs and telemedicine for substance use services.

Epidemiology:

- Public health experts from Seattle performed a retrospective analysis of 124 COVID-19 positive patients who received Emergency Medical Services, finding that 46% of patients resided in long-term care facilities, 37.9% had 3 or more chronic health comorbidities, and 52.3% died. Additionally, 43 of 147 encounters (29.3%) were negative for fever, cough, or shortness of breath. Authors conclude that this heterogeneity in symptomatology highlights the need to improve current COVID-19 screening tools, and prevent nosocomial transmission in pre-hospital settings.
- This case series documents COVID-19 disease course in 4 febrile hospitalized neonates, all of whom had favorable outcomes. Two neonates required ICU admission for respiratory insufficiency, two neonates had a co-infection (E. Coli., human metapneumovirus), and one neonate was successfully treated with remdesivir. These findings suggest that neonates presenting with fever, a common condition, should be assessed for potential COVID-19 infection during the pandemic.

Understanding the Pathology:

- A retrospective cohort study involving 127 children with COVID-19 found that "decreased levels of globulin, IgA, and CD4+CD25+ T lymphocyte percentage and increased concentration of hs-CRP, procalcitonin, and IL-10 were associated with the presentation of pneumonia in chest radiologic findings". These findings suggest that "immune-related factors may participate in the pathogenesis of pneumonia in children with COVID-19" similarly to adults.
- A literature review by Chinese researchers describe the pathophysiology of SARS-CoV-2 infection in patients with intracerebral hemorrhage (ICH). Specifically, they discusses virus entry into the brain through ACE2 receptors, subsequent disruption of two pathways in the brain involved in maintaining cerebral homeostasis (i.e. ACE2–Ang (1–7)–MasR axis and ACE–Ang II–AT1R axis), destruction of the blood brain barrier allowing infiltration of immune cells into the brain, and oxidative tissue damage due to the immune response. This review highlights the increased risk of poor outcomes in ICH patients with COVID-19 and the need for early diagnosis, isolation, and treatment.

Transmission and Prevention:

- An analysis conducted on COVID-19 mortality and bacillus Calmette–Guérin (BCG) vaccine data collected until 22 April 2020 found a global negative association between BCG vaccination policy and COVID-19 mortality. When potential confounding variables such as Human Development Index (life expectancy, education level, and per capita income), ≥15% of population over 65 years of age, and urbanization were mitigated, the overall significance was reduced, but countries with stronger BCG vaccination policies still had a lower COVID-19 mortality rate. These results suggest the BCG vaccine may confer protection from COVID-19 by enhancing the innate immune system, however, further randomized trials and data are needed.
- Researchers in the Netherlands analyzed the effectiveness of social media education campaigns. They administered an initial survey of 16,072 participants through social media with questions about handwashing, face touching, and physical distancing, followed by a multimedia campaign with virologist and social media influencer Govert Sweep and a popular national newspaper, “De Telegraaf.” A post-campaign survey 3 days later revealed that participants who saw both components of the campaign reported an improvement in personal hygiene and physical distancing during the COVID-19 crisis, suggesting a potential value for the use of similar multimedia campaigns to improve these behaviors.

Management:

- A systematic review conducted at Geneva University Hospital in Geneva, Switzerland of 11 studies (n=1,369) found that venous thromboembolism (VTE) is a more common complication of COVID-19 in inpatients than in outpatients.

Additionally, guidelines continue to recommend VTE prophylaxis in all hospitalized COVID-19 patients regardless of symptoms. However authors note that the dosing of VTE prophylaxis varies between guidelines, suggesting more research needs to be done to determine the therapeutic dose.

- A review of 11 studies by Greek researchers found significant heterogeneity in the reported venous thromboembolic (VTE) phenotypes of hospitalized COVID-19 patients. Authors suggest the heterogeneity could be due to specific risk factors, including patient age, sex, VTE history, and SARS-CoV-2 specific factors (ie., coagulopathy, endothelial injury/microthrombosis). Due to this variation and unpredictability as well as evidence suggesting VTE is associated with more severe disease (see below), they recommend increased d-dimer screening for VTE and thromboprophylaxis in all hospitalized patients.

Adjusting Practice During the Pandemic:

- Experts in psychiatry and neuro-ethics argue that tele-psychiatry should continue to be utilized after the COVID-19 pandemic passes. They develop their stance through the lens of medical ethics principles and maintain the following:
  1) Continuing to offer tele-psychiatry services is necessary for the sake of patient benefice and autonomy.
  2) Doing so would likely yield significant cost-savings for patients and other stakeholders.
  3) Increasing tele-psychiatry accessibility would yield a greater degree of distributive justice.

R&D Diagnosis and Treatment:

- Radiologists in Wuhan, China conducted retrospectively compared chest computed tomography (CT) findings between survivors (n=83) and non-survivors (n=41) of COVID-19 infection. They found that non-survivors had more bilateral (97% vs 73%) and diffuse (39% vs 8%) findings, and a predominant "crazy-paving" pattern on chest CT (appearance of ground class opacity with superimposed interlobular septal thickening). Curve estimation showed rapidly increased total CT score (0 = no involvement to 25 = maximum involvement) in non-survivors that remained high until acute respiratory distress syndrome (ARDS) and subsequent death occurred, while total CT score increased slowly followed by a gradual decline in survivors. Authors suggest crazy-paving pattern predominance and total CT score trends may assist in identifying high risk patients prior to clinical deterioration.
- A neural network program that analyzed electronic health records from 77,167 COVID-19 patients at the Mayo Clinic to better categorize symptomatology. They found that anosmia/dysguesia was increased 27.1 fold in COVID-19 positive patients, and was the earliest sign of infection. Additionally, cough plus fever/chills (4.2 fold), myalgia/arthralgia (2 fold), and diarrhea (1.7 fold) were also seen in RT-PCR positive patients. These findings highlight the utility of artificial intelligence methods in enhancing the EHR to facilitate real-time diagnostic support of COVID-19 infection.
- A literature review from the Department of Rheumatic and Immunologic Diseases at the Cleveland Clinic highlights the use of IL-1 antagonists such as anakinra and canakinumab as effective drug choices to improve outcomes of patients with cytokine release syndrome secondary to COVID-19. Modulation of IL-1 may decrease hyperactive pulmonary macrophages from releasing IL-1 and other inflammatory cytokines. Preliminary evidence indicates that anakinra and canakinumab, drugs that block the action of IL-1 and have a good safety profile and improve the outcomes of patients with COVID-19 cytokine release syndrome. Results from large, randomized clinical trials are pending.

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CLIMATE

COVID-19 CLINICAL TRIALS: UNRAVELLING A METHODOLOGICAL GORDIAN KNOT

Mathioudakis AG, Fally M, Hashad R, Knight S, Felton T, Vestbo J.. Am J Respir Crit Care Med. 2020 Jul 7. doi: 10.1164/rccm.202005-1942ED. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

International experts discuss the flood of research studies on COVID-19 which sometimes forces studies to compete for the same patient population. In addition, the vast number of trials causes data fragmentation with no collaboration between trials globally. The experts believe this ultimately this slows the development of effective treatments for COVID-19 and suggest time could be saved by conducting interim data meta-analysis on the results of similar trials.

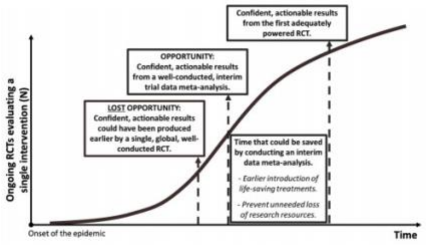
SUMMARY

Within six months of COVID-19 being discovered, over 2,150 research studies, including 1,200 interventional trials have been registered. These interventional trials seek to recruit over two million participants, forcing competition for enrolling patients into trials. Many of these trials have similar interventions and are running independently of one another. As an example, there are currently 178 registered trials with chloroquine or hydroxychloroquine as an intervention for COVID-19. Because these trials are generally run independently, there is limited awareness of other trials, causing data fragmentation, which ultimately leads to slower results regarding efficacy and safety. Many trials are running independently, however, there are several, such as the Solidarity trial run by the World Health Organization conducting large-scale collaborative randomized clinical trials.

Because there are multiple stages and presentations of COVID-19 infection, there is a good reason to conduct multiple trials on the same intervention. Conducting trials of the same medication for prophylaxis, early-stage of the disease, or in critically-ill patients is important in determining when an intervention is safe and efficacious.

Because of all these challenges, the authors stress the importance of collecting and analyzing all the data available. Conducting meta-analyses based on the preliminary data may be important in gathering conclusions at a quicker rate than individual trials (Figure 1).

FIGURES



Graphical representation of the timeline to the acquisition of confident, actionable results regarding the safety and clinical effectiveness of clinical interventions for COVID-19 infection, demonstrating the benefits of conducting an interim data meta-analysis.

Figure 1. Graphical representation of the timeline to the acquisition of confident, actionable results regarding the safety and clinical effectiveness of clinical interventions for COVID-19 infection, demonstrating the benefits of conducting an interim data meta-analysis.

DISPARITIES

SPATIOTEMPORAL CHARACTERISTICS OF COVID-19 EPIDEMIC IN THE UNITED STATES

Wang Y, Liu Y, Struthers J, Lian M.. Clin Infect Dis. 2020 Jul 8:ciaa934. doi: 10.1093/cid/ciaa934. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Researchers at Washington University mapped current trends in COVID-19 transmission using ArcGIS software and county-level data on cases between January 22 and May 13, 2020. They found cases had decreased in the Northeastern states (down 16.6% per week) and have consistently increased in the Midwest, South, and Western states (up 13.2%, 5.6%, and 5.7% per week, respectively) (Figure 1). Additionally, the incidence of COVID-19 has been consistently increasing in rural counties and counties with majority-minority populations (Figure 2 & 3). These findings suggest that the COVID-19 pandemic is not over in the United States and that social distancing measures should be maintained.

ABSTRACT

BACKGROUND: A range of near-real-time online/mobile mapping dashboards and applications have been used to track the COVID-19 pandemic worldwide. It remains unknown about small area-based spatiotemporal patterns of COVID-19 in the United States. METHODS: We obtained county-based counts of COVID-19 cases confirmed in the United States from January 22 to May 13, 2020 (N=1,386,050). We characterized the dynamics of COVID-19 epidemic through detecting weekly hotspots of newly confirmed cases using Spatial and Space-Time Scan Statistics and quantifying the trends of incidence of COVID-19 by county characteristics using the Joinpoint analysis. RESULTS: Along with the national plateau reached in early April, COVID-19 incidence significantly decreased in the Northeast (estimated weekly percentage changes [EWPC]: -16.6%), but remained increasing in the Midwest, South and West Regions (EWPCs: 13.2%, 5.6%, and 5.7%, respectively). Higher risks of clustering and incidence of COVID-19 were consistently observed in metropolitan vs rural counties, counties closest to core airports, most populous counties, and counties with highest proportion of racial/ethnic minority counties. However, geographic differences in the incidence have shrunk since early April, driven by a significant decrease in the incidence in these counties (EWPC range: -2.0% - -4.2%) and a consistent increase in other areas (EWPC range: 1.5% - 20.3%). CONCLUSIONS: To substantially decrease the nationwide incidence of COVID-19, strict social distancing measures should be continuously implemented, especially in geographic areas with increasing risks, including rural areas. Spatiotemporal characteristics and trends of COVID-19 should be considered in decision-making on the timeline of re-opening for states and localities.

FIGURES

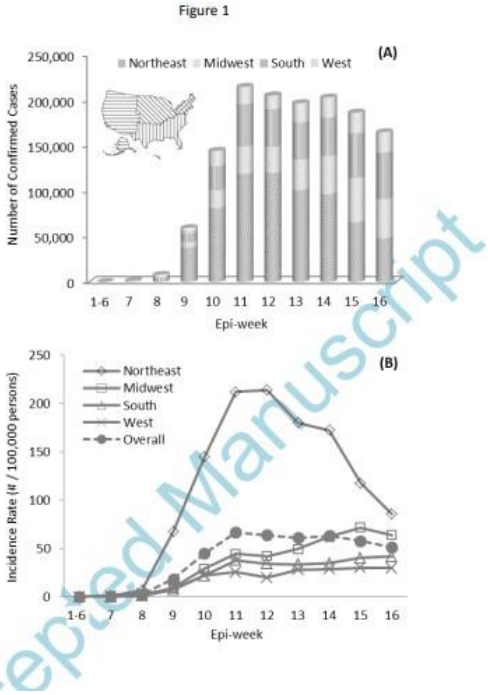


Figure 1. The temporal trend of weekly number of confirmed cases (A) and weekly incidence (B) of COVID-19 across four geographic regions in the United States over 16 epi-weeks, January 22–May 13, 2020.

Figure 2

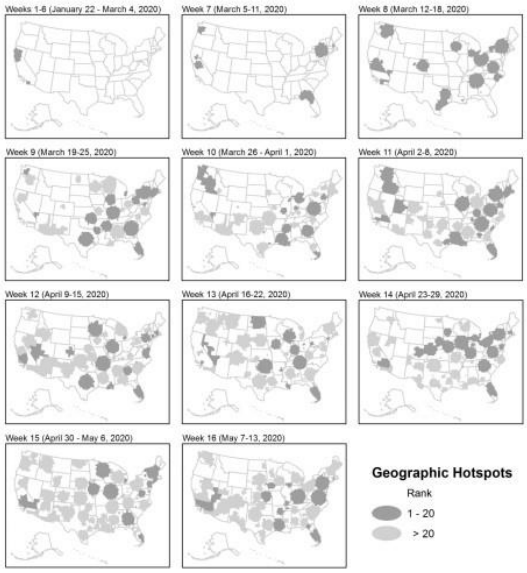


Figure 2. Weekly dynamics of geographic clustering of newly confirmed COVID-19 cases in the United States over 16 epi-weeks, January 22–May 13, 2020.

Figure 3

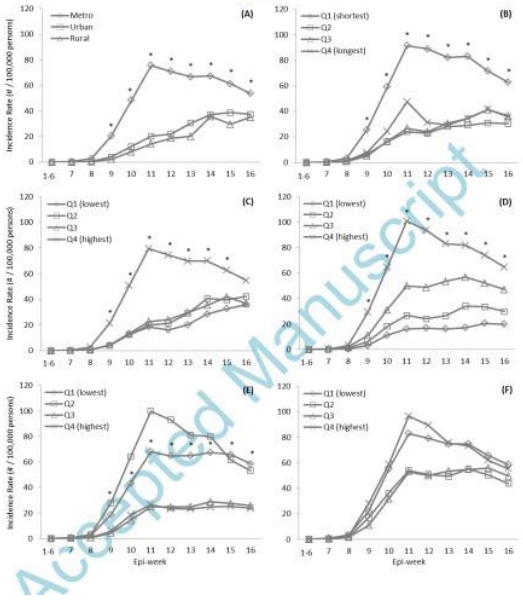


Figure 2. Weekly dynamics of geographic clustering of newly confirmed COVID-19 cases in the United States over 16 epi-weeks, January 22–May 13, 2020.

COVID-19 VULNERABILITY AMONG PEOPLE WHO USE DRUGS: RECOMMENDATIONS FOR GLOBAL PUBLIC HEALTH PROGRAMMES AND POLICIES

Holloway IW, C Spaulding A, Miyashita Ochoa A, A Randall L, R King A; HBOU Study Team, Frew PM.. J Int AIDS Soc. 2020 Jul;23(7):e25551. doi: 10.1002/jia2.25551.
Level of Evidence: Other - Expert Opinion

BLUF

Authors highlight the vulnerabilities faced by people who use drugs (PWUD) during the COVID-19 pandemic because of their increased risk for homelessness, interactions with the criminal justice system, and need for in-person substance use

treatment. To address these vulnerabilities, they recommend international stakeholders create policies and programs to invest in public health infrastructure, prioritize decriminalization, and increase access to harm reduction programs and telemedicine for substance use services.

SUMMARY

PWUD face increased exposure to high-risk settings due to homelessness, prison overcrowding with limited COVID-19 testing and PPE, and limited hand hygiene supplies on the streets. In community settings, PWUD may have limited access to drugs due to interruptions in the global supply chain and limited access to harm reduction programs due to social distancing measures. The authors recommend community advocates, researchers, and international stakeholders create comprehensive policies that encourage investment in public health infrastructure such as homeless shelters and temporary housing, decriminalization of PWUD and increased access to harm reduction services such as syringe exchange and naloxone distribution, as well as increasing access to telemedicine for PWUD to engage with healthcare professionals, counselors, and addiction medicine specialists.

A CALL FOR A GENDER-RESPONSIVE, INTERSECTIONAL APPROACH TO ADDRESS COVID-19

Ryan NE, El Ayadi AM.. Glob Public Health. 2020 Jul 7:1-9. doi: 10.1080/17441692.2020.1791214. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

An article by United States authors discusses gender disparities during the COVID-19 pandemic and how the use of an intersectional approach (understanding dimensions of power, social determinants, and structural inequalities) can be used define risks and consequences of COVID-19 across populations, leading to informed action (Carbado et al., 2013; Crenshaw, 1991; Hankivsky et al., 2010). Authors suggest implementing gender-specific guidelines (see Summary) to mitigate consequences of gender inequalities via an equity-informed evidence-based COVID-19 response.

SUMMARY

Summary of healthcare, public health and policy recommendations as follows:
- Support essential workers (including frontline healthcare responders) with PPE, paid time off, equitable compensation, and psychosocial support.
- Equal access and quality of healthcare including maternity care, sexual and reproductive health services, infertility services and mental health care.
- Innovate service delivery via mobile health provision for critical services (i.e. sexual/reproductive health care and case management for gender-based violence).
- Equity-based surveillance with appropriate data disaggregation, including sub-group assessment within clinical trials of therapeutics and vaccines.
- Collect diverse data from multiple sources (i.e. governments, practitioners and civil society) and with multiple methodologies to capture health needs of those affected.
- Contextualize data within systems of power (social forces influence on social status) to allow for mapping of pathways through which gender roles, norms and relations are reinforced or disrupted during the pandemic.
- Support disaggregated surveillance, research, and programming through gender-based budgeting.
- Mainstream intersectionality through research design, program delivery, and evaluation
- Community participation (including lived experiences of women of oppressions/inequalities) to address needs of women and allow for tailoring/adaptation of evidence-based interventions.
- Utilize assets-based approach in programs and capitalize on existing community strengths/resources.
- Ensure educational access for females whose schooling may be challenged by concurrent domestic labor or caregiving responsibilities.
- Provide COVID-19 guidance on gender mainstreaming by global public health organizations (i.e. World Health Organization [WHO]) to encourage assessment of policy implications based on gender.
- Gender equality in COVID-19 working groups and support of women in leadership positions (across government, industry, and non-profit sectors) to promote gender-informed decision making.

Authors suggest despite some progress in generating a gender-responsive approach, much work remains such as providing fair compensation for global health/social care workforce (comprised of 70% women [World Health Organization, 2019]), reporting of sex-disaggregated COVID-19 data, and promoting COVID-19 funding for women-centered organizations.

ABSTRACT

ABSTRACT The COVID-19 pandemic exacerbates existing health inequities, including gender disparities, and we must learn from previous global public health threats to build a gender-responsive, intersectional approach to address immediate and long-term consequences. While a narrow gender focus alone can reinforce binary and competing understandings of disease burden by gender, an intersectionality approach encourages understanding of the dimensions of power, historical structural inequalities, and the role of social determinants and lived experience to inform a multidimensional, gender-informed response to this and future emerging infectious diseases. We provide specific, actionable recommendations for critical healthcare, public health, and policy to use an intersectional approach to COVID-19 pandemic preparedness, response and resiliency.

CLINICAL CHARACTERISTICS OF PATIENTS WITH CORONAVIRUS DISEASE 2019 (COVID-19) RECEIVING EMERGENCY MEDICAL SERVICES IN KING COUNTY, WASHINGTON

Yang BY, Barnard LM, Emert JM, Drucker C, Schwarcz L, Counts CR, Murphy DL, Guan S, Kume K, Rodriquez K, Jacinto T, May S, Sayre MR, Rea T.. JAMA Netw Open. 2020 Jul 1;3(7):e2014549. doi: 10.1001/jamanetworkopen.2020.14549.
Level of Evidence: 4 - Case-series or casecontrol studies, or poor quality prognostic cohort study

BLUF

Authors from the University of Washington, Seattle Fire Department, and Public Health–Seattle and King County performed a retrospective study of 124 COVID-19 positive patients who received Emergency Medical Services from February 1 to March 18, 2020 in King County, WA. Among the patients, 46% resided in long-term care facilities, 37.9% had 3 or more chronic health comorbidities, 52.3% died as of June 1, 2020, and 43 of 147 encounters (29.3%) were negative for fever, cough, or shortness of breath (Table 1-2). The authors concluded that typical symptoms of COVID-19 were heterogeneous, suggesting the need to improve current COVID-19 screening tools, specifically in pre-hospital emergency settings.

ABSTRACT

Importance: The ability to identify patients with coronavirus disease 2019 (COVID-19) in the prehospital emergency setting could inform strategies for infection control and use of personal protective equipment. However, little is known about the presentation of patients with COVID-19 requiring emergency care, particularly those who used 911 emergency medical services (EMS). Objective: To describe patient characteristics and prehospital presentation of patients with COVID-19 cared for by EMS. Design, Setting, and Participants: This retrospective cohort study included 124 patients who required 911 EMS care for COVID-19 in King County, Washington, a large metropolitan region covering 2300 square miles with 2.2 million residents in urban, suburban, and rural areas, between February 1, 2020, and March 18, 2020. Exposures: COVID-19 was diagnosed by reverse transcription-polymerase chain reaction detection of severe acute respiratory syndrome coronavirus 2 from nasopharyngeal swabs. Test results were available a median (interquartile range) of 5 (3-9) days after the EMS encounter. Main Outcomes and Measures: Prevalence of clinical characteristics, symptoms, examination signs, and EMS impression and care. Results: Of the 775 confirmed COVID-19 cases in King County, EMS responded to 124 (16.0%), with a total of 147 unique 911 encounters. The mean (SD) age was 75.7 (13.2) years, 66 patients (53.2%) were women, 47 patients (37.9%) had 3 or more chronic health conditions, and 57 patients (46.0%) resided in a long-term care facility. Based on EMS evaluation, 43 of 147 encounters (29.3%) had no symptoms of fever, cough, or shortness of breath. Based on individual examination findings, fever, tachypnea, or hypoxia were only present in a limited portion of cases, as follows: 43 of 84 encounters (51.2%), 42 of 131 (32.1%), and 60 of 112 (53.6%), respectively. Advanced care was typically not required, although in 24 encounters (16.3%), patients received care associated with aerosol-generating procedures. As of June 1, 2020, mortality among the study cohort was 52.4% (65 patients). Conclusions and Relevance: The findings of this cohort study suggest that screening based on conventional COVID-19 symptoms or corresponding examination findings of febrile respiratory illness may not possess the necessary sensitivity for early diagnostic suspicion, at least in the prehospital emergency setting. The findings have potential implications for early identification of COVID-19 and effective strategies to mitigate infectious risk during emergency care.

FIGURES

Table 1. Characteristics of Patients With Coronavirus Disease 2019 With 911 Emergency Medical Services Encounters

Characteristic	No. (%)			P value
	All patients (N = 124)	Residence in long-term care facility (n = 56)	Residence other than long-term care facility (n = 68)	
Age, mean (SD), y	75.7 (13.2)	80.7 (9.7)	71.4 (14.3)	<.001
Women	66 (53.2)	30 (53.6)	36 (52.9)	.72
Chronic health conditions				
None reported or missing	19 (15.3)	6 (10.7)	13 (19.1)	.08
1	21 (16.9)	7 (12.5)	14 (20.6)	
2	37 (29.8)	15 (26.8)	22 (32.4)	
≥3	47 (37.9)	28 (50.0)	19 (27.9)	
Individual health conditions				
Hypertension	44 (35.5)	20 (35.7)	24 (35.3)	.99
Any cardiac disease	41 (33.1)	20 (35.7)	21 (30.9)	.70
Cardiomyopathy	21 (16.9)	15 (26.8)	6 (8.8)	.02
Atrial fibrillation or other arrhythmias	16 (12.9)	11 (19.6)	5 (7.4)	.06
Any lung disease[a]	26 (21.0)	15 (26.8)	11 (16.2)	.19
Diabetes	25 (20.2)	9 (16.1)	16 (23.5)	.37
Dementia	23 (18.5)	16 (28.6)	7 (10.3)	.01
Neurologic or other	12 (9.7)	7 (12.5)	5 (7.4)	.55
Stroke or TIA	11 (8.9)	5 (8.9)	6 (8.8)	.99
Kidney disease or dialysis	7 (5.6)	6 (10.7)	1 (1.5)	.04
Cancer	5 (4.0)	4 (7.1)	1 (1.5)	.17
Immunocompromised	4 (3.2)	1 (1.8)	3 (4.4)	.63
Other[b]	15 (12.1)	8 (14.3)	7 (10.3)	.99
Recent history of pneumonia	18 (14.5)	10 (17.9)	8 (11.8)	.60
Mortality[c]	65 (52.4)	41 (73.2)	24 (35.3)	<.001

Table 2. Characteristics of EMS Encounters With Patients With COVID-19

Characteristic	All encounters (N = 147)	Encounter at long-term care facility (n = 63)	Encounter not at long-term care facility (n = 84)	P value
Location of presentation				
Home	70 (47.6)	NA	70 (83.3)	NA
Facility				
Long-term care	63 (42.9)	63 (100)	NA	
Skilled nursing	51 (34.7)	51 (81.0)	NA	
Assisted living	12 (8.2)	12 (19.0)	NA	
Outpatient	11 (7.5)	NA	11 (13.1)	
Public or street	3 (2.0)	NA	3 (3.6)	
Initial dispatch code				
Illness of unknown origin	41 (27.9)	17 (27.0)	24 (28.6)	.14
Difficulty breathing	37 (25.2)	15 (23.8)	22 (26.2)	
Trauma	22 (15.0)	12 (19.0)	10 (11.9)	
Infectious disease	19 (12.9)	7 (11.1)	12 (14.3)	
Cardiac	14 (9.5)	5 (7.9)	9 (10.7)	
Bleeding or pain, nontraumatic	8 (5.4)	6 (9.5)	2 (2.4)	
Stroke or headache	6 (4.1)	0	6 (7.1)	
Documented symptoms				
Fever, cough, or shortness of breath	104 (70.7)	41 (65.1)	63 (75.0)	.20
Cough	43 (29.3)	9 (14.3)	34 (40.5)	.001
Fever	68 (46.3)	28 (44.4)	40 (47.6)	.74
Shortness of breath	64 (43.5)	28 (44.4)	36 (42.9)	.87
Fatigue	59 (40.1)	16 (25.4)	43 (51.2)	.002
Altered mental status	41 (27.9)	21 (33.3)	20 (23.8)	.27
Nausea or vomiting	14 (9.5)	1 (1.6)	13 (15.5)	.004
Diarrhea	9 (6.1)	1 (1.6)	8 (9.5)	.08
Headache	4 (2.7)	1 (1.6)	3 (3.6)	.64
Sore throat	3 (2.0)	0	3 (3.6)	.26
Muscle aches or joint pain	1 (0.7)	0	1 (1.2)	.99
Other[a]	5 (3.4)	4 (6.3)	1 (1.2)	.17
Temperature, mean (SD), °C[b]	37.9 (1.1)	38.1 (1.0)	37.7 (1.2)	.16
Abnormal initial vital sign results, No./total No. (%)				
Heart rate ≥100 bpm	47/137 (34.3)	19/62 (30.6)	28/75 (37.3)	.47
Body temperature ≥38 °C	43/84 (51.2)	24/42 (57.1)	19/42 (45.2)	.38
Respiratory rate ≥24	42/131 (32.1)	27/58 (46.6)	15/73 (20.5)	.002
Oxygenation saturation ≤92%	60/112 (53.6)	30/55 (54.5)	30/57 (52.6)	.85
Glasgow Coma Scale score <15	29/108 (26.9)	22/53 (41.5)	7/55 (12.7)	<.001
Systolic blood pressure ≤90 mm Hg	16/134 (11.9)	8/60 (13.3)	8/74 (10.8)	.79
Emergency medical services primary impression				
Flu-like symptoms	36 (24.5)	15 (23.8)	21 (25)	.40
Respiratory	30 (20.4)	12 (19.0)	18 (21.4)	
Weakness	19 (12.9)	5 (7.9)	14 (16.7)	
Injury or pain	14 (9.5)	9 (14.3)	5 (6)	
COVID-19[c]	12 (8.2)	6 (9.5)	6 (7.1)	
Altered mental status	8](5.4)	4 (6.3)	4 (4.8)	
Cardiac	7 (4.8)	2 (3.2)	5 (6.0)	
Other[d]	21 (14.3)	10 (15.9)	11 (13.1)	

(continued)

Table 2. Characteristics of EMS Encounters With Patients With COVID-19 (continued)

Characteristic	All encounters (N = 147)	Encounter at long-term care facility (n = 63)	Encounter not at long-term care facility (n = 84)	P value
EMS documented COVID-19				
Lab-confirmed COVID	10 (6.8)	4 (6.3)	6 (7.1)	.63
COVID-19 suspected by EMS	64 (43.5)	25 (39.7)	39 (46.4)	
No mention of COVID-19	73 (49.7)	34 (54.0)	39 (46.4)	
EMS care provided				
Oxygenation and ventilation support	49 (33.3)	27 (42.9)	22 (26.2)	.05
Highest level of support				.07
Nasal cannula or simple face mask	26 (17.7)	12 (19)	14 (16.7)	
Nonrebreather mask	19 (12.9)	11 (17.5)	8 (9.5)	
CPAP or BVM	2 (1.4)	2 (3.2)	0	
Intubation	2 (1.4)	2 (3.2)	0	
Intravenous fluid	16 (10.9)	9 (14.3)	7 (8.3)	.30
Nebulizer therapy	3 (2)	2 (3.2)	1 (1.2)	.58
Medication	7 (4.8)	4 (6.3)	3 (3.6)	.46
CPR	1 (0.7)	0	1 (1.2)	.43
Aerosol-generating procedures[a]	24 (16.3)	16 (25.4)	8 (9.5)	.01
Disposition				.008
Not transported	26 (17.7)	7 (11.1)	19 (22.6)	
BLS transport, fire and private ambulance	93 (63.3)	44 (69.8)	49 (58.3)	
ALS transport	23 (15.6)	12 (19.0)	11 (13.1)	
Transported by private vehicle	5 (3.4)	0	5 (6.0)	

ADULTS

CORONAVIRUS DISEASE 2019 CASE SURVEILLANCE - UNITED STATES, JANUARY 22-MAY 30, 2020

32555134. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020
Level of Evidence: Other - Mechanism-based reasoning

BLUF

This report includes the "demographic characteristics, underlying health conditions, symptoms, and outcomes among 1,320,488 laboratory-confirmed COVID-19 cases individually reported to CDC during January 22–May 30, 2020" and found that "the most common underlying health conditions were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Hospitalizations were six times higher and deaths 12 times higher among those with reported underlying conditions compared with those with none reported." This study highlights the efficacy of governmental surveillance in identifying populations at risk as well as the need for community mitigation programs to protect these vulnerable populations.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic resulted in 5,817,385 reported cases and 362,705 deaths worldwide through May, 30, 2020, including 1,761,503 aggregated reported cases and 103,700 deaths in the United States. Previous analyses during February-early April 2020 indicated that age >=65 years and underlying health conditions were associated with a higher risk for severe outcomes, which were less common among children aged <18 years (1-3). This report describes demographic characteristics, underlying health conditions, symptoms, and outcomes among 1,320,488 laboratory-confirmed COVID-19 cases individually reported to CDC during January 22-May 30, 2020. Cumulative incidence, 403.6 cases per 100,000 persons, was similar among males (401.1) and females (406.0) and highest among persons aged >=80 years (902.0). Among 599,636 (45%) cases with known information, 33% of persons were Hispanic or Latino of any race (Hispanic), 22% were non-Hispanic black (black), and 1.3% were non-Hispanic American Indian or Alaska Native (AI/AN). Among 287,320 (22%) cases with sufficient data on underlying health conditions, the most common were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Overall, 184,673 (14%) patients were hospitalized, 29,837 (2%) were admitted to an intensive care unit (ICU), and 71,116 (5%) died. Hospitalizations were six times higher among patients with a reported underlying condition (45.4%) than those without reported underlying conditions (7.6%). Deaths were 12 times higher among patients with reported underlying conditions (19.5%) compared with those without reported underlying conditions (1.6%). The COVID-19 pandemic continues to be severe, particularly in certain population groups. These preliminary findings underscore the need to build on current efforts to collect and analyze case data, especially among those with underlying health conditions. These data are used to monitor trends in COVID-19 illness, identify and respond to localized incidence increase, and inform policies and practices designed to reduce transmission in the United States.

FIGURES

TABLE 2. Reported underlying health conditions* and symptoms† among persons with laboratory-confirmed COVID-19, by sex and age group — United States, January 22–May 30, 2020

Characteristic	Total	No. (%) Sex		Age group (yrs)							
		Male	Female	≤9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	≥80
Total population	**1,320,488**	**646,358**	**674,130**	**20,458**	**49,245**	**182,469**	**214,849**	**219,139**	**235,774**	**179,007**	**105,252**	**114,295**
Underlying health condition§												
Known underlying medical condition status¶	**287,320 (21.8)**	138,887 (21.5)	148,433 (22.0)	2,896 (14.2)	7,123 (14.5)	27,436 (15.0)	33,483 (15.6)	40,572 (18.5)	54,717 (23.2)	50,125 (28.0)	34,400 (32.7)	36,568 (32.0)
Any cardiovascular disease#	**92,546 (32.2)**	47,567 (34.2)	44,979 (30.3)	78 (2.7)	164 (2.3)	1,177 (4.3)	3,588 (10.7)	8,198 (20.2)	16,954 (31.0)	21,466 (42.8)	18,763 (54.5)	22,158 (60.6)
Any chronic lung disease	**50,148 (17.5)**	20,930 (15.1)	29,218 (19.7)	363 (12.5)	1,285 (18)	4,537 (16.5)	5,110 (15.3)	6,327 (15.1)	8,722 (15.9)	9,200 (18.4)	7,436 (21.6)	7,368 (20.1)
Renal disease	**21,908 (7.6)**	12,144 (8.7)	9,764 (6.6)	21 (0.7)	34 (0.5)	204 (0.7)	587 (1.8)	1,273 (3.1)	2,789 (5.1)	4,764 (9.5)	5,401 (15.7)	6,835 (18.7)
Diabetes	**86,737 (30.2)**	45,089 (32.5)	41,648 (28.1)	12 (0.4)	225 (3.2)	1,409 (5.1)	4,106 (12.3)	9,636 (23.8)	19,589 (35.8)	22,314 (44.5)	16,994 (48.2)	12,852 (35.1)
Liver disease	**3,953 (1.4)**	2,439 (1.8)	1,514 (1.0)	5 (0.2)	19 (0.3)	132 (0.5)	390 (1.2)	573 (1.4)	878 (1.6)	1,074 (2.1)	583 (1.7)	299 (0.8)
Immunocompromised	**15,265 (5.3)**	7,345 (5.3)	7,920 (5.3)	61 (2.1)	146 (2.0)	646 (2.4)	1,253 (3.7)	2,005 (4.9)	3,190 (5.8)	3,421 (6.8)	2,496 (7.2)	2,057 (5.6)
Neurologic/ Neurodevelopmental disability	**13,665 (4.8)**	6,193 (4.5)	7,472 (5.0)	41 (1.4)	113 (1.6)	395 (1.4)	533 (1.6)	734 (1.8)	1,338 (2.4)	2,006 (4.0)	2,759 (8.0)	5,746 (15.7)
Symptom¶												
Known symptom status†	**373,883 (28.3)**	178,223 (27.6)	195,660 (29.0)	5,188 (25.4)	12,689 (25.8)	51,464 (28.2)	59,951 (27.9)	62,643 (28.6)	70,040 (29.7)	52,178 (29.1)	28,583 (27.2)	31,147 (27.3)
Fever, cough, or shortness of breath	**260,706 (69.7)**	125,768 (70.6)	134,938 (69.0)	3,278 (63.2)	7,584 (59.8)	35,072 (68.1)	42,016 (70.1)	45,361 (72.4)	51,283 (73.2)	37,701 (72.3)	19,583 (68.5)	18,828 (60.4)
Fever††	**161,071 (43.1)**	80,578 (45.2)	80,493 (41.1)	2,404 (46.3)	4,443 (35.0)	20,381 (39.6)	25,887 (43.2)	28,407 (45.3)	32,375 (46.2)	23,591 (45.2)	12,190 (42.6)	11,393 (36.6)
Cough	**187,953 (50.3)**	89,178 (50.0)	98,775 (50.5)	1,912 (36.9)	5,257 (41.4)	26,284 (51.1)	31,313 (52.2)	34,031 (54.3)	38,305 (54.7)	27,150 (52.0)	12,837 (44.9)	10,864 (34.9)
Shortness of breath	**106,387 (28.5)**	49,834 (28.0)	56,553 (28.9)	339 (6.5)	2,070 (16.3)	13,649 (26.5)	16,851 (28.1)	18,978 (30.3)	21,327 (30.4)	16,018 (30.7)	8,971 (31.4)	8,184 (26.3)
Myalgia	**135,026 (36.1)**	61,922 (34.7)	73,104 (37.4)	537 (10.4)	3,737 (29.5)	21,153 (41.1)	26,464 (44.1)	28,064 (44.8)	28,594 (40.8)	17,360 (33.3)	6,015 (21.0)	3,102 (10.0)
Runny nose	**22,710 (6.1)**	9,900 (5.6)	12,810 (6.5)	354 (6.8)	1,025 (8.1)	4,591 (8.9)	4,406 (7.3)	4,141 (6.6)	4,100 (5.9)	2,671 (5.1)	923 (3.2)	499 (1.6)
Sore throat	**74,840 (20.0)**	31,244 (17.5)	43,596 (22.3)	664 (12.8)	3,628 (28.6)	14,493 (28.2)	14,855 (24.8)	14,490 (23.1)	13,930 (19.9)	8,192 (15.7)	2,867 (10.0)	1,721 (5.5)
Headache	**128,560 (34.4)**	54,721 (30.7)	73,839 (37.7)	785 (15.1)	5,315 (41.9)	23,723 (46.1)	26,142 (43.6)	26,245 (41.9)	26,057 (37.2)	14,735 (28.2)	4,163 (14.6)	1,395 (4.5)
Nausea/Vomiting	**42,813 (11.5)**	16,549 (9.3)	26,264 (13.6)	306 (5.8)	1,314 (10.4)	6,648 (12.9)	7,661 (12.8)	8,091 (12.9)	8,737 (12.5)	5,953 (11.4)	2,380 (8.3)	1,523 (4.9)
Abdominal pain	**28,443 (7.6)**	11,553 (6.5)	16,890 (8.6)	349 (6.7)	978 (7.7)	4,211 (8.2)	5,150 (8.6)	5,531 (8.8)	6,134 (8.8)	3,809 (7.3)	1,449 (5.1)	832 (2.7)
Diarrhea	**72,039 (19.3)**	32,993 (18.0)	39,046 (20.4)	704 (13.6)	1,712 (13.5)	9,867 (19.2)	12,769 (21.3)	13,958 (22.3)	15,536 (22.2)	10,349 (19.8)	4,402 (15.4)	2,742 (8.8)
Loss of smell or taste	**31,191 (8.3)**	12,717 (7.1)	18,474 (9.6)	67 (1.3)	1,257 (9.9)	6,828 (13.3)	6,907 (11.5)	6,361 (10.2)	5,828 (8.3)	2,930 (5.6)	775 (2.7)	238 (0.8)

Abbreviation: COVID-19 = coronavirus disease 2019.

* Status of underlying health conditions known for 287,320 persons. Status was classified as "known" if any of the following conditions were reported as present or absent: diabetes mellitus, cardiovascular disease (including hypertension), severe obesity (body mass index ≥40 kg/m^2), chronic renal disease, chronic liver disease, chronic lung disease, immunocompromising condition, autoimmune condition, neurologic condition (including neurodevelopmental, intellectual, physical, visual, or hearing impairment), psychologic/psychiatric condition, and other underlying medical condition not otherwise specified.

† Symptom status was known for 373,883 persons. Status was classified as "known" if any of the following symptoms were reported as present or absent: fever (measured >100.4°F [38°C] or subjective), cough, shortness of breath, wheezing, difficulty breathing, chills, rigors, myalgia, rhinorrhea, sore throat, chest pain, nausea or vomiting, abdominal pain, headache, fatigue, diarrhea (≥3 loose stools in a 24-hour period), or other symptom not otherwise specified on the form.

§ Responses include data from standardized fields supplemented with data from free-text fields. Information for persons with loss of smell or taste was exclusively extracted from a free-text field; therefore, persons exhibiting this symptom were likely underreported.

¶ Includes persons with reported hypertension.

** Includes all persons with at least one of these symptoms reported.

†† Persons were considered to have a fever if information on either measured or subjective fever variables if "yes" was reported for either variable.

TABLE 3. Reported hospitalizations,*,† intensive care unit (ICU) admissions,§ and deaths¶ among laboratory-confirmed COVID-19 patients with and without reported underlying health conditions,** by sex and age — United States, January 22–May 30, 2020

Characteristic (no.)	Outcome, no./total no. (%)†† Reported hospitalizations*,† (including ICU)			Reported ICU admission§			Reported deaths¶		
	Among all patients	Among patients with reported underlying health conditions	Among patients with no reported underlying health conditions	Among all patients	Among patients with reported underlying health conditions	Among patients with no reported underlying health conditions	Among all patients	Among patients with reported underlying health conditions	Among patiences with no reported underlying health conditions
Sex									
Male (646,358)	101,133/646,358 (15.6)	49,503/96,839 (51.1)	3,596/42,048 (8.6)	18,394/646,358 (2.8)	10,302/96,839 (10.6)	864/42,048 (2.1)	38,773/646,358 (6.0)	21,667/96,839 (22.4)	724/42,048 (1.7)
Female (674,130)	83,540/674,130 (12.4)	40,098/102,040 (39.9)	3,087/46,393 (6.7)	11,443/674,130 (1.7)	6,672/102,040 (6.5)	479/46,393 (1.0)	32,343/674,130 (4.8)	17,145/102,040 (16.8)	707/46,393 (1.5)
Age group (yrs)									
≤9 (20,458)	848/20,458 (4.1)	138/619 (22.3)	84/2,277 (3.7)	141/20,458 (0.7)	31/619 (5.0)	16/2,277 (0.7)	13/20,458 (0.1)	4/619 (0.6)	2/2,277 (0.1)
10–19 (49,245)	1,234/49,245 (2.5)	309/2,076 (14.9)	115/5,047 (2.3)	216/49,245 (0.4)	72/2,076 (3.5)	17/5,047 (0.3)	33/49,245 (0.1)	16/2,076 (0.8)	4/5,047 (0.1)
20–29 (182,469)	6,704/182,469 (3.7)	1,559/8,906 (17.5)	498/18,530 (2.7)	864/182,469 (0.5)	300/8,906 (3.4)	56/18,530 (0.3)	273/182,469 (0.1)	122/8,906 (1.4)	24/18,530 (0.1)
30–39 (214,849)	12,570/214,849 (5.9)	3,596/14,854 (24.2)	828/18,629 (4.4)	1,879/214,849 (0.9)	787/14,854 (5.3)	135/18,629 (0.7)	852/214,849 (0.4)	411/14,854 (2.8)	21/18,629 (0.1)
40–49 (219,139)	19,318/219,139 (8.8)	7,151/24,161 (29.6)	1,057/16,411 (6.4)	3,316/219,139 (1.5)	1,540/24,161 (6.4)	208/16,411 (1.3)	2,083/219,139 (1.0)	1,077/24,161 (4.5)	58/16,411 (0.4)
50–59 (235,774)	31,588/235,774 (13.4)	14,659/40,297 (36.3)	1,380/14,420 (9.6)	5,986/235,774 (2.5)	3,335/40,297 (8.3)	296/14,420 (2.1)	5,639/235,774 (2.4)	3,158/40,297 (7.8)	131/14,420 (0.9)
60–69 (179,007)	39,422/179,007 (22.0)	21,064/42,206 (49.9)	1,216/7,919 (15.4)	7,403/179,007 (4.1)	4,588/42,206 (10.9)	291/7,919 (3.7)	11,947/179,007 (6.7)	7,050/42,206 (16.7)	187/7,919 (2.4)
70–79 (105,252)	35,844/105,252 (34.1)	20,457/31,601 (64.7)	780/2,799 (27.9)	5,959/105,252 (5.6)	3,771/31,601 (11.9)	199/2,799 (7.1)	17,510/105,252 (16.6)	10,008/31,601 (31.7)	286/2,799 (10.2)
≥80 (114,295)	37,145/114,295 (32.5)	21,294/34,159 (62.3)	725/2,409 (30.1)	4,093/114,295 (3.6)	2,550/34,159 (7.5)	125/2,409 (5.2)	32,766/114,295 (28.7)	16,966/34,159 (49.7)	718/2,409 (29.8)
Total (1,320,488)	**184,673/1,320,488 (14.0)**	**90,201/198,879 (45.4)**	**6,683/88,441 (7.6)**	**29,837/1,320,488 (2.3)**	**16,974/198,879 (8.5)**	**1,343/88,441 (1.5)**	**71,116/1,320,488 (5.4)**	**38,812/198,879 (19.5)**	**1,431/88,441 (1.6)**

Abbreviation: COVID-19 = coronavirus disease 2019.

* Hospitalization status was known for 600,860 (46%). Among 184,673 hospitalized patients, the presence of underlying health conditions was known for 96,884 (53%).

† Includes reported ICU admissions.

§ ICU admission status was known for 186,563 (14%) patients among the total case population, representing 34% of hospitalized patients. Among 29,837 patients admitted to the ICU, the status of underlying health conditions was known for 18,317 (61%).

¶ Death outcomes were known for 480,565 (36%) patients. Among 71,116 reported deaths through case surveillance, the status of underlying health conditions was known for 40,243 (57%) patients.

** Status of underlying health conditions was known for 287,320 (22%) patients. Status was classified as "known" if any of the following conditions were noted as present or absent: diabetes mellitus, cardiovascular disease including hypertension, severe obesity body mass index ≥40 kg/m^2, chronic renal disease, chronic liver disease, chronic lung disease, any immunocompromising condition, any autoimmune condition, any neurologic condition including neurodevelopmental, intellectual, physical, visual, or hearing impairment, any psychologic/psychiatric condition, and any other underlying medical condition not otherwise specified.

†† Outcomes were calculated as the proportion of persons reported to be hospitalized, admitted to an ICU, or who died among total in the demographic group. Outcome underreporting could result from outcomes that occurred but were not reported through national case surveillance or through clinical progression to severe outcomes that occurred after time of report.

PEDIATRICS

SARS-COV-2 INFECTION IN FEBRILE NEONATES

Wardell H, Campbell JI, VanderPluym C, Dixit A.. J Pediatric Infect Dis Soc. 2020 Jul 9:piaa084. doi: 10.1093/jpids/piaa084. Online ahead of print.

Level of Evidence: 4 - Case-series

BLUF

This case series documents the COVID-19 disease course in 4 febrile hospitalized neonates, all of whom had favorable outcomes. Two neonates required ICU admission for respiratory insufficiency, two neonates had a co-infection (E. Coli., human metapneumovirus), and one neonate was successfully treated with remdesivir. These findings suggest that neonates presenting with fever, a common condition, should be assessed for potential COVID-19 infection during the pandemic.

SUMMARY

All 4 neonatal patients below (all full-term males) were found to have COVID-19, detected via nasopharyngeal swab, in addition to being fully evaluated for neonatal sepsis.

Case 1: 19-day-old neonate with one day fever and fussiness. Chest X-ray initially normal. Two days later, neonate develops respiratory distress and subsequent CXR showed bilateral opacities. Evidence of myocardial injury with high-sensitivity troponins, NT-proBNPs; D-dimer also elevated. Mildly depressed ventricular function (EF = 49%). Neonate was given total of 7 doses of remdesivir (5 mg/kg initially, 2.5 mg/kg daily). Cardiac markers eventually normalized. Patient discharged week 9 with daily low-dose aspirin.

Case 2: 24-day-old neonate with fever, lethargy, and poor oral intake. Neonate received fluid resuscitation, but had persistent tachycardia. Labs found co-infection with human metapneumovirus. Labs also showed elevated BNP, D-dimer, normal troponin. No ventricular dysfunction on echo. Neonate discharged on day 3, but returned due to fever and drowsiness. Chest X-ray revealed bibasilar opacities and perihilar/bronchial thickening. Received 1L of supplemental oxygen and cefepime. Discharged day 2 of second visit.

Case 3: 21-day-old neonate with fever, lethargy, and poor oral intake. Fever was reduced with ceftriaxone. Received fluid resuscitation for poor oral intake. Labs found co-infection with E. Coli. Received 10-day course of cephalexin and discharged home day 3. Over 4 weeks, patient returned 5 times for recurrent fevers. Notably tested positive for COVID-19, 20 days after initial positive test.

Case 4: 21-day-old neonate with fever, congestion, and cough. He received empiric treatment with ceftriaxone, and remained afebrile without respiratory distress. Discharged day 2.

ABSTRACT

Most severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in pediatric patients are mild or asymptomatic. However, infants have emerged at higher risk of hospitalization and severe outcomes in pediatric coronavirus disease 2019 (COVID-19). We report a case series of four full term neonates hospitalized with fever and found to have SARS-CoV-2 infection with a spectrum of illness severities. Two neonates required admission to the intensive care unit for respiratory insufficiency and end organ involvement. Half of the patients were found to have a co-infection. One neonate received antiviral therapy with remdesivir and is, to our knowledge, the youngest patient to receive this drug for COVID-19. All neonates had favorable outcomes.

IMMUNE-RELATED FACTORS ASSOCIATED WITH PNEUMONIA IN 127 CHILDREN WITH CORONAVIRUS DISEASE 2019 IN WUHAN

Li Y, Deng W, Xiong H, Li H, Chen Z, Nie Y, Wang Z, Li K, Li J.. Pediatr Pulmonol. 2020 Jun 16. doi: 10.1002/ppul.24907. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cohort study involving 127 children with COVID-19 found that "decreased levels of globulin, IgA, and CD4+CD25+ T lymphocyte percentage and increased concentration of hs-CRP, procalcitonin, and IL-10 were associated with the presentation of pneumonia in chest radiologic findings" (Figure 1). These findings suggest that "immune-related factors may participate in the pathogenesis of pneumonia in children with COVID-19" and should be the focus of future studies.

ABSTRACT

OBJECTIVE: Information regarding the association of immune-related factors with pneumonia in children with coronavirus disease 2019 (COVID-19) is scarce. This study aims to summarize the immune-related factors and their association with pneumonia in children with COVID-19. METHODS: Children with COVID-19 at Wuhan Children's Hospital from January 28 to March 12, 2020 were enrolled. Pneumonia due to causes other than COVID-19 were excluded. The clinical and laboratory information including routine blood tests, blood biochemistry, lymphocyte subsets, immunoglobulins, cytokines and inflammatory factors were analyzed retrospectively in 127 patients. Normal ranges and mean values of laboratory markers were applied as parameters for logistic regression analyses of their association with pneumonia. RESULTS: In non-intensive care unit patients, 48.8% and 22.4% of patients had increased levels of procalcitonin and hypersensitive C-reactive protein (hs-CRP) respectively. 12.6% and 18.1% of patients had decreased levels of immunoglobulin (Ig) A and interleukin (IL)-10 respectively. Approximately 65.8% of patients had pneumonia. These patients had decreased levels of globulin (odds ratio [OR] 3.13, 95% confidence interval [CI] 1.41-6.93, P=0.005), IgA (OR 4.00, 95% CI 1.13-14.18, P=0.032), and increased levels of hs-CRP (OR 3.14, 95% CI 1.34-7.36, P=0.008), procalcitonin (OR 3.83, 95% CI 2.03-7.24, P<0.001), IL-10 (OR 7.0, 95% CI 1.59-30.80, P=0.010), and CD4+CD25+ T lymphocyte < 5.0 % (OR 1.93, 95% CI 1.04-3.61, P=0.038). CONCLUSION: Decreased IgA and CD4+CD25+ T lymphocyte percentage, and increased hs-CRP, procalcitonin and IL-10 were associated with pneumonia, suggesting that the immune-related factors may participate in the pathogenesis of pneumonia in children with COVID-19. This article is protected by copyright. All rights reserved.

FIGURES

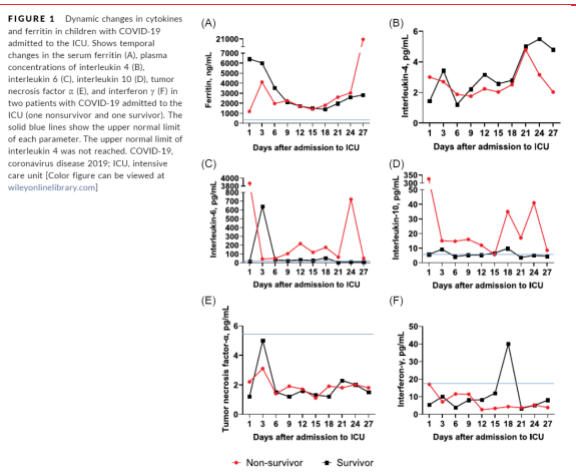


FIGURE 1 Dynamic changes in cytokines and ferritin in children with COVID-19 admitted to the ICU. Shows temporal changes in the serum ferritin (A), plasma concentrations of interleukin 4 (B), interleukin 6 (C), interleukin 10 (D), tumor necrosis factor α (E), and interferon γ (F) in two patients with COVID-19 admitted to the ICU (one nonsurvivor and one survivor). The solid blue lines show the upper normal limit of each parameter. The upper normal limit of interleukin 4 was not reached. COVID-19, coronavirus disease 2019; ICU, intensive care unit [Color figure can be viewed at wileyonlinelibrary.com]

PATHOPHYSIOLOGY OF SARS-COV-2 INFECTION IN PATIENTS WITH INTRACEREBRAL HEMORRHAGE

Dong S, Liu P, Luo Y, Cui Y, Song L, Chen Y.. Aging (Albany NY). 2020 Jul 7;12. doi: 10.18632/aging.103511. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A literature review by researchers associated with several universities in China describe the pathophysiology of SARS-CoV-2 infection in patients with intracerebral hemorrhage (ICH). The review specifically discusses virus entry into the brain through ACE2 receptors, subsequent disruption of two pathways in the brain involved in maintaining cerebral homeostasis (i.e. ACE2–Ang (1–7)–MasR axis and ACE–Ang II–AT1R axis), destruction of the blood brain barrier allowing infiltration of immune cells into the brain, and oxidative tissue damage due to the immune response. This review highlights the increased risk of poor outcomes in ICH patients with COVID-19 and the need for early diagnosis, isolation, and treatment.

ABSTRACT

Intracerebral hemorrhage (ICH) is associated with old age and underlying conditions such as hypertension and diabetes. ICH patients are vulnerable to SARS-CoV-2 infection and develop serious complications as a result of infection. The pathophysiology of ICH patients with SARS-CoV-2 infection includes viral invasion, dysfunction of the ACE2-Ang (1-7)-MasR and ACE-Ang II-AT1R axes, overactive immune response, cytokine storm, and excessive oxidative stress. These patients have high morbidity and mortality due to hyaline membrane formation, respiratory failure, neurologic deficits, and multiple organ failure.

IN VITRO

SARS, MERS, COVID-19: CLINICAL MANIFESTATIONS AND ORGAN-SYSTEM COMPLICATIONS: A MINI REVIEW

Harb JG, Noureldine HA, Chedid G, Eldine MN, Abdallah DA, Chedid NF, Nour-Eldine W.. Pathog Dis. 2020 Jul 7:ftaa033. doi: 10.1093/femspd/ftaa033. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review study conducted in Lebanon by Gilbert and Rose-Marie Chagoury School of Medicine compared and contrasted MERS, SARS, and SARS-CoV-2 in their capacity to cause pneumonia, renal and cardiac injury, endothelial dysfunction, sepsis, hypercoaguability, and cytokine storm. This study suggests that the distinctions between these coronaviruses must be understood and the heightened immune response induced by COVID-19 must be targeted in therapy. Highlighted findings for various sequelae can be found in the summary below and the mechanism of the injuries induced by cytokine storm is demonstrated in Figure 1.

SUMMARY

- One study outlined that acute respiratory distress syndrome (ARDS) is seen in 30% of SARS, 40% of MERS, and 30% of COVID-19 patients who have been hospitalized.
- 70-90% of MERS patients developed pneumonia while 25.9% of COVID-19 patients with pneumonia required ICU admission
- A Saudi cohort study demonstrated up to 15.7% of MERS patients developed cardiac complications while up to 22.5 % of COVID-19 patients developed cardiac complications in a study in Jiangsu
- Acute kidney injury (AKI) was seen in 58% of critically ill MERS patient while 50% of non-surviving COVID-19 patients suffered an AKI
- Hepatic injury was noted in 31.4 % of MERS patient but only 3.75% of COVID-19 patients
- Sepsis was noted in 70-100% of COVID-19 fatalities
- Gastrointestinal complications such as diarrhea and nausea were noted in 20.3% of SARS patients, 30% of MERS patients, and 10% of COVID-19 patients

ABSTRACT

Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) and Coronavirus Disease 2019 (COVID-19) are caused by three distinct coronaviruses belonging to the same genus. COVID-19 and its two predecessors share many important features in their clinical presentations, and in their propensity for progression to severe disease which is marked by high rates of morbidity and mortality. However, comparison of the three viral illnesses also reveals a number of

specific differences in clinical manifestations and complications, which suggest variability in the disease process. This narrative review delineates the pulmonary, cardiac, renal, gastrointestinal, hepatic, neurological, and hematologic complications associated with these three respiratory coronaviruses. It further describes the mechanisms of immune hyperactivation-particularly cytokine release syndrome-implicated in the multi-organ system injury seen in severe cases of MERS, SARS, and COVID-19.

FIGURES

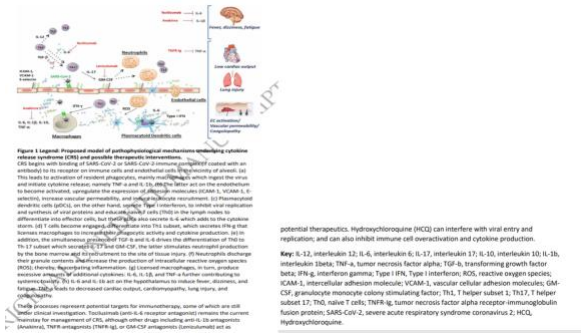


Figure 1 Legend: Proposed model of pathophysiological mechanisms underlying cytokine release syndrome (CRS) and possible therapeutic interventions.

CRS begins with binding of SARS-CoV-2 or SARS-CoV-2-immune complex (virus coated with an antibody) to its receptor on immune cells and endothelial cells in the vicinity of alveoli. (a) This leads to activation of resident phagocytes, mainly macrophages which ingest the virus and initiate cytokine release, namely TNF-α and IL-1b. (b) The latter act on the endothelium to become activated, upregulate the expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin), increase vascular permeability, and cause leukocyte recruitment. (c) Plasmacytoid dendritic cells (pDCs), on the other hand, secrete Type I interferon, to inhibit viral replication and synthesis of viral proteins and educate naïve T cells (Th0) in the lymph nodes to differentiate into effector cells, but these cells also secrete IL-6 which adds to the cytokine storm. (d) T cells become engaged and differentiate into Th1 subset, which secretes IFN-g that licenses macrophages to increase phagocytic activity and cytokine production. (e) In addition, the simultaneously produced TGF-b and IL-6 drives the differentiation of Th0 to Th-17 subset which secretes IL-17 and GM-CSF, the latter stimulates neutrophil production by the bone marrow and its recruitment to the site of tissue injury. (f) Neutrophils discharge their granule contents and increase the production of intracellular reactive oxygen species (ROS), thereby, aggravating inflammation. (g) Licensed macrophages, in turn, produce excessive amounts of additional cytokines: IL-6, IL-1β, and TNF-α further contributing to systemic toxicity. (h) IL-6 and IL-1b act on the hypothalamus to induce fever, dizziness, and fatigue. This leads to decreased cardiac output, cardiomyopathy, lung injury, and coagulopathy.

These processes represent potential targets for immunotherapy, some of which are still under clinical investigation. Tocilizumab (anti-IL-6 receptor antagonist) remains the current mainstay for management of CRS, although other drugs including anti-IL-1b antagonists (Anakinra), TNFR-antagonists (TNFR-Ig), or GM-CSF antagonists (Lenzilumab) act as potential therapeutics. Hydroxychloroquine (HCQ) can interfere with viral entry and replication; and can also inhibit immune cell overactivation and cytokine production.

Key: IL-12, interleukin 12; IL-6, interleukin 6; IL-17, interleukin 17; IL-10, interleukin 10; IL-1b, interleukin 1beta; TNF-a, tumor necrosis factor alpha; TGF-b, transforming growth factor beta; IFN-g, interferon gamma; Type I IFN, Type I interferon; ROS, reactive oxygen species; ICAM-1, intercellular adhesion molecule; VCAM-1, vascular cellular adhesion molecules; GM-CSF, granulocyte monocyte colony stimulating factor; Th1, T helper subset 1; Th17, T helper subset 17; Th0, naïve T cells; TNFR-Ig, tumor necrosis factor alpha receptor-immunoglobulin fusion protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HCQ, Hydroxychloroquine.

BCG VACCINE PROTECTION FROM SEVERE CORONAVIRUS DISEASE 2019 (COVID-19)

Escobar LE, Molina-Cruz A, Barillas-Mury C.. Proc Natl Acad Sci U S A. 2020 Jul 9:202008410. doi: 10.1073/pnas.2008410117. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

An analysis conducted on COVID-19 mortality and bacillus Calmette–Guérin (BCG) vaccine data collected until 22 April 2020 found a global negative association between BCG vaccination policy and COVID-19 mortality (Figure 1). When potential confounding variables such as Human Development Index (life expectancy, education level, and per capita income), ≥15% of population over 65 years of age, and urbanization were mitigated, the overall significance was reduced but countries with stronger BCG vaccination policies still had a lower COVID-19 mortality rate (Figure 2). These results suggest the BCG vaccine may confer protection from COVID-19 by enhancing the innate immune system, however, further randomized trials and data are needed.

ABSTRACT

A series of epidemiological explorations has suggested a negative association between national bacillus Calmette-Guerin (BCG) vaccination policy and the prevalence and mortality of coronavirus disease 2019 (COVID-19). However, these comparisons are difficult to validate due to broad differences between countries such as socioeconomic status, demographic structure, rural vs. urban settings, time of arrival of the pandemic, number of diagnostic tests and criteria for testing, and national control strategies to limit the spread of COVID-19. We review evidence for a potential biological basis of BCG cross-protection from severe COVID-19, and refine the epidemiological analysis to mitigate effects of potentially confounding factors (e.g., stage of the COVID-19 epidemic, development, rurality, population density, and age structure). A strong correlation between the BCG index, an estimation of the degree of universal BCG vaccination deployment in a country, and COVID-19 mortality in different socially similar European countries was observed ($r^2 = 0.88$; $P = 8 \times 10^{-7}$), indicating that every 10% increase in the BCG index was associated with a 10.4% reduction in COVID-19 mortality. Results fail to confirm the null hypothesis of no association between BCG vaccination and COVID-19 mortality, and suggest that BCG could have a protective effect. Nevertheless, the analyses are restricted to coarse-scale signals and should be considered with caution. BCG vaccination clinical trials are required to corroborate the patterns detected here, and to establish causality between BCG vaccination and protection from severe COVID-19. Public health implications of a plausible BCG cross-protection from severe COVID-19 are discussed.

FIGURES

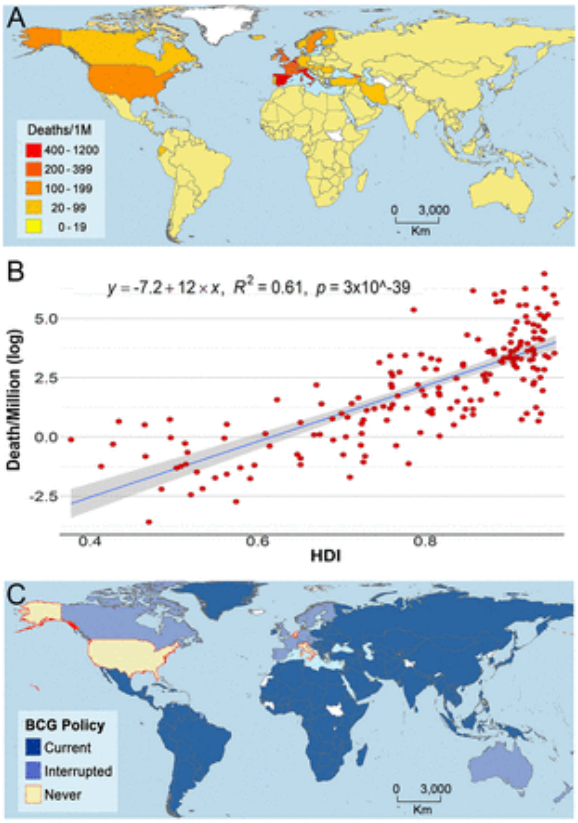


Figure 1: COVID-19 mortality, human development, and BCG vaccination policy by country. (A) Map showing the COVID-19 mortality per million inhabitants in countries worldwide. COVID-19–related deaths per country per million inhabitants denoting countries with low (yellow) to high (red) mortality. (B) COVID-19 mortality per million inhabitants (log) vs. HDI in different countries worldwide. United States data appear by state. (C) Map showing the BCG vaccination policy in countries that currently have universal BCG vaccination program (Current), countries with interrupted BCG vaccination programs (Interrupted), and countries that never implemented a universal vaccination program (Never). Countries without information appear in white.

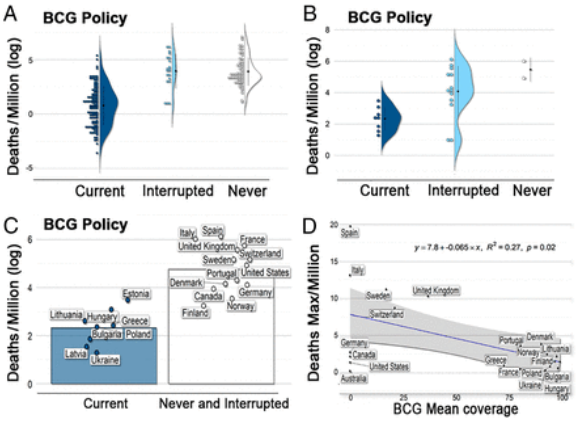


Figure 2: Linkage between COVID-19 mortality and BCG vaccination. (A) Coarse analysis of COVID-19 mortality per million inhabitants in countries with current, interrupted, or that never had BCG vaccination programs. United States data appear by state. (B) Filtered analysis of COVID-19 mortality per million inhabitants in countries with current, interrupted, or that never had BCG vaccination programs and similar social, economic, and epidemic stage conditions. (C) Filtered analysis of COVID-19 mortality per million inhabitants in countries with current vs. interrupted or that never had BCG vaccination programs, including only countries with similar social, economic, and epidemic stage conditions. (D) Negative association between percentage of vaccination coverage (mean) between 1980 and 2018, as a proxy of population protection, and maximum COVID-19 deaths per million inhabitants registered by country in a day, as a proxy of COVID-19 severity. Full list of analyses is available in SI Appendix, Tables S2–S4.

EFFECTIVENESS OF CLOTH MASKS FOR PROTECTION AGAINST SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Chughtai AA, Seale H, Macintyre CR.. Emerg Infect Dis. 2020 Jul 8;26(10). doi: 10.3201/eid2610.200948. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

An online report by authors at the University of New South Wales discusses how cloth masks may be used by community members to prevent spread of SARS-CoV-2 but should not be used by healthcare workers, due to the lower filtration effectiveness, until cloth masks are proven to be equally effective as medical or N95 masks. This suggests that cloth masks should not be mandated for healthcare workers but are adequate for protective use among community members to limit spread of SARS-CoV-2, and the authors emphasize the need for further research on the effectiveness and engineering design of cloth masks.

ABSTRACT

Cloth masks have been used in healthcare and community settings to protect the wearer from respiratory infections. The use of cloth masks during the coronavirus disease (COVID-19) pandemic is under debate. The filtration effectiveness of cloth masks is generally lower than that of medical masks and respirators; however, cloth masks may provide some protection if well designed and used correctly. Multilayer cloth masks, designed to fit around the face and made of water-resistant fabric with a high number of threads and finer weave, may provide reasonable protection. Until a cloth mask design is proven to be equally effective as a medical or N95 mask, wearing cloth masks should not be mandated for healthcare workers. In community settings, however, cloth masks may be used to prevent community spread of infections by sick or asymptomatically infected persons, and the public should be educated about their correct use.

PREVENTION IN THE COMMUNITY

ASSOCIATION OF A PUBLIC HEALTH CAMPAIGN ABOUT CORONAVIRUS DISEASE 2019 PROMOTED BY NEWS MEDIA AND A SOCIAL INFLUENCER WITH SELF-REPORTED PERSONAL HYGIENE AND PHYSICAL DISTANCING IN THE NETHERLANDS

Yousuf H, Corbin J, Sweep G, Hofstra M, Scherder E, van Gorp E, Zwetsloot PP, Zhao J, van Rossum B, Jiang T, Lindemans JW, Narula J, Hofstra L.. JAMA Netw Open. 2020 Jul 1;3(7):e2014323. doi: 10.1001/jamanetworkopen.2020.14323.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

This study conducted in the Netherlands consisted of an initial survey of 16,072 participants through social media with questions about handwashing, face touching, and physical distancing, followed by a multimedia campaign launched on March 21, 2020 with virologist and social media influencer Govert Sweep (Figure 1) and a popular national newspaper, “De Telegraaf.” A post-campaign survey was administered on March 24, 2020, repeating the same questions as the first survey and collecting data on whether the participants saw the different aspects of the media campaign. The results of both surveys (Table 2) revealed that participants who saw both components of the campaign reported an improvement in personal hygiene and physical distancing during the COVID-19 crisis, suggesting a potential value for the use of similar multimedia campaigns to improve these behaviors.

ABSTRACT

Importance: In the absence of a vaccine and therapeutic agent, personal hygiene and physical distancing are essential measures to contain the coronavirus disease 2019 pandemic. Objective: To determine whether a social media campaign, targeted at the gaps in behavior on personal hygiene and physical distancing and distributed nationwide via digital news media, may be an effective method to improve behavior and help to inhibit person-to-person transmission of severe acute respiratory syndrome coronavirus 2. Design, Setting, and Participants: This survey study was designed to uncover self-reported gaps in behavior regarding personal hygiene and physical distancing in the Netherlands. A diagnostic survey was distributed by a large national newspaper (De Telegraaf) and a popular social influencer (Govert Sweep) on March 17, 2020, and was completed by 16 072 participants. Analysis of these outcomes showed that coughing and sneezing in the elbow was

done well, but that handwashing, face touching, and physical distancing showed serious gaps compared with advised behavior. This diagnostic information was used to design infographics and a video targeted at repairing these gaps in behavior. The video and infographics were distributed on a national level on March 21, 2020, followed by a postcampaign survey to measure the results on March 24, 2020. Data analysis was performed from March to April 2020. Exposure: Exposed participants were those who viewed the infographics and/or video. Main Outcomes and Measures: Improvement on the extent of handwashing in all areas, handwashing duration of 20 seconds or longer, awareness on face touching, and physical distancing were measured according to responses on the postcampaign survey. Results: A total of 17 189 participants (mean [SD] age, 47.61 [13.57] years; 9100 women [52.9%]) responded to the postcampaign survey. The news article in De Telegraaf was read more than 2 million times, and the influencer video was watched more than 80 000 times. Cross-sectional analysis of the postcampaign survey using logistic regression correcting for age, gender, and educational level showed that exposure to the video plus infographics (827 participants) (adjusted odds ratio [OR], 2.14; 95% CI, 1.83-2.50; P < .001) and to the infographics alone (11 348 participants) (adjusted OR, 1.31; 95% CI, 1.22-1.40; P < .001) were positively associated with washing hands in all areas compared with the unexposed group (4751 participants). In addition, exposure to the video plus infographics (adjusted OR, 1.86; 95% CI, 1.59-2.16; P < .001) and to the infographics alone (adjusted OR, 1.27; 95% CI, 1.19-1.36; P < .001) were positively associated with washing hands long enough compared with the unexposed group. Exposure to the video alone was not associated with improved handwashing. Compared with the unexposed group, exposure to the infographics alone and video plus infographics were associated with improvements in physical distancing when the participant had COVID-19 syptoms (infographics alone, adjusted OR, 1.10; 95% CI, 1.03-1.17; P = .006; video plus infographics, adjusted OR, 0.79; 95% CI, 0.69-0.91; P = .001) and face touching (infographics alone, adjusted OR, 1.29; 95% CI, 1.22-1.38; P < .001; infographics and video, adjusted OR, 1.49, 95% CI, 1.30-1.71; P < .001). Conclusions and Relevance: These findings suggest that a targeted behavioral change campaign, promoted by a news platform and social media, was associated with self-reported improvement in personal hygiene with the aim to prevent person-to-person transmission of severe acute respiratory syndrome coronavirus 2. This method of evidence-based campaigning may be an effective way to improve critical public health issues, such as the coronavirus disease 2019 pandemic.

FIGURES

Figure 1. Screenshots From Evidence-Based Campaign Video and News Article With Infographics. A - Govert Sweep designed a video containing a thorough instruction of how to wash hands properly, and he interviewed a well-known virologist on the importance of physical distancing and avoiding face touching. B - On the basis of the results of our diagnostic survey, the newspaper De Telegraaf created a news article with infographics showing gaps in behavior. The news article included a link to our evidence-based campaign video with the social influencer Govert Sweep.

Table 2. Overview of Results for All Outcomes

	Diagnostic survey group vs postcampaign survey unexposed group				Postcampaign survey exposed groups			
	Score, mean (SD) [95% CI]				Score, mean (SD) [95% CI]			
Outcome	Diagnostic survey (n = 16 072)	Unexposed postcampaign (n = 4751)	Difference between groups	P value	Infographic only (n = 11 348)	Video only (n = 263)	Infographic and video (n = 827)	P value
Handwashing, mean (95% CI), % of respondents								
All required areas	29 (28-29)	40 (38-41)	11	<.001	48 (47-49)	40 (34-46)	62 (58-65)	<.001
Duration ≥20 s	33 (33-33)	45 (43-46)	12	<.001	52 (51-53)	49 (43-55)	60 (57-62)	<.001
Try not to touch face[a]	3.10 (1.04) [3.08-3.12]	3.16 (1.05) [3.13-3.19]	0.06	<.001	3.33 (0.94) [3.17-3.35]	3.10 (1.01) [2.98-3.22]	3.42 (0.91) [3.36-3.48]	<.001
Spent time with people outside one's household[b]								
With 1-5 people outside household	2.19 (1.29) [2.17-2.21]	1.85 (1.18) [1.81-1.88]	−0.34	<.001	1.72 (1.09) [1.70-1.74]	1.86 (1.21) [1.72-2.01]	1.67 (1.09) [1.59-1.74]	<.001
With ≥5 people outside household	1.46 (1.02) [1.45-1.48]	1.24 (0.80) [1.22-1.27]	−0.22	<.001	1.17 (0.66) [1.16-1.19]	1.21 (0.64) [1.13-1.29]	1.23 (0.78) [1.18-1.29]	<.001
Was at public place with ≥20 people present	1.73 (0.96) [1.71-1.75]	1.52 (0.84) [1.49-1.54]	−0.21	<.001	1.44 (0.77) [1.43-1.46]	1.45 (0.76) [1.36-1.54]	1.41 (0.80) [1.36-1.47]	<.001
Physical distance[c]								
When household member had symptoms	3.48 (1.43) [3.46-3.50]	3.63 (1.46) [3.59-3.67]	0.15	<.001	3.79 (1.41) [3.76-3.81]	3.58 (1.42) [3.41-3.75]	3.80 (1.41) [3.7-3.89]	<.001
When the respondent had symptoms	3.87 (1.32) [3.85-3.90]	4.01 (1.34) [3.97-4.05]	0.13	<.001	4.10 (1.31) [4.07-4.12]	3.57 (1.49) [3.39-3.7]	3.86 (1.46) [3.76-3.96]	<.001

[a] Face touching was scored as 1 (never), 2 (rarely), 3 (sometimes), 4 (often), and 5 (always).

[b] Spending time with people outside of one's own household was scored as 1 (never), 2 (1 time), 3 (2-3 times), 4 (4-5 times), and 5 (> 5 times).

[c] Physical distancing when symptoms were present was scored as 1 (never), 2 (rarely), 3 (sometimes), 4 (often), and 5 (always).

Table 2. Overview of Results for All Outcomes.

CASE 23-2020: A 76-YEAR-OLD WOMAN WHO DIED FROM COVID-19

Stone JR, Tran KM, Conklin J, Mino-Kenudson M.. N Engl J Med. 2020 Jul 8. doi: 10.1056/NEJMcpc2004974. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

Physicians at Massachusetts General Hospital, Boston, present the case of a 76-yo woman who died from COVID-19 6 days after admission to the hospital. The patient was not resuscitated or intubated according to the patient's wishes. After a discussion with the family, an autopsy was performed (Figures 2 and 3). The authors highlight the critical role of autopsies in revealing the pathological mechanisms of COVID-19 and provide recommendations on how to approach patients and families to offer autopsies.

SUMMARY

Case Presentation:

- The patient, who had history of asthma, diabetes, and hypertension, presented with delirium and incontinence to the emergency department. She had a temperature of 38.8°C and a 94% oxygen saturation on supplemental oxygen. Lab results and computed tomographic pulmonary angiography of the chest are shown in Table 1 and Figure 1. Acetaminophen and empirical ceftriaxone, azithromycin, and hydroxychloroquine were administered. On the second hospital day, the patient experienced intermittent episodes of fever while the delirium and hypoxemia worsened. On the fourth hospital day, the patient appeared to be in distress with increased work of breathing. The patient died 36 hours after the status was changed from "do not resuscitate and do not intubate" to "comfort measures only".

The authors propose the following recommendations for discussing autopsy with family:

- Clinicians may have a conversation about autopsy with the family either before or after the patient's death; it may also be appropriate to have this conversation with the patient.
- They should approach the family or the patient without any assumptions regarding the family or patient's emotional state. Cultural and religious values should be taken into consideration.
- It may be more appropriate to use terms such as "offer," instead of "request," "permission," or "consent" during a discussion about the autopsy.
- Clinicians should explain the procedure of the autopsy to the families and take into account the family's preference regarding the fate of retained organs.
- They should also communicate with the family that the findings of the autopsy will be shared and discussed with them upon the completion of the procedure.

FIGURES

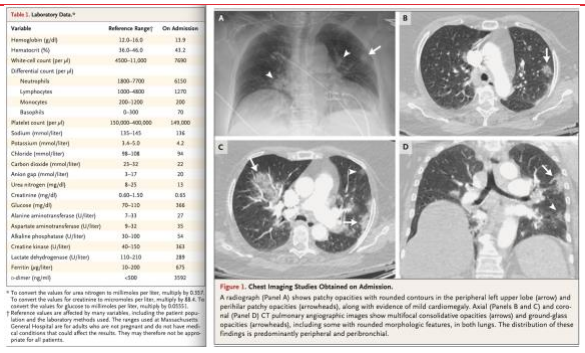


Table 1. Laboratory Data.*

Variable	Reference Range†	On Admission
Hemoglobin (g/dl)	12.0–16.0	13.9
Hematocrit (%)	36.0–46.0	43.2
White-cell count (per µl)	4500–11,000	7690
Differential count (per µl)		
Neutrophils	1800–7700	6150
Lymphocytes	1000–4800	1270
Monocytes	200–1200	200
Basophils	0–300	70
Platelet count (per µl)	150,000–400,000	149,000
Sodium (mmol/liter)	135–145	136
Potassium (mmol/liter)	3.4–5.0	4.2
Chloride (mmol/liter)	98–108	94
Carbon dioxide (mmol/liter)	23–32	22
Anion gap (mmol/liter)	3–17	20
Urea nitrogen (mg/dl)	8–25	13
Creatinine (mg/dl)	0.60–1.50	0.65
Glucose (mg/dl)	70–110	366
Alanine aminotransferase (U/liter)	7–33	27
Aspartate aminotransferase (U/liter)	9–32	35
Alkaline phosphatase (U/liter)	30–100	54
Creatine kinase (U/liter)	40–150	363
Lactate dehydrogenase (U/liter)	110–210	389
Ferritin (µg/liter)	10–200	675
D-dimer (ng/ml)	<500	3592

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.0555.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

Figure 1. Chest Imaging Studies Obtained on Admission.
A radiograph (Panel A) shows patchy opacities with rounded contours in the peripheral left upper lobe (arrow) and perihilar patchy opacities (arrowheads), along with evidence of mild cardiomegaly. Axial (Panels B and C) and coronal (Panel D) CT pulmonary angiographic images show multifocal consolidative opacities (arrows) and ground-glass opacities (arrowheads), including some with rounded morphologic features, in both lungs. The distribution of these findings is predominantly peripheral and peribronchial.

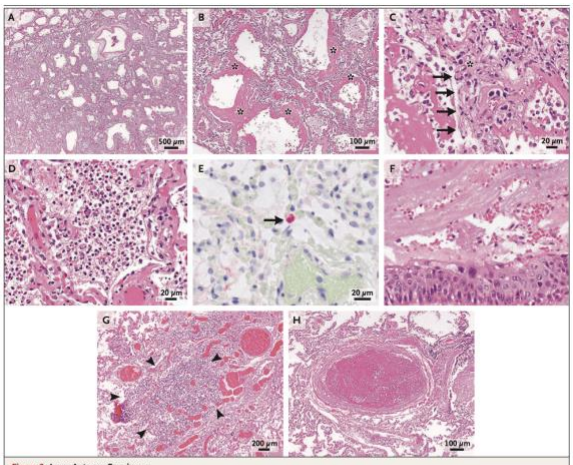


Figure 2. Lung Autopsy Specimens.

On hematoxylin and eosin staining, both lungs show architecturally preserved alveolar parenchyma (Panel A) with thick hyaline membranes (Panel B, asterisks) associated with pneumocyte denudation (Panel C, arrows). In some areas, alveolar walls show increased cellularity with some spindled fibroblast-like cells (Panel C, asterisk). These findings are consistent with an exudative to early proliferative phase of diffuse alveolar damage. There are also rare foci with neutrophilic and histiocytic infiltrates in alveolar spaces (Panel D), features suggestive of a focal pneumonic process. Immunohistochemical staining for SARS nucleocapsid protein highlights scattered pneumocytes (Panel E, arrow) and alveolar macrophages, findings supportive of a diagnosis of SARS-CoV-2 infection in the lungs. Thick mucin and epithelial denudation are seen in the majority of bronchi, and squamous metaplasia with reactive changes is focally replacing the denuded lining (Panel F). Only a few scattered perivascular chronic inflammatory aggregates (Panel G, arrowheads) and rare fibrin thrombi in small pulmonary arteries (Panel H) are present in this case.

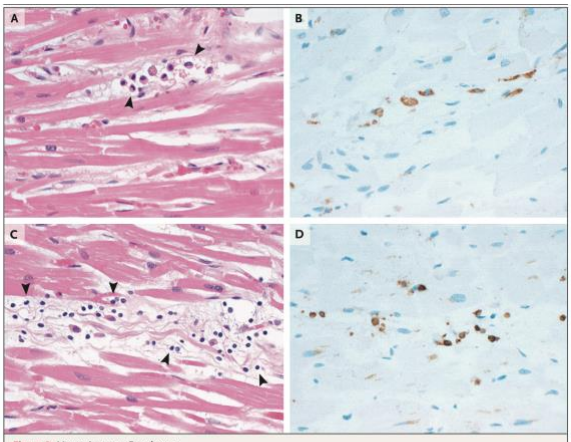


Figure 3. Heart Autopsy Specimens.

On hematoxylin and eosin staining, there is increased infiltration of the myocardium by macrophages (Panel A, arrowheads); on immunohistochemical staining, the macrophages express the marker CD68 (Panel B, in brown). There is also focal infiltration of the myocardium by lymphocytes (Panel C, arrowheads), which express the marker CD3 (Panel D, in brown). These findings are not associated with myocyte injury.

CRITICAL CARE

VENOUS THROMBOEMBOLISM IN COVID-19: SYSTEMATIC REVIEW OF REPORTED RISKS AND CURRENT GUIDELINES

Fontana P, Casini A, Robert-Ebadi H, Glauser F, Righini M, Blondon M.. Swiss Med Wkly. 2020 Jun 21;150:w20301. doi: 10.4414/smw.2020.20301. eCollection 2020 Jun 15.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A systematic review conducted at Geneva University Hospital in Geneva, Switzerland of 11 studies consisting of 1369 patients (Figure 1) found that VTE is a more common complication of COVID-19 in inpatients (Figure 2) than in outpatients with COVID-19. Additionally, guidelines continue to recommend VTE prophylaxis in all inpatient COVID-19 patients regardless of symptoms. Finally, the dosing of VTE prophylaxis varies between guidelines, suggesting more research needs to be done to adequately provide prophylaxis for VTE in COVID-19 positive inpatients.

ABSTRACT

AIMS OF THE STUDY: Many centres have noticed a high number of venous thromboembolism (VTE) events among critically ill inpatients with COVID-19 pneumonia. The aims of this study were (1) to summarise the reported risk of VTE associated with COVID-19 infections and (2) to summarise guidance documents on thromboprophylaxis in COVID-19 patients, in a systematic review. METHODS: We systematically searched for peer-reviewed evidence on the risk of VTE in patients with COVID-19, in PubMed, Embase and Twitter, and for guidelines or guidance documents for thromboprophylaxis, from international or national societies relevant to the field of thrombosis and haemostasis, up to April 30 2020. RESULTS: We found 11 studies (1 clinical trial, 7 retrospective cohorts and 3 prospective cohorts), which included a range of 16 to 388 in patients with COVID-19 (total of 1369 inpatients). The diagnoses of COVID-19 and VTE were of high quality, but the follow-up was often unclear. Most studies reported universal in-hospital thromboprophylaxis. Among all inpatients and among intensive care unit (ICU) inpatients with COVID-19, reported risks of VTE were 4.4–8.2% (three studies) and 0–35.3% (six studies), respectively. Two studies at least partially screened for VTE in ICU inpatients with COVID-19, and found risks of 24.7–53.8%. We found 12 guidelines for thromboprophylaxis of COVID-19 patients. The majority suggested universal pharmacological thromboprophylaxis in all COVID-19 inpatients, but there was heterogeneity in the suggested intensity of thromboprophylaxis: seven advised considering intensified doses of heparin according to the clinical or biological severity of the disease, especially in the ICU setting. CONCLUSIONS: Venous thromboembolism very commonly complicates the clinical course of inpatients with COVID-19, despite thromboprophylaxis. The risk appears highest among critically ill inpatients. We found no estimates of risks among outpatients. Many questions remain unresolved, as delineated by the heterogeneity of national and international guidelines. This situation calls for fast randomised clinical trials, comparing different schemes of thromboprophylaxis in COVID-19 inpatients.

FIGURES

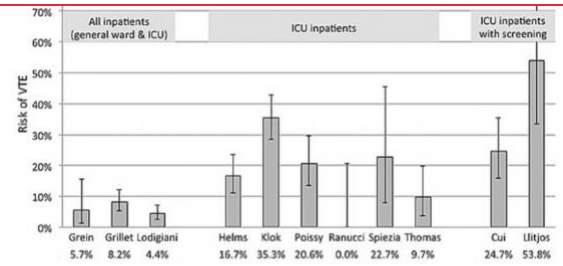


Figure 2

Risks of venous thromboembolism (VTE) in individual studies, obtained from simple proportions (n VTE / n at risk). Error bars represent 95% confidence intervals. ICU = intensive care unit

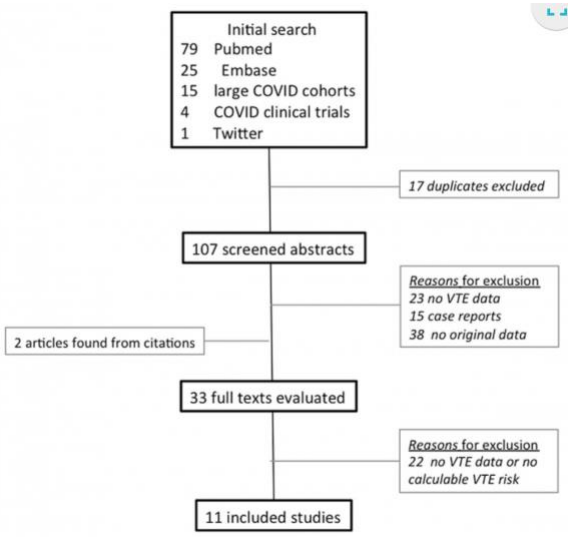


Figure 1: Flow-chart of inclusion and exclusion criteria for peer-reviewed studies included in this systematic review.

BILATERAL PARESTHESIA ASSOCIATED WITH CARDIOVASCULAR DISEASE AND COVID-19

Moreira MS, Neves ILI, de Bernoche CYSM, Sarra G, Santos-Paul MAD, Campos Neves da Silva F, Schroter GT, Montano TCP, de Carvalho CMA, Simões Neves R.. Oral Dis. 2020 Jul 8. doi: 10.1111/odi.13539. Online ahead of print.

Level of Evidence: Other - Case Report

BLUF

A case report by authors within the fields of dentistry and cardiovascular medicine describe a 19-year-old female with acutely decompensated chronic heart failure, oral dental carries, and COVID-19 infection. The patient developed bilateral paresthesia of the inferior alveolar nerve 4 days after oral intervention and eventually succumbed to refractory septic shock (details summarized below). The authors emphasize the role of dentistry in this COVID-19 case and propose that neurological symptoms, such as bilateral paresthesia of the inferior alveolar nerve, could have prognostic value for COVID-19 in cardiac patients.

SUMMARY

A19-year-old female with a prior history of dilated cardiomyopathy and heart failure presented to the Emergency Department at Heart Institute of the Hospiral das Clinicas from Mmedical School of the Universidade de Sao Paolo with fever, dyspnea on exertion, nausea, and vomiting on February 19, 2020. The patient was initially diagnosed with acutely decompensated chronic heart failure secondary to pneumonia and admitted to the intensive care unit. However, onset of bacteremia (post-admission day 10) lead to the finding of deep dental caries that required oral cavity extraction. Four days after her dental procedure, the patient developed bilateral paresthesia of the inferior alveolar nerve and severe respiratory symptoms. CT imaging revealed pulmonary consolidation and pulmonary embolism and ensuing COVID-19 testing via RT-PCR was positive. Despite treatment, the patient eventually died from refractory septic shock.

HETEROGENEITY IN REPORTING VENOUS THROMBOEMBOLIC PHENOTYPES IN COVID-19: METHODOLOGICAL ISSUES AND CLINICAL IMPLICATIONS

Kollias A, Kyriakoulis KG, Stergiou GS, Syrigos K.. Br J Haematol. 2020 Jul 4. doi: 10.1111/bjh.16993. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Greek researchers present a literature review of 11 studies which found significant heterogeneity in the reported venous thromboembolic (VTE) phenotypes of hospitalized COVID-19 patients. Authors suggest the heterogeneity could be due to specific risk factors, including patient age, sex, VTE history, and SARS-CoV-2 specific factors (ie., coagulopathy, endothelial injury/microthrombosis). Due to this variation and unpredictability as well as evidence suggesting VTE is associated with more severe disease (see below), they recommend increased d-dimer screening for VTE and thromboprophylaxis in all hospitalized patients.

SUMMARY

Prior studies have shown increased rates of VTE prevalence that vary in thromboembolic phenotypes in COVID-19 patients in the intensive care unit (47%) in comparison to the general ward patients (3%). As a result, the authors urge early identification of VTE in COVID-19 patient and increased VTE screening (ie., clinical findings or biochemical values) or diagnostic methodologies (ie., ultrasound or computed tomography). Patients with severe COVID-19 have been shown to have 7-fold higher d-dimer levels compared to cohorts with less severe disease indicating that this biochemical value can help predict increased VTE development. The authors recommend hospitalized patients with high d-dimer levels be screened for VTE and administered thromboprophylaxis.

ABSTRACT

COVID-19 is associated with increased risk of venous thromboembolic events (VTE). However, there is significant heterogeneity in the thromboembolic phenotypes of COVID-19 patients (deep vein thrombosis, pulmonary embolism/thrombosis). The latter might be partly attributed to the variation in VTE risk factors in COVID-19 patients including: (i) patients' characteristics; (ii) hospitalization conditions and interventions; (iii) SARS-Cov-2 specific factors (coagulopathy, endothelial injury/microthrombosis). Furthermore, there is methodological heterogeneity in relation to the assessment of VTE (indications for screening, diagnostic methodology, etc). Physicians should be aware of the increased VTE risk, strongly consider VTE screening, and use thromboprophylaxis in all hospitalized patients.

MEDICAL SUBSPECIALTIES

COULD ANTI-HYPERTENSIVE DRUG THERAPY AFFECT THE CLINICAL PROGNOSIS OF HYPERTENSIVE PATIENTS WITH COVID-19 INFECTION? DATA FROM CENTERS OF SOUTHERN ITALY

Sardu C, Maggi P, Messina V, Iuliano P, Sardu A, Iovinella V, Paolisso G, Marfella R.. J Am Heart Assoc. 2020 Jul 7:e016948. doi: 10.1161/JAHA.120.016948. Online ahead of print.
Level of Evidence: 3 - 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.)

BLUF

A prospective multicenter study conducted in Naples, Italy enrolled 62 consecutive hypertensive patients hospitalized for COVID-19 (diagnosed via real-time reverse transcription polymerase chain reaction) and found that antihypertensive drugs did not correlate with worse prognosis in COVID-19 patients, although the lowest values of left ventricle ejection fraction (LVEF; an index of systolic heart function in hypertensive disease) predicted deaths (Table 1). Authors conclude that personalized anti-inflammatory and immune therapies in addition to chronic antihypertensive therapy may improve clinical outcomes or prevent worse prognosis in hypertensive patients with COVID-19 infection.

SUMMARY

Summary of additional study findings below (Table 1):
- Data were collected prospectively from electronic medical records (EMR) in each participants' institutions and then analyzed.
- Three groups of patients on anti-hypertensive therapy (stable does ≥ 4 weeks) were established: angiotensin converting enzyme inhibitors (ACEi, n=24), angiotensin receptor blockers (ARBs, n=21) and calcium channel blockers (CCBs, n=17). No significant difference in the study endpoints were observed between groups (p> 0.05).
- Lowest LVEF values predicted death (odds ratio [OR] 1.142; 95%CI [1.008-1.294], p <0.05)
- Highest values of IL6 predicted ICU admission (OR 1.617; 95%CI [1.094-2.389]), mechanical ventilation (OR 1.149; 95% CI [1.082-1.219]), cardiac injury with high levels of high sensitive troponin (OR 1.367; 95% CI [1.054-1.772]) and deaths (OR 4.742; 95%CI [1.788-8.524]).
- Chest radiography and computed tomography (CT) findings: unilateral and bilateral pneumonia was observed in 15 (24.1%) and 47 (74.8%) of participants, respectively. Multiple motting and ground glass opacity was found in 33 (53.2%) of participants

ABSTRACT

Background Coronavirus-19 (COVID-19) is the cause of a pandemic disease, with severe acute respiratory syndrome by binding target epithelial lung cells through angiotensin converting enzyme 2 (ACE2) in humans. Thus, hypertensive patients with COVID-19 could have worse prognosis. Indeed, angiotensin converting enzyme (ACEi) inhibitors and/or angiotensin receptor blockers (ARBs) may interfere with ACE2 expression/activity. Thus, hypertensive patients undergoing ACEi and/or ARBs drug therapy may be at a higher risk of contracting a serious COVID-19 infection and should be monitored. Moreover, in the present study we investigated the effects of ACEi vs. ARBs vs. calcium channel blockers on clinical outcomes as mechanical ventilation, Intensive Care Unit (ICU) admissions, heart injury and death in 62 hypertensive patients hospitalized for COVID-19 infection. Methods and Results The multicenter study was prospectively conducted at Department of Infectious Diseases of Sant'Anna Hospital of Caserta, and of University of Campania "Luigi Vanvitelli" of Naples, at Department of Advanced Surgical and Medical Sciences of University of Campania "Luigi Vanvitelli", Naples, and at General Medical Assistance Unit "FIMG", Naples, Italy. Lowest values of left ventricle ejection fraction predicted deaths (1.142; [1.008-1.294], p <0.05), while highest values of interleukin 6 (IL6) predicted the admission to ICU (1.617; [1.094-2.389]), mechanical ventilation (1.149; [1.082-1.219]), heart injuries (1.367; [1.054-1.772]) and deaths (4.742; [1.788-8.524]). ConclusionsAnti-hypertensive drugs didn't affect the prognosis in COVID-19 patients. Consequently, tailored anti-inflammatory and immune therapies in addition to chronic antihypertensive therapy, could prevent a worse prognosis, as well as improve the clinical outcomes in hypertensive patients with COVID-19 infection.

FIGURES

Clinical study variables	Overall (n 62)	ACEi (n 24)	ARBs (n 21)	CCBs (n 17)	P value
Age, years	58±18	56±19	58±16	59±17	0.522†; 0.293‡;0.520¥
Sex, (male, %)	41 (66.1)	15 (62.5)	14 (66.7)	12 (70.5)	0.509†; 0.318‡; 0.539¥
Smoking, (%)	7 (11.2)	3 (12.5)	2 (9.5)	2 (11.7)	0.565†; 0.692‡; 0.613¥
Body mass index, (kg/m2)	25.7±7.2	25.4±6.9	26.1±7.3	25,8±7.1	0.686†; 0.917‡; 0.582¥
Systolic blood pressure values, (mmHg)	130±5	131±4	129±5	131±5	0.337†; 0.826‡; 0.608¥
Diastolic blood pressure values, (mmHg)	81±6	82±6	80±7	82±7	0.456†; 0.501‡; 0.447¥
Signs and symptoms at admission					
Fever	50 (80.6)	19 (79.2)	17 (80.9)	14 (82.3)	0.590†; 0.408‡;0.440¥
Cough	22 (35.4)	8 (33.3)	8 (38)	6 (35.2)	0.491†; 0.585‡; 0.565¥
Shortness of breath	18 (29)	7 (29.2)	6 (28.6)	5 (29.4)	0.613†; 0.533‡; 0.617¥
Fatigue	12 (19.3)	4 (16.7)	5 (23.8)	3 (17.6)	0.410†; 0.592‡; 0.478¥
Sputum production	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721†; 0.646‡; 0.701¥
Muscle ache	4 (6.4)	2 (8.3)	1 (4.7)	1 (5.8)	0.551†; 0.652‡; 0.701¥
Diarrhea	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721†; 0.646‡; 0.701¥
Chest pain	4 (6.4)	2 (8.3)	1 (4.7)	1 (5.8)	0.551†; 0.652‡; 0.701¥
Sore throat	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721†; 0.646‡; 0.701¥
Rhinorrea	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721†; 0.646‡; 0.701¥
Headache	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721†; 0.646‡; 0.701¥
Chronic medical illness					
Diabetes, (%)	16 (25.8)	6 (25)	5 (23.8)	5 (29.4)	0.602†; 0.649‡; 0.643¥
Coronary heart disease, (%)	21 (33.9)	8 (33.3)	7 (33.3)	6 (35.2)	0.625†; 0.524‡; 0.584¥
Previous AMI	11 (17.8)	4 (16.7)	4 (19)	3 (17.6)	0.422†; 0.456‡; 0.624¥
CABG	3 (9)	1 (4.2)	1 (4.7)	1 (5.8)	0.721†; 0.646‡; 0.701¥
PTCA	18 (5.6)	7 (29.2)	6 (28.6)	5 (29.4)	0.613†; 0.580‡; 0.617¥
Chronic obstructive pulmonary disease, (%)	10 (16.1)	4 (16.7)	3 (14.3)	3 (17.6)	0.578†; 0.592‡; 0.560¥
Cerebrovascular disease (%)	7 (11.3)	3 (12.5)	2 (9.5)	2 (11.7)	0.565†; 0.692‡; 0.613¥

Table 1: Characteristics of study population of 62 consecutive hypertensive patients with COVID-19. First p value is for ACEi vs. ARBs and marked with "†"; second p value is for ACEi vs. CCBs and marked with "‡"; third p value is for ARBs vs. CCBs and marked with "¥". Analysis began February 29. 2020. AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; PTCA: percutaneous coronary angioplasty; PT: Pro-thrombin time; ACEi: angiotensin converting enzyme inhibitors; APTT: activated pro-thrombin time; ARBs: angiotensin receptor blockers; AST: aspartate amino transferase; ALT: alanine amino transferase: CCBs: calcium blockers; CK-MB: Creatinine kinasemyocardial band; LDH: lactate dehydrogenase; BNP: B type natriuretic peptide; Hb1Ac: glycatedhemoglobin; PaO2/FiO2: Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration; hs: high specificity; LVTDd: left ventricle end-diastolic diameter; LVTSd: left ventricle end-sistolic diameter; LVEF: left ventricle ejection fraction; VT/VF: ventricular tachycardia/ventricular fibrillation; ARDS: Acute respiratory distress syndrome

Chronic renal failure (%)	6 (9.7)	2 (8.3)	2 (9.5)	2 (11.7)	0.643†; 0.529‡; 0.613¥
Cancer	5 (8)	2 (8.3)	2 (9.5)	1 (5.8)	0.643†; 0.652‡; 0.613¥
Laboratory findings at admission					
Red blood cells, n x10⁶ (μ/L)	3.8 [3.6-4.4]	3.8 [3.7-4.0]	3.9 [3.6-4.1]	3.8 [3.6-4.5]	0.212†; 0.254‡; 0.115¥
Haemoglobin, g/dl	12.1 [10.8-13.9]	12 [11.5-13.4]	12.2 [11.7-13.3]	12.2 [10.7-14.1]	0.132†; 0.322‡; 0.205¥
White blood cells, n (μ/L)	7948 [3810-11040]	7973 [3496-10389]	8263 [3727-10593]	8021 [3682-11102]	0.171†; 0.216‡; 0.156¥
Lymphocytes, n (μ/L)	974 [560-1128]	983 [672-1347]	978 [589-1132]	964 [546-1212]	0.426†;0.182‡; 0.345¥
Neutrophils, n (μ/L)	6936 [2410-10118]	6875 [1852-7899]	6943 [1972-8101]	6836 [1824-10201]	0.150†; 0.181‡; 0.342¥
Pro-thrombin time (PT), s	12.7 [12.1-15.3]	12.8 [12.1-13.3]	12.7 [12.3-13.2]	12.7 [12.2-15.5]	0.181†; 0.085‡; 0.214¥
APTT, s	29.9 [27.5-35.6]	28.5 [27.8-32.2]	31.1 [20.1-32.1]	29.2 [20.3-36.8]	0.476†; 0.406‡; 0.159¥
D-dimer, (mg/mL)	3.72 [0.12-22.38]	3.21 [0.49-19.1]	3.70 [0.52-20.7]	4.01 [0.26-22.38]	0.094†; 0.076‡; 0.101¥
Cholesterol, mg/dl	148±14.7	146±14.4	150±14.2	146±14.9	0.076†; 0.173‡; 0.082¥
AST, mg/dl	42.3±3.1	40.4±4.5	42.1±3.7	42.3±3.3	0.105†; 0.092‡; 0.643¥
ALT, md/dl	39±2.8	38±2.5	38±3.2	39±2.5	0.109†; 0.074‡; 0.086¥
CK-MB, mg/dl	166±17.1	167±14.5	165±16.8	164±18.2	0.238†; 0.146‡; 0.139¥
LDH, mg/dl	620±139	622±136	620±142	623±140	0.093†; 0.082‡; 0.105¥
High sensitivity Troponin I, μg/L	0.39 [0.12-1.47]	0.38 [0.12-1.49]	0.40 [0.13-1.57]	0.43 [0.21-1.62]	0.577†; 0.195‡; 0.081¥
Myohemoglobin, μg/L	49.67±28.2	49.81±28.1	49.37±30.3	50.05±28.1	0.469†; 0.337‡; 0.878¥
Creatinine, mg/dL	0.81±0.22	0.92±0.18	0.88±0.25	0.89±0.23	0.128†; 0.243‡; 0.341¥
BNP, pg/ml	36.4±3.1	36.1±2.9	36.9±2.8	35.9±3.3	0.062†; 0.498‡; 0.148¥
Glucose, mg/dl	121±29	123±27	118±33	120±30	0.055†; 0.325‡; 0.701¥
Hb1Ac, %	5.8±0.4	5.8±0.6	5.7±0.9	5.6±0.8	0.201†; 0.084‡; 0.110¥
Sodium, mEq/L	135.3±2.6	136.8±2.8	134.4±2.4	135.4±2.4	0.070†; 0.312‡; 0.568¥
Potassium, mEq/L	3.7±0.3	3.7±0.2	3.8±0.3	3.6±0.4	0.104†; 0.120‡; 0.064¥
PaO2/FiO2, mmHg	81 [64-109]	78 [66-108]	82 [72-110]	79 [67-112]	0.085†; 0.148‡; 0.092¥
Inflammatory markers					
Interleukin 1, pg/dl	387.5 [321.8-422.1]	383.4 [332.6-404.5]	389.9 [339.8-408.9]	392.4 [329.8-431.9]	0.093†; 0.074‡; 0.203¥
Interleukin 6, pg/dl	243.2 [202.7-251.2]	242.1 [216.8-248.9]	245.3 [222.1-250.1]	248.3 [222.1-253.2]	0.083†; 0.064‡; 0.126¥
Tumor necrosis alpha, mg/dl	3.1 [1.94-4.89]	2.9 [2.6-4.32]	3.3 [3.0-4.64]	3.2 [3.0-4.92]	0.093†0.184‡; 0.233; ¥
hs-C Reactive Protein, mg/dl	6.2 [1.2-17.12]	5.7 [4.3-16.7]	5.6 [1.2-18.7]	6.4 [3.6-19.7]	0.341†; 0.072‡; 0.063¥

Table 1 Continued.

Pro-calcitonin, ng/ml	0.21 [0.04-0.44]	0.22 [0.06-0.39]	0.24 [0.05-0.46]	0.20 [0.04-0.47]	0.075[1]; 0.091[1]; 0.062[2]
Echocardiographic parameters					
LVTDd mm	49.4±4.5	49.3±4.7	48.6±4.6	49.8±4.2	0.121[1]; 0.122[1]; 0.317[2]
LVTSd mm	34.1±2.8	34.1±2.8	36.1±2.7	35.6±3.1	0.469[1]; 0.383[1]; 0.151[2]
LVEF %	53.8±8.2	54.5±6.7	52.2±6.4	55.1±8.4	0.446[1]; 0.317[1]; 0.121[2]
Mitral insufficiency : Low (%). Moderate (%). Severe (%)	 41 (66.1) 21 (33.9) /	 16 (66.7) 8 (33.3)	 14 (66.7) 7 (33.3)	 11 (64.7) 6 (35.3)	 0.623[1]; 0.524[1]; 0.584[2] 0.625[1]; 0.524[1]; 0.584[2]
Chest radiography and computed tomography findings					
Pneumonia: Unilateral Bilateral	 15 (24.1) 47 (75.8)	 6 (25) 18 (77.5)	 5 (23.8) 16 (76.2)	 4 (23.5) 13 (76.5)	 0.602[1]; 0.649[1]; 0.643[2] 0.454[1]; 0.475[1]; 0.624[2]
Multiple matting and ground-glass opacity	33 (53.2)	13 (54.2)	11 (52.4)	9 (52.9)	0.555[1]; 0.475[1]; 0.615[2]
Chronic drug therapy					
Anti platelets, (%) Cardioaspirin, (%) Clopidrogel, (%) Prasugrel, (%)	 24 (38.7); 14 (22.6); /	 9 (37.5) 5 (225)	 8 (38.1) 5 (23.8)	 7 (41.2) 4 (23.5)	 0.604[1]; 0.472[1]; 0.555[2] 0.546[1]; 0.525[1]; 0.643[2]
Beta blockers, (%)	21 (33.9)	8 (33.3)	8 (38.1)	5 (29.4)	0.491[1]; 0.585[1]; 0.416[2]
Loop diuretics, (%)	8 (12.9)	3 (12.5)	3 (14.2)	2 (11.8)	0.846[1]; 0.565[1]; 0.565[2]
Thiazides, (%)	12 (19.3)	4 (16.7)	5 (23.8)	3 (17.6)	0.410[1]; 0.592[1]; 0.478[2]
Statins, (%)	27 (43.5)	10 (41.6)	10 (47.6)	7 (41.2)	0.587[1]; 0.576[1]; 0.527[2]
Hypoglycemic drugs, (%)	13 (21)	5 (20.8)	5 (23.8)	3 (17.6)	0.546[1]; 0.601[1]; 0.478[2]
Insulin therapy, (%)	4 (6.5)	2 (0.8)	1 (0.5)	1 (0.6)	0.551[1]; 0.652[1]; 0.701[2]
COVID-19 therapy					
Antiviral, (%)	62 (100)	24 (100)	21 (100)	17 (100)	/
Antibiotics, (%)	53 (85.5)	21 (87.5)	17 (80.9)	15 (88.2)	0.601[1]; 0.471[1]; 0.387[2]
Hydroxyl-cloroquine, (%)	51 (82.2)	20 (83.3)	17 (80.9)	14 (82.3)	0.578[1]; 0.592[1]; 0.560[2]
Glutocorticoids, (%)	48 (77.4)	19 (79.2)	16 (76.2)	13 (76.5)	0.590[1]; 0.408[1]; 0.624[2]
Oxygen inhalation, (%)	50 (80.6)	19 (79.2)	17 (80.9)	14 (82.3)	0.431[1]; 0.212[1]; 0.604[2]
Non invasive ventilation, (%)	13 (21)	5 (20.8)	5 (23.8)	3 (17.6)	0.546[1]; 0.601[1]; 0.478[2]
Anticoagulant, (%)	12 (19.3)	4 (16.7)	5 (23.8)	3 (17.6)	0.410[1]; 0.592[1]; 0.478[2]
Complications					
VT/VF, (%)	10 (16.1)	4 (16.7)	3 (14.2)	3 (17.6)	0.578[1]; 0.592[1]; 0.560[2]
ARDS, (%)	32 (51.6)	12 (50)	11 (52.3)	9 (52.9)	0.571[1]; 0.578[1]; 0.615[2]
Coagulopathy, (%)	36 (58)	14 (58.3)	12 (57.1)	10 (58.8)	0.491[1]; 0.524[1]; 0.555[2]
Liver injury, (%)	11 (17.7)	4 (16.7)	4 (19)	3 (17.6)	0.168[1]; 0.592[1]; 0.592[2]
Kidney injury, (%)	21 (33.9)	8 (33.3)	7 (33.3)	6 (35.2)	0.625[1]; 0.524[1]; 0.584[2]
Study endpoints					
Hospital admissions at Intensive Care Unit, (%)	12 (19.3)	4 (16.7)	5 (23.8)	3 (17.6)	0.410[1]; 0.592[1]; 0.478[2]
Mechanical Ventilation, (%)	26 (41.9)	10 (41.7)	9 (42.9)	7 (41.2)	0.578[1]; 0.576[1]; 0.590[2]
Cardiac injury, (%)	14 (22.5)	5 (20.8)	5 (23.8)	4 (23.5)	0.546[1]; 0.525[1]; 0.643[2]
Deaths, (%)	9 (14.5)	4 (16.6)	3 (14.3)	2 (11.8)	0.592[1]; 0.061[1]; 0.565[2]

Table 1 Continued.

PEDIATRICS

LUNG MECHANICS IN COVID-19 RESEMBLE RDS NOT ARDS: COULD SURFACTANT BE A TREATMENT?

Koumbourlis AC, Motoyama EK.. Am J Respir Crit Care Med. 2020 Jun 24. doi: 10.1164/rccm.202004-1471LE. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

This cohort study involving a comparison between 12 pediatric patients with mechanically ventilated respiratory distress syndrome (RDS) and 13 pediatric patients with acute respiratory distress syndrome (ARDS) (due to meconium aspiration syndrome) at Children's Hospital of Pittsburgh showed that RDS was more consistent with SARS-CoV-2 infection due to the presence of alveolar collapse. This suggests that exogenous surfactant may provide benefit for pediatric COVID-19 patients and should be the focus of future randomized controlled trials.

TELEPSYCHIATRY IN THE AGE OF COVID: SOME ETHICAL CONSIDERATIONS

Chin HP, Palchik G.. Camb Q Healthc Ethics. 2020 Jun 24:1-7. doi: 10.1017/S0963180120000523. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Experts in psychiatry and neuro-ethics argue that tele-psychiatry should continue to be utilized after the COVID-19 pandemic passes. They develop their stance through the lens of medical ethics principles and maintain the following:
1) continuing to offer tele-psychiatry services is necessary for the sake of patient benefice and autonomy;
2) doing so would likely yield significant cost-savings for patients and other stakeholders; and
3) increasing tele-psychiatry accessibility would yield a greater degree of distributive justice.

SUMMARY

"Momentum, fueled by patient preference alone, may cement telepsychiatry's place as a mainstay of treatment regardless of the COVID-19 pandemic. Indeed, its promise to increase access and quality of care may be transformative for the field. Nevertheless its future development must be minded by continued rigorous study of its efficacy, and diligent advocacy to assure safe and secure use in accessing care for all. These efforts would be the manifestations of ongoing adherence to the core concepts within medical ethics, which must continue to tether the changes to and in psychiatry, current and upcoming."

POSSIBILITY OF HIV-1 PROTEASE INHIBITORS-CLINICAL TRIAL DRUGS AS REPURPOSED DRUGS FOR SARS-COV-2 MAIN PROTEASE: A MOLECULAR DOCKING, MOLECULAR DYNAMICS AND BINDING FREE ENERGY SIMULATION STUDY

Ancy I, Sivanandam M, Kumaradhas P.. J Biomol Struct Dyn. 2020 Jul 6:1-8. doi: 10.1080/07391102.2020.1786459. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

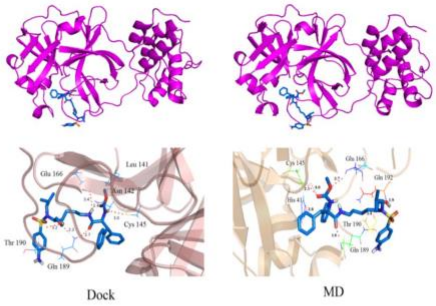
BLUF

Molecular biologists from India conducted an in-silico study exploring molecular characteristics of two HIV-1 drug candidates (protease inhibitors TMB607 and TMC310911) and found that while both interact with the active site of SARS-CoV-2's Mpro enzyme, TMB607 binds more strongly and with more stability to key amino acids (Figure 4, Tables 1-2), making it a potential drug candidate for treatment of COVID-19.

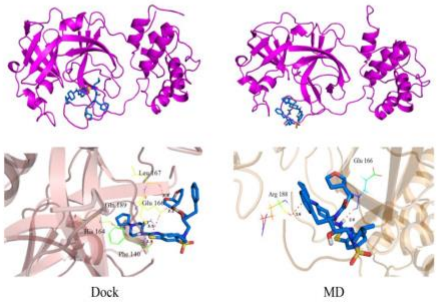
ABSTRACT

Initially, the SARS-CoV-2 virus was emerged from Wuhan, China and rapidly spreading across the world and urges the scientific community to develop antiviral therapeutic agents. Among several strategies, drug repurposing will help to react immediately to overcome the COVID-19 pandemic. In the present study, we have chosen two clinical trial drugs against HIV-1 protease namely, TMB607 and TMC310911 to use as the inhibitors of SARS-CoV-2 main protease (Mpro) enzyme. To make use of these two inhibitors as the repurposed drugs for COVID-19, it is essential to know the molecular basis of the binding mechanism of these two molecules with the SARS-CoV-2 Mpro. To understand the binding mechanism, we have performed molecular docking, molecular dynamics (MD) simulations, and binding free energy calculations against the SARS-CoV-2 Mpro. The docking results indicate that both molecules form intermolecular interactions with the active site amino acids of Mpro enzyme. However, during the MD simulations, TMB607 forms strong interaction with the key amino acids of Mpro, and remains intact. The RMSD and RMSF values of both complexes were stable throughout the MD simulations. The MM-GBSA binding free energy values of both complexes are -43.7 and -34.9 kcal/mol, respectively. This in silico study proves that the TMB607 molecule binds strongly with the SARS-CoV-2 Mpro enzyme and it may be suitable for the drug repurposing of COVID-19 and further drug designing. Communicated by Ramaswamy H. Sarma.

FIGURES



(a)



(b)

Figure 4: Intermolecular interactions of (a) TMB607-SARS-CoV-2 M^{pro} and (b) TMC310911-SARS-CoV-2 M^{pro} complexes obtained from docking and the MD simulations.

Table 1. Intermolecular interaction distances of TMB607···SARS-CoV-2 M^{pro} complex.

	Distance (Å)	
TMB607··· SARS-CoV-2 M^{pro}	Dock	MD
Hydrogen bonding interactions		
C24···NE2/His41	4.0	2.8
C33···O/Leu141	3.2	–
O6···HD21/HA/Asn142	2.4, 2.6	–
H27···SG/Cys145	3.0	–
O6···HB2/Cys145	7.6	2.5
H23···HN/Glu166	3.4	–
O5···HN/Glu166	–	2.7
O1···HE21/Gln189	2.1	–
O4···HE22/Gln189	2.7	1.9
H24, C6···O/Thr190	2.5, -	-, 3.4
O1···HN/Gln192	–	1.9
Hydrophobic interactions		
Ring II···His41 (π-π-stacked)	4.2	–
Ring I···SD/Met49 (π-orbital···Sulfur)	4.9	5.3
Ring I···SG/Cys145(π-orbital···Sulfur)	5.0	5.3
C33···His163 (alkyl···π-orbital)	4.8	4.8
C33···His172 (alkyl···π-orbital)	5.1	–

Table 2: Intermolecular interaction distances of TMC310911···SARS-CoV-2 M^{pro} complex.

TMC310911···SARS-CoV-2 M^{pro}	Distance (Å)	
	Dock	MD
Hydrogen bonding interactions		
S2···O/Phe140	2.4	-
H40···O/His164	3.5	-
H15···OE1/Glu166	2.2	-
H20···OGlu166	-	2.0
H21···OGlu166	-	2.5
S···OE2/Glu166	3.5	-
C17···O/Leu167	3.4	-
H45···OArg188	--	2.7
C32···OE1/Gln189	3.7	-
Electrostatic interaction		
Lig···OE2/Glu166 (Anion···π-orbital)	3.6	-
Hydrophobic interactions		
Lig···His41 (π-alkyl···π-orbital)	4.9	-
Lig···Met49	-	5.0
Lig···Met165 (alkyl···alkyl)	4.7	5.5
Lig···Pro168 (alkyl···alkyl)	4.3	4.2

DIFFERENT COMPUTED TOMOGRAPHY PATTERNS OF CORONAVIRUS DISEASE 2019 (COVID-19) BETWEEN SURVIVORS AND NON-SURVIVORS

Pan F, Zheng C, Ye T, Li L, Liu D, Li L, Hesketh RL, Yang L.. Sci Rep. 2020 Jul 9;10(1):11336. doi: 10.1038/s41598-020-68057-4.

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

BLUF

Radiologists in Wuhan, China conducted a retrospective case control study comparing chest computed tomography (CT) findings between survivors (n=83) and non-survivors (n=41) of COVID-19 infection between 12 January and 20 February 2020 and found that non-survivors had predominant crazy-paving pattern on chest CT (p=0.001; Table 3). Curve estimation showed rapidly increased total CT score (0 [no involvement] to 25 [maximum involvement]) in non-survivors that remained high until acute respiratory distress syndrome (ARDS) and subsequent death occurred, while total CT score increased slowly followed by a gradual decline in survivors (Figures 2, 3). Authors suggest crazy-paving pattern predominance and total CT score trends may assist in identifying high risk patients prior to clinical deterioration.

ABSTRACT

This study aimed to compare the chest computed tomography (CT) findings between survivors and non-survivors with Coronavirus Disease 2019 (COVID-19). Between 12 January 2020 and 20 February 2020, the records of 124 consecutive patients diagnosed with COVID-19 were retrospectively reviewed and divided into survivor (83/124) and non-survivor (41/124) groups. Chest CT findings were qualitatively compared on admission and serial chest CT scans were semi-quantitively evaluated between two groups using curve estimations. On admission, significantly more bilateral (97.6% vs. 73.5%, p = 0.001) and diffuse lesions (39.0% vs. 8.4%, p < 0.001) with higher total CT score (median 10 vs. 4, p < 0.001) were observed in non-survivor group compared with survivor group. Besides, crazy-paving pattern was more predominant in non-survivor group than survivor group (39.0% vs. 12.0%, p < 0.001). From the prediction of curve estimation, in survivor group total CT score increased in the first 20 days reaching a peak of 6 points and then gradually decreased for more than other 40 days (R2 = 0.545, p < 0.001). In non-survivor group, total CT score rapidly increased over 10 points in the first 10 days and gradually increased afterwards until ARDS occurred with following death events (R2 = 0.711, p < 0.001). In conclusion, persistent progression with predominant crazy-paving pattern was the major manifestation of COVID-19 in non-survivors. Understanding this CT feature could help the clinical physician to predict the prognosis of the patients.

FIGURES

	Total, n = 124	Survivor group, n = 83	Non-survivor group, n = 41	p value
Pulmonary involvement				
No involvement	3 (2.4)	3 (3.6)	0 (0.0)	0.550
Unilateral	20 (16.1)	19 (22.9)	1 (2.4)	**0.003**
Bilateral	101 (81.5)	61 (73.5)	40 (97.6)	**0.001**
Distribution of pulmonary lesions				
No lesion	3 (2.4)	3 (3.6)	0 (0.0)	0.550
Subpleural	76 (61.3)	58 (69.9)	18 (43.9)	**0.005**
Random	22 (17.7)	15 (18.1)	7 (17.1)	0.891
Diffuse	23 (18.5)	7 (8.4)	16 (39.0)	**< 0.001**
Major CT findings				
GGO	103 (83.1)	69 (83.1)	34 (82.9)	0.977
Consolidation	75 (60.5)	48 (57.8)	27 (65.9)	0.390
Crazy-paving pattern	53 (42.7)	26 (31.3)	27 (65.9)	**< 0.001**
Predominant CT findings				
No lesions	3 (2.4)	3 (3.6)	0 (0.0)	0.550
GGO	27 (21.8)	23 (27.7)	4 (9.8)	**0.023**
Crazy-paving pattern	26 (21.0)	10 (12.0)	16 (39.0)	**0.001**
Consolidation	44 (35.5)	31 (37.3)	13 (31.7)	0.537
Mixed	24 (19.4)	16 (19.3)	8 (19.5)	0.975
Total CT score (IQR)	5 (2–10)	4 (2–7)	10 (5–13)	**< 0.001**

Table 3: Major CT findings on admission.

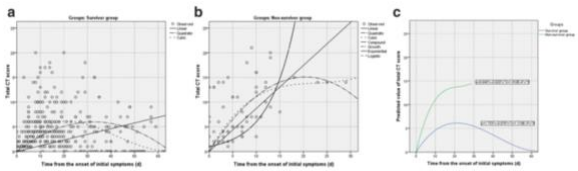


Figure 2: Curve estimations between survivor and non-survivor groups. (a) The curve estimations involved linear, quadratic, and cubic fitting, in which cubic fitting demonstrated the optimal equation (R2 = 0.545, p < 0.001); (b) the curve estimations involved linear, quadratic, cubic, compound, growth, exponential, and logistic fitting, in which cubic fitting demonstrated the optimal equation (R2 = 0.711, p < 0.001); (c) The comparison of optimal fitting curves between survivor and non-survivor

groups (Equations of y=1.753×x−0.076×x2+1.119E−3×x3 and y=0.649×x−0.020×x2+1.610E−4×x3, respectively). All images were obtained from SPSS 24.0 software.

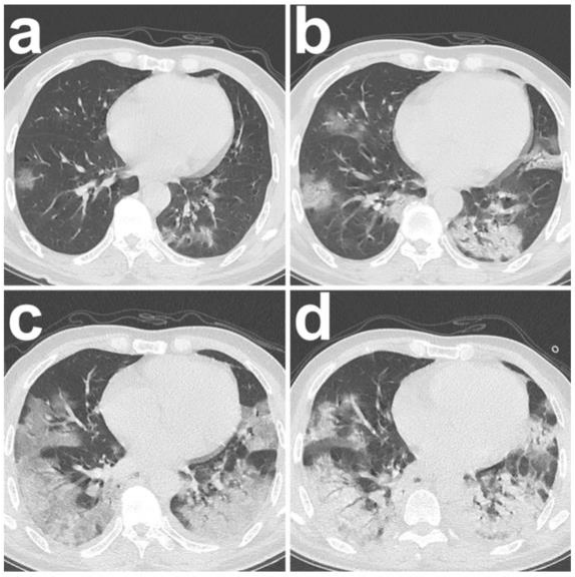


Figure 2: Curve estimations between survivor and non-survivor groups. (a) The curve estimations involved linear, quadratic, and cubic fitting, in which cubic fitting demonstrated the optimal equation (R2 = 0.545, p < 0.001); (b) the curve estimations involved linear, quadratic, cubic, compound, growth, exponential, and logistic fitting, in which cubic fitting demonstrated the optimal equation (R2 = 0.711, p < 0.001); (c) The comparison of optimal fitting curves between survivor and non-survivor groups (Equations of y=1.753×x−0.076×x2+1.119E−3×x3 and y=0.649×x−0.020×x2+1.610E−4×x3, respectively). All images were obtained from SPSS 24.0 software.

DEVELOPMENTS IN DIAGNOSTICS

AUGMENTED CURATION OF CLINICAL NOTES FROM A MASSIVE EHR SYSTEM REVEALS SYMPTOMS OF IMPENDING COVID-19 DIAGNOSIS

Wagner T, Shweta F, Murugadoss K, Awasthi S, Venkatakrishnan AJ, Bade S, Puranik A, Kang M, Pickering BW, O'Horo JC, Bauer PR, Razonable RR, Vergidis P, Temesgen Z, Rizza S, Mahmood M, Wilson WR, Challener D, Anand P, Liebers M, Doctor Z, Silvert E, Solomon H, Anand A, Barve R, Gores G, Williams AW, Morice WG, Halamka J, Badley Md A, Soundararajan V.. Elife. 2020 Jul 7;9:e58227. doi: 10.7554/eLife.58227. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

The authors utilized a neural network program to parse through the Mayo Clinic Electronic Health Records' (EHRs) (n=77,167 patient records, 74,850 COVID-negative, 2,317 COVID-positive) clinical notes to identify symptoms seen with greater proportions in COVID-positive patients (Table 1): anosmia/dysguesia (27.1 fold, earliest sign of infection), cough plus fever/chills (4.2 fold), fever/chills (2.6 fold), respiratory distress (2.2 fold), cough (2.2 fold), myalgia/arthralgia (2 fold), and diarrhea (1.7 fold). These findings highlight the utility of artificial intelligence methods in enhancing the EHR to facilitate real-time diagnostic support of COVID-19 infection.

ABSTRACT

Understanding temporal dynamics of COVID-19 patient symptoms could provide fine-grained resolution to guide clinical decision-making. Here, we use deep neural networks over an institution-wide platform for the augmented curation of clinical notes from 77,167 patients subjected to COVID-19 PCR testing. By contrasting Electronic Health Record (EHR)-derived symptoms of COVID-19-positive (COVIDpos; n=2,317) versus COVID-19-negative (COVIDneg; n=74,850) patients for the week preceding the PCR testing date, we identify anosmia/dysgeusia (27.1-fold), fever/chills (2.6-fold), respiratory difficulty (2.2-fold), cough (2.2-fold), myalgia/arthralgia (2-fold), and diarrhea (1.4-fold) as significantly amplified in COVIDpos over COVIDneg patients. The combination of cough and fever/chills has 4.2-fold amplification in COVIDpos patients during the week prior to PCR testing, and along with anosmia/dysgeusia, constitutes the earliest EHR-derived signature of COVID-19.

This study introduces an Augmented Intelligence platform for the real-time synthesis of institutional biomedical knowledge. The platform holds tremendous potential for scaling up curation throughput, thus enabling EHR-powered early disease diagnosis.

FIGURES

Symptom *(p-value < 1E-10 in gray)*	COVID+ Count (%) (N=2317)	COVID- Count (%) (N = 74850)	(COVID+/COVID-) Relative Ratio	Relative Ratio (95% CI)	2-tailed p-value	BH-corrected p-value
Altered or diminished sense of taste or smell	145 (6.3%)	173 (0.2%)	27.08	(21.81, 33.62)	<1E-300	<1E-300
Fever / chills	750 (32.4%)	9421 (12.6%)	2.57	(2.42, 2.74)	3.57E-169	4.64E-168
Cough	769 (33.2%)	11083 (14.8%)	2.24	(2.11, 2.38)	4.60E-129	3.99E-128
Respiratory difficulty	681 (29.4%)	10082 (13.5%)	2.18	(2.04, 2.33)	3.06E-105	1.99E-104
Myalgia/Arthralgia	288 (12.4%)	4620 (6.2%)	2.01	(1.8, 2.25)	5.35E-34	2.78E-33
Rhinitis	200 (8.6%)	2947 (3.9%)	2.19	(1.92, 2.52)	2.25E-29	9.75E-29
Headache	325 (14.0%)	6124 (8.2%)	1.71	(1.55, 1.9)	1.34E-23	4.98E-23
Congestion	228 (9.8%)	4261 (5.7%)	1.73	(1.53, 1.96)	4.45E-17	1.45E-16
GI upset	195 (8.4%)	10670 (14.3%)	0.59	(0.52, 0.68)	1.74E-15	5.03E-15
Wheezing	49 (2.1%)	3765 (5.0%)	0.42	(0.32, 0.56)	1.82E-10	4.73E-10
Dermatitis	26 (1.1%)	2519 (3.4%)	0.33	(0.23, 0.5)	2.60E-09	6.15E-09
Generalized symptoms	169 (7.3%)	8129 (10.9%)	0.67	(0.58, 0.78)	4.82E-08	1.04E-07
Respiratory Failure	73 (3.2%)	1363 (1.8%)	1.73	(1.38, 2.19)	3.09E-06	6.18E-06
Diarrhea	228 (9.8%)	5452 (7.3%)	1.35	(1.19, 1.53)	3.47E-06	6.44E-06
Pharyngitis	160 (6.9%)	3635 (4.9%)	1.42	(1.22, 1.66)	7.05E-06	1.22E-05
Chest pain/pressure	148 (6.4%)	6122 (8.2%)	0.78	(0.67, 0.92)	1.88E-03	3.06E-03
Change in appetite/intake	95 (4.1%)	2271 (3.0%)	1.35	(1.11, 1.66)	3.37E-03	5.15E-03
Otitis	13 (0.6%)	874 (1.2%)	0.48	(0.29, 0.85)	6.98E-03	1.01E-02
Cardiac	95 (4.1%)	2443 (3.3%)	1.26	(1.03, 1.54)	2.62E-02	3.59E-02
Fatigue	229 (9.9%)	8268 (11.0%)	0.89	(0.79, 1.02)	7.83E-02	1.02E-01
Conjunctivitis	9 (0.4%)	167 (0.2%)	1.74	(0.95, 3.52)	1.00E-01	1.24E-01
Dry mouth	5 (0.2%)	316 (0.4%)	0.51	(0.24, 1.3)	1.28E-01	1.51E-01
Hemoptysis	13 (0.6%)	283 (0.4%)	1.48	(0.89, 2.65)	1.61E-01	1.78E-01
Dysuria	16 (0.7%)	732 (1.0%)	0.71	(0.45, 1.18)	1.64E-01	1.78E-01
Diaphoresis	35 (1.5%)	979 (1.3%)	1.15	(0.84, 1.63)	3.99E-01	4.15E-01
Neuro	150 (6.5%)	4952 (6.6%)	0.98	(0.84, 1.15)	7.86E-01	7.86E-01

Table 1. Augmented curation of the unstructured clinical notes from the EHR reveals specific clinically confirmed phenotypes that are amplified in COVIDpos patients over COVIDneg patients in the week prior to the SARS-CoV-2 PCR testing date. The key COVIDpos amplified symptoms in the week preceding PCR testing (i.e. day = -7 to day = -1) are highlighted in gray (p-value < 1E-10). The ratio of COVIDpos to COVIDneg proportions represents the fold change amplification of each phenotype in the COVIDpos patient set (symptoms are sorted based on this column). Symptoms highlighted with a superscript (*) are still rare in COVIDpos patients at this time, thus mitigating their statistical significance.

DEVELOPMENTS IN TREATMENTS

BTK/ITK DUAL INHIBITORS: MODULATING IMMUNOPATHOLOGY AND LYMPHOPENIA FOR COVID-19 THERAPY

McGee MC, August A, Huang W.. J Leukoc Biol. 2020 Jul 8. doi: 10.1002/JLB.5COVR0620-306R. Online ahead of print.
Level of Evidence: 4 - Review / Literature Review

BLUF

Researchers from Louisiana State and Cornell describe clinical studies that utilized tocilizumab, a monoclonal antibody that blocks IL-6 signaling, and BTK inhibitors to decrease the cytokine storm that is associated with increased morbidity and mortality in SARS-CoV-2 infection (Figure 1). Amongst the tocilizumab studies were a February 2020 study in Wuhan, China on 21 critically ill COVID-19 patients and a multicenter phase III trial by Roche in the US on severely ill patients beginning in April 2020 – both of which showed marked improvement in patient outcomes. Additional trials by AstraZeneca with a selective BTK inhibitor alabrutinib and BeiGene with zanubrutinib, another BTK inhibitor, showed decreased IL-6 levels. The authors infer that targeting the BTK/ITK pathway may be vital to combatting COVID-19 severity. They recommend further study of the actions, side effects, and toxicity of drugs that promote these anti-inflammatory pathways.

ABSTRACT

Bruton's tyrosine kinase (BTK) signaling is involved in innate immune responses and regulates the production of proinflammatory cytokines that can contribute to COVID-19 immunopathology. Clinical trials with BTK inhibitors in COVID-19 treatment have been proposed, and previous studies have attempted to investigate the therapeutic effects of ibrutinib and underlying mechanisms in treating viral pneumonia. These attempts, however, did not consider potential off target effect of BTK inhibitors on T cell differentiation, function, and survival, which may be beneficial in treatment for COVID-19. Here, we summarize the current knowledge of BTK/IL-2-inducible T-cell kinase (ITK) signaling in immunopathology and lymphopenia and discuss the potential of BTK/ITK dual inhibitors such as ibrutinib in modulating immunopathology and lymphopenia, for COVID-19 therapy.

FIGURES

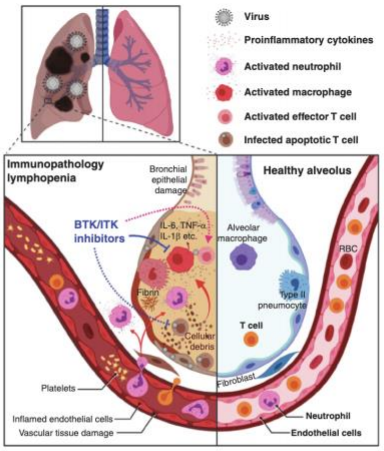


FIGURE 1 Potential of BTK/ITK inhibitors for attenuating immunopathology and lymphopenia in COVID-19. SARS-CoV-2 infection in the lungs set off proinflammatory cytokine production by lung cells and immune cells such as macrophages and neutrophils. Cytokine release syndrome further engages pulmonary and vascular tissue damages, leukocyte recruitment, T cell activation, and other cytotoxic immune responses. T cells are possible targets of SARS-CoV-2 infection. Infected and over reactive T cells may be prompted toward apoptosis and cytolysis, resulting in infection-induced lymphopenia. BTK/ITK inhibitors may function to down-regulate proinflammatory cytokine production by innate immune populations and reduce cytotoxic T cell death while sustaining virus-specific effector T cell function, therefore exhibit therapeutic functions against immunopathology and lymphopenia. Solid-line arrows indicate known functions and dashed-line arrows indicate functions awaiting investigation

CYTOKINE RELEASE SYNDROME AND THE PROSPECTS FOR IMMUNOTHERAPY WITH COVID-19. PART 2: THE ROLE OF INTERLEUKIN 1

Calabrese LH, Calabrese C.. Cleve Clin J Med. 2020 Jul 9. doi: 10.3949/ccjm.87a.ccc044. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A literature review conducted by the Department of Rheumatic and Immunologic Diseases at the Cleveland Clinic highlights the use of IL-1 antagonists such as anakinra and canakinumab (Table 1) as effective drug choices to improve outcomes of patients with cytokine release syndrome secondary to COVID-19 (Figure 1). The authors suggest that larger, unbiased clinical trials with drugs targeting IL-1 to reduce inflammatory processes are warranted in order to label these drugs as effective treatments for patients with COVID-19.

ABSTRACT

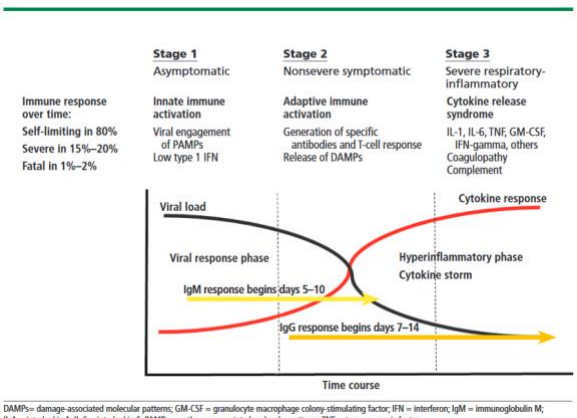
Interleukin 1 (IL-1) is a potential target of therapy in COVID-19 during the severe respiratory-inflammatory phase ("cytokine release syndrome"), when pulmonary macrophages are hyperactivated, releasing IL-1 and other cytokines. Preliminary evidence indicates that anakinra and canakinumab, drugs that block the action of IL-1 and have a good safety profile, improve the outcomes of patients with COVID-19 cytokine release syndrome. Results from large, randomized clinical trials are pending.

FIGURES

TABLE 1
Currently available interleukin 1 inhibitors

Agent	Mechanism of action	Current FDA-approved indications and dosing	Contraindications and cautions
Anakinra (Kineret)	Recombinant human IL-1 receptor antagonist Inhibits activity of IL-1 alpha and IL-1 beta	**Rheumatoid arthritis:** 100 mg subcutaneously once a day **CAPS/NOMID:** 1-2 mg/kg subcutaneously once a day; can increase by 0.5-1 mg/kg increments; maximum dose 8 mg/kg **Renal dosing:** if creatinine clearance is < 30 mL/min or patient is in end-stage renal disease, consider alternate dosing	**Use with caution** in patients with: Concomitant TNF inhibitor use Serious active infection Neutropenia
Canakinumab (Ilaris)	Human monoclonal anti-IL-1 beta Neutralizes IL-1 beta activity	**Systemic juvenile idiopathic arthritis:** 4 mg/kg subcutaneously once a month; not to exceed 300 mg/dose (≥ 2 years and weight ≥ 7.5 kg) **CAPS:** If 15-40 kg, 2 mg/kg subcutaneously every 8 weeks If ≥ 40 kg, 150 mg subcutaneously every 8 weeks **FMF, TRAPS and HIDS/MVD:** If ≤ 40 kg, 2 mg/kg subcutaneously every 4 weeks, can increase to 4 mg/kg every 4 weeks If > 40 kg, 150 mg subcutaneously every 4 weeks; can increase to 300 mg every 4 weeks	**Use with caution** in patients with serious active infection
Rilonacept (Arcalyst)	Fusion protein of extracellular domains of IL-1 RAcP and IL-1 R1 fused to FC portion of human IgG1 Binds to IL-1 alpha and IL-1 beta to block IL-1 signaling	**CAPS:** Adults—loading dose 320 mg subcutaneously, followed by 160 mg subcutaneously weekly Children (12-17 years)—loading dose of 4.4 mg/kg (maximum dose 320 mg), followed by 2.2 mg/kg subcutaneously weekly (maximum dose 160 mg)	**Use with caution** in patients with serious active infection

CAPS = cryopyrin-associated periodic syndromes; FC = fragment crystallizable; FMF = familial Mediterranean fever; HIDS/MKD = hyperimmunoglobulin D syndrome/mevalonate kinase deficiency; IG = immunoglobulin; IL = interleukin; IL-1 RAcP = IL-1 receptor accessory protein; IL-1 R1 = interleukin 1 receptor, type I; NOMID = neonatal-onset multisystem inflammatory disease; TNF = tumor necrosis factor; TRAPS = tumor necrosis factor receptor associated periodic syndrome



DAMPs= damage-associated molecular patterns; GM-CSF = granulocyte macrophage colony-stimulating factor; IFN = interferon; IgM = immunoglobulin M; IL-1 = interleukin 1; IL-6 = interleukin 6; PAMPs = pathogen-associated molecular patterns; TNF = tumor necrosis factor

Figure 1. Three stages of COVID-19 disease.

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