

# The Daily COVID-19 Literature Surveillance Summary

**August 24, 2020**



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# COVID-19 Daily Literature Surveillance

COVID19LST



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

# LEVEL OF EVIDENCE

## Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
<b>How common is the problem?</b>	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
<b>Is this diagnostic or monitoring test accurate? (Diagnosis)</b>	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
<b>What will happen if we do not add a therapy? (Prognosis)</b>	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
<b>Does this intervention help? (Treatment Benefits)</b>	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
<b>What are the COMMON harms? (Treatment Harms)</b>	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
<b>What are the RARE harms? (Treatment Harms)</b>	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control or historically controlled studies**	Mechanism-based reasoning
<b>Is this (early detection) test worthwhile? (Screening)</b>	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>

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# EXECUTIVE SUMMARY

## Climate

- Physicians affiliated with the Icahn School of Medicine at Mount Sinai, Harvard School of Medicine, and Duke University Medical Center consider the downside of "pressurized research" in the context of previous healthcare crises and reflect on the [shortcomings of poor research](#) that have occurred during previous calamities, including the secondary pneumonias that followed trials of immunotherapies during the 1918 influenza epidemic and cases of Guillain-Barre syndrome following swine flu vaccination in 1976. The authors recognize the challenges to meet demands for effective therapies and vaccine development, however they urge for caution and humility in research during the current pandemic to avoid such shortcomings.
- Researchers affiliated with the University of Minnesota and Starkey Hearing Technologies examine the relationship between COVID-19 hospitalization and patient race/ethnicity in 12 states and found that White and Asian patients represented smaller proportions of COVID-19 hospitalizations relative to their respective state population proportion and Black and American Indian/Alaskan Native patients represented significantly larger proportions of COVID-19 hospitalizations relative to their respective state population proportion. The authors suggest that understanding of these [ethnic and racial health disparities](#) during the COVID-19 pandemic may help create valuable solutions.

## Epidemiology

- Researchers from the Brown University Department of Epidemiology and Department of Medicine examined data from the COVID-19 Data Repository at Johns Hopkins University to determine the [relationship between United States state stay-at-home orders and SARS-CoV-2 doubling time in each state](#) and found that stay-at-home mandates correlated with virus doubling times from 2.68 days prior to mitigation efforts to 15 days after. Additionally, states without stay-at-home orders saw an increase in doubling time of 34% whereas states with stay-at-home orders saw a increase of 72%. Although limited by surveillance data, these findings support that present efforts at social distancing help control COVID-19 spread within communities.
- A team of global health and computational biology experts from Stanford University discuss how [artificial intelligence \(AI\) has contributed to racial disparities during the COVID-19 pandemic](#) and cite a systematic review that found high or unclear risk of bias in all (n=66) models screened with the Prediction Model Risk of Bias Assessment Tool and are particularly wary about how these models are applied in regards to allocation of resources. Moving forward, authors propose transparency in AI algorithms used for public health and regulatory frameworks that facilitate open data transfer to facilitate the creation of an accessible international database and produce unbiased representative training data for AI algorithms.
- A systematic review of 47 studies analyzed the impact of [smoking on the severity of COVID-19](#). Authors found that:
  1. Current smokers were at an increased risk of severe or critical COVID-19 but these individuals did not have increased in-hospital mortality.
  2. Patients with a history of smoking had an increased risk of severe COVID-19 as well as an increased in-hospital mortality, disease progression, and need for mechanical ventilation.
  3. The use of aggregated data prevented the authors from performing covariate analyses to determine the impact of age, gender, and other variables on outcomes for current and former smokers.The review highlights the need for further investigation into the molecular underpinnings for the relationship between smoking and COVID-19 and emphasizes the necessity of public health interventions to promote and support smoking cessation.

## Management

- A retrospective cohort study using Electronic Health Record (EHR) data from the Mayo Clinic Health System in Rochester, Minnesota found 246 COVID-19 positive patients had higher plasma fibrinogen levels and lower platelet counts than COVID-19 negative patients (n=13,666) at time of testing but as the infection progressed COVID-19 positive patients showed declining fibrinogen and increased platelet counts, while 31% (n=76/246) developed at least one clot diagnosis . Authors suggest that understanding the evolution and range of [COVID-19 associated coagulopathy \(CAC\)](#) may provide insight for advancement in thrombophylaxis therapy.

## **Adjusting Practice During COVID-19**

- Members of the Neuroscience Section at the University of Milan in Italy propose [guidelines for care of patients with neuromuscular disorders \(NMD\) during the SARS-CoV-2 pandemic](#) recommending outpatient care, minimizing immune-compromising medications and in-person interactions, and maintenance of regular follow-up by utilizing telehealth. Additionally, they suggest providers caring for NMD patients admitted to the hospital with SARS-CoV-2 consider which medications have NMD side effects and consult neurologists for all such patients., suggesting that these measures can optimize outcomes for this group at increased risk for severe disease course.

## **R&D: Diagnosis & Treatments**

- A meta-analysis of 40 studies conducted across 31 provinces in China of severe and critically-ill COVID-19 patients (n=5,872) found [severe disease](#) was associated with older age (weighted mean difference [WMD]=10.69), higher lactate dehydrogenase (LDH; WMD=137.4), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), D-dimer and procalcitonin (PCT), as well as significantly decreased platelet count (WMD= -18.63) and lymphopenia. Authors suggest these laboratory markers and age could be useful for early detection and prediction of worsening illness in COVID-19 patients.
- Researchers conducted an analysis of safety metrics and mortality rate in 5000 hospitalized patients with severe or life-threatening COVID-19 who received [transfusions of ABO-compatible human COVID-19 convalescent plasma](#) that was pre-screened for SARS-CoV-2 via clinical laboratory or antibody test and found that thirty-six patients (less than 1%) had severe adverse events within four hours of transfusion with a 0.08% mortality rate at the four hour mark; the seven day mortality rate for the study group was 14.9% compared to the case fatality rate of 10-20% for hospitalized COVID-19 patients. The authors note several risks of convalescent plasma transfusion, but given the high mortality rates expected in a critically ill population, they are optimistic that this could be a viable treatment option once further efficacy studies are performed.

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## CLIMATE

### BIOMEDICAL RESEARCH IN TIMES OF EMERGENCY: LESSONS FROM HISTORY

Doroshow D, Podolsky S, Barr J.. Ann Intern Med. 2020 Aug 18;173(4):297-299. doi: 10.7326/M20-2076. Epub 2020 May 7.  
Level of Evidence: Other - Review / Literature Review

#### BLUF

Physicians affiliated with the Icahn School of Medicine at Mount Sinai, Harvard School of Medicine, and Duke University Medical Center consider the downside of "pressurized research" in the context of previous healthcare crises (namely 1918 Influenza epidemic, swine flu vaccine development and mustard gas experiments of World War I). They reflect the shortcomings of poor research that have occurred during previous calamities, including the secondary pneumonias that followed trials of immunotherapies during the 1918 influenza epidemic and cases of Guillain-Barre syndrome following swine flu vaccination in 1976. The authors recognize the challenges to meet demands for effective therapies and vaccine development, however they urge for caution and humility in research during the current pandemic to avoid such shortcomings.

## DISPARITIES

### ASSESSMENT OF COVID-19 HOSPITALIZATIONS BY RACE/ETHNICITY IN 12 STATES

Karaca-Mandic P, Georgiou A, Sen S.. JAMA Intern Med. 2020 Aug 17. doi: 10.1001/jamainternmed.2020.3857. Online ahead of print.

Level of Evidence: 1 - Local and current random sample surveys (or censuses)

#### BLUF

Authors affiliated with the University of Minnesota and Starkey Hearing Technologies examine the relationship between COVID-19 hospitalization and patient race/ethnicity in 12 states from April 30, 2020 to June 24, 2020. The researchers found that White and Asian patients represented smaller proportions of COVID-19 hospitalizations relative to their respective state population proportion. Further, Black and American Indian/Alaskan Native patients represented significantly larger proportions of COVID-19 hospitalizations relative to their respective state population proportion (Figure). The authors suggest that understanding of these ethnic and racial health disparities during the COVID-19 pandemic may help create valuable solutions.

## SUMMARY

In all 12 states included in the study, the proportion of non-Hispanic Black COVID-19 hospitalizations exceeded their respective state population proportion. American Indian/Native Alaskan COVID-19 hospitalizations were routinely documented in Arizona and Utah; this population exhibited similarly high proportions of COVID-19 hospitalizations relative to their respective population proportion. Asian and White patients experienced opposite odds, where their respective population proportion was greater than their respective COVID-19 hospitalization share. The researchers noted that their study did not control for age, sex, comorbidities, or socioeconomic influences.

## FIGURES

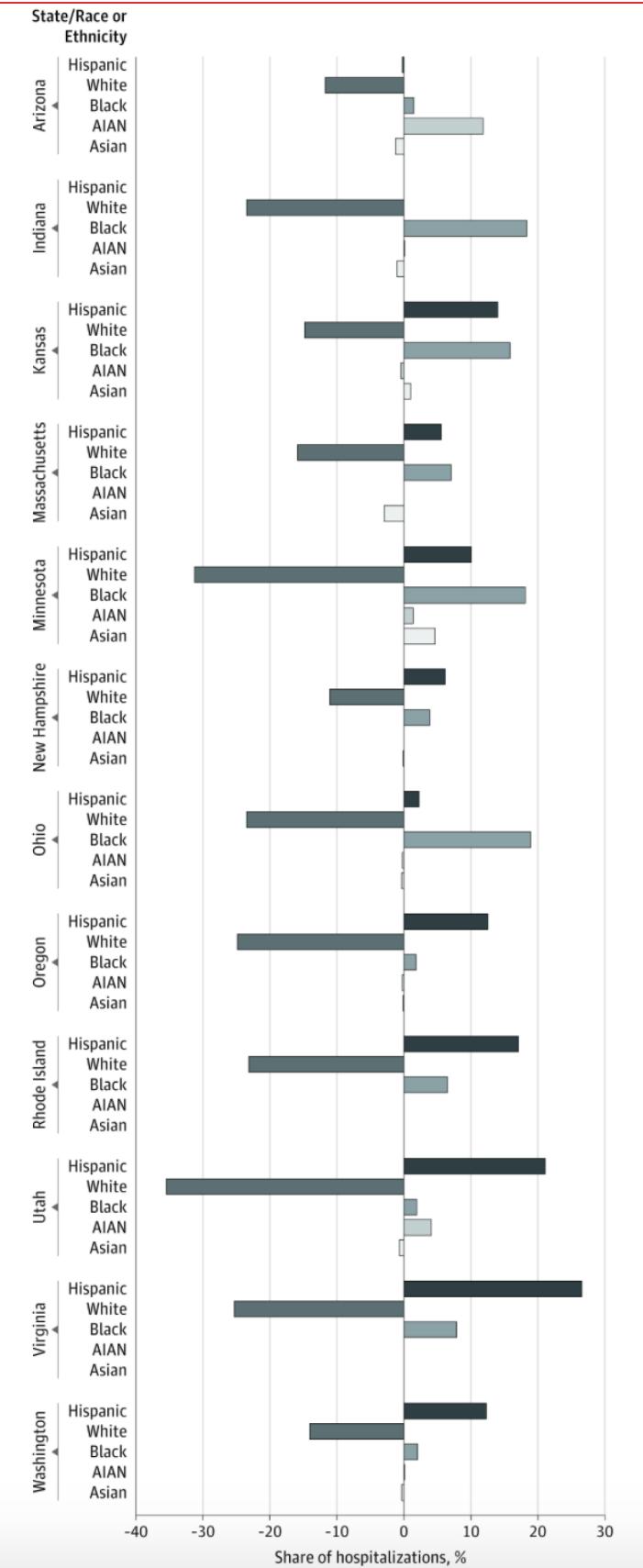


Figure. Hospitalizations vs Population of Racial/Ethnic Subgroups in 12 States.

The bars represent the difference between the cumulative percentage of hospitalizations and the proportion of state population by each racial/ethnic subgroup. AIAN indicates American Indian/Alaskan Native.

# CRISIS STANDARDS OF CARE IN THE USA: A SYSTEMATIC REVIEW AND IMPLICATIONS FOR EQUITY AMIDST COVID-19

Cleveland Manchanda EC, Sankar C, Appel JM.. J Racial Ethn Health Disparities. 2020 Aug 13. doi: 10.1007/s40615-020-00840-5. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

## BLUF

Authors affiliated with Boston University School of Medicine and Icahn School of Medicine at Mount Sinai conducted a review of Critical Standards of Care (CSC) guidelines for 29 states (Figure 2) between April 13 and April 17, 2020 and found 23 CSCs explicitly described ethical principles, 19 stated that "identity-based" characteristics (i.e. race, ethnicity) should not be considered in decisions, and 21 included methods for prioritizing patients for critical care resources (i.e. ventilators; Table 2). The authors suggest that wide variability in CSCs across the United States calls for inclusion of diverse stakeholders in CSC development (i.e. politicians, disability activists, representatives from marginalized groups) to avoid perpetuating inequities and disproportionate resource allocation.

## ABSTRACT

**BACKGROUND:** Crisis Standards of Care (CSC) provide a framework for the fair allocation of scarce resources during emergencies. The novel coronavirus disease (COVID-19) has disproportionately affected Black and Latinx populations in the USA. No literature exists comparing state-level CSC. It is unknown how equitably CSC would allocate resources. **METHODS:** The authors identified all publicly available state-level CSC through online searches and communication with state governments. Publicly available CSC were systematically reviewed for content including ethical framework and prioritization strategy. **RESULTS:** CSC were identified for 29 states. Ethical principles were explicitly stated in 23 (79.3%). Equity was listed as a guiding ethical principle in 15 (51.7%); 19 (65.5%) said decisions should not factor in race, ethnicity, disability, and other identity-based factors. Ten states (34.4%) allowed for consideration of societal value, which could lead to prioritization of health care workers and other essential personnel. Twenty-one (72.4%) CSC provided a specific strategy for prioritizing patients for critical care resources, e.g., ventilators. All incorporated Sequential Organ Failure Assessment scores; 15 (71.4%) of these specific CSC considered comorbid conditions (e.g., cardiac disease, renal failure, malignancy) in resource allocation decisions. **CONCLUSION:** There is wide variability in the existence and specificity of CSC across the USA. CSC may disproportionately impact disadvantaged populations due to inequities in comorbid condition prevalence, expected lifespan, and other effects of systemic racism.

## FIGURES

Table 2 Comparison of available state-level Crisis Standards of Care guidance for the allocation of critical care resources

State	Date of identified document*	Specific guidance for allocation of critical care resources, including ventilators	Factors included in specific guidance for ventilator allocation, if any			
			Exclusion criteria for access to critical care	Use of SOFA or MSOFA for determining priority	Consideration of long-term comorbidities	Consideration of pregnancy**
Alabama	4/2010	Yes	Yes	Yes	No	No
Alaska	3/2020	Yes	No	Yes	No	No
Arizona	2020	Yes	No	Yes	No	Yes*
California	4/2020	Yes	No	Yes	No	No
Colorado	4/2020	Yes	No	Yes	Yes	Yes**
Connecticut*	10/2010	No	n/a	n/a	n/a	Yes*
Illinois*	3/2018; 3/2020	No	n/a	n/a	n/a	Yes*
Kansas	9/2013	Yes	Yes	Yes	No	No
Kentucky	3/2020	No	n/a	n/a	n/a	n/a
Louisiana	9/2011	Yes	Yes	Yes	No	No
Maine	6/2015	No	n/a	n/a	n/a	n/a
Massachusetts	4/2020	Yes	Yes	Yes	Yes	Yes**
Michigan	11/2012	No	n/a	n/a	n/a	n/a
Minnesota	12/2013	Yes	No	Yes	Yes	No
Mississippi	2/2017	No	n/a	n/a	n/a	n/a
Missouri	4/2020	Yes	No	Yes	No	Yes*
Nevada	4/2020	No	n/a	n/a	n/a	n/a
New Jersey	4/2020	Yes	No	Yes	No	Yes**
New Mexico	6/2018	Yes	No	Yes	No	Yes*
New York	11/2015	Yes	Yes	Yes	No	No
Ohio	4/2020	Yes	Yes	Yes	Yes	No
Oklahoma	4/2020	Yes	No	Yes	No	Yes**
Oregon	6/2018	Yes	Yes	Yes	Yes	Yes*
Pennsylvania	4/2020	Yes	No	Yes	Yes	No
Tennessee	7/2016	Yes	Yes	Yes	No	No
Utah	6/2018	Yes	Yes	Yes	Yes	No
Vermont	5/2019	Yes	No	Yes	Yes	No
Washington	3/2020	Yes	Yes	Yes	Yes	No
Wyoming	6/2019	No	n/a	n/a	n/a	n/a

SOFA Sequential Organ Failure Assessment, MSOFA Modified Sequential Organ Failure Assessment

\*Where more than one document was identified, both were reviewed. Details presented here reflect a combination of available information from these guidelines

\*\*Variable consideration; some CSC (MA, PA, UT) increased priority based on gestational age and fetal viability; CO incorporated pregnancy as a third-tier tie-breaker; OR stated it can be considered, although no specific guidance is given as to how

\*CSC included language noting that essential workers, including healthcare personnel, could or should receive priority for scarce resources, although exactly how this should be factored into specific resource allocation frameworks was not discussed

\*\*Essential worker status was used as a tie-breaker, if needed, after consideration of exclusion criteria, acuity of illness (SOFA/MSOFA), and/or comorbidities

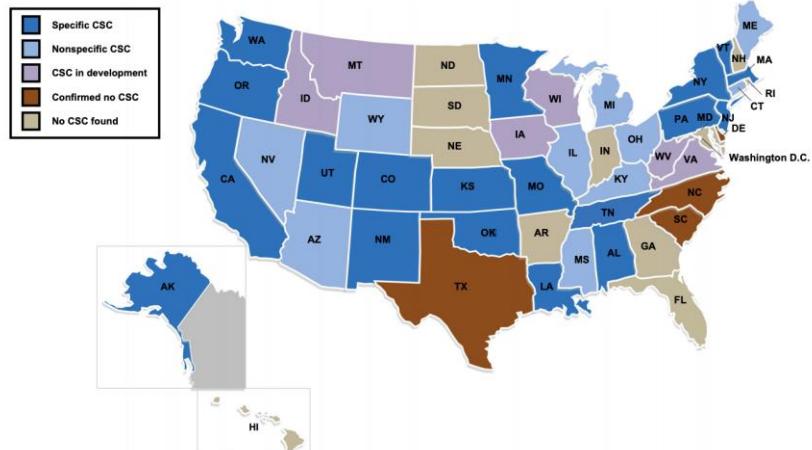


Fig. 2 Crisis Standards of Care across the USA, by status of development as of May 3, 2020

## EPIDEMIOLOGY

### ADJUSTING CORONAVIRUS PREVALENCE ESTIMATES FOR LABORATORY TEST KIT ERROR

Sempos CT, Tian L.. Am J Epidemiol. 2020 Aug 17:kwa174. doi: 10.1093/aje/kwa174. Online ahead of print.

Level of Evidence: 5 - Guidelines and Recommendations

#### BLUF

Authors affiliated with Vitamin D Standardization Program LLC and Lu Department of Biomedical Data Science pose that "small deviations from 100% sensitivity and specificity will result in biased prevalence estimates" for COVID-19 test kits. They provide a framework (illustrated below) to standardize COVID-19 tests and correct prevalence estimates, suggesting that universal use of such a framework can help to "harmonize" results for better prevalence estimates and assistance with policy decision-making.

#### SUMMARY

According to the authors, "the framework would consist of

- (i) selecting an established well-validated test, with documented sensitivity and specificity as close to 100%, as possible, to use as the reference-point assay or test kit;
- (ii) Using that reference-point test kit to develop a series of true positive and true negative test samples; and
- (iii) Using that set of test samples to estimate the sensitivity/specificity of the study test kit or PPV/NPV of the study test kit in the study." The authors note that "it may also be important to know the sensitivity and specificity of the reference-point assay or test kit."

#### ABSTRACT

Testing representative populations to determine the prevalence or percent of the population with active SARS-CoV-2 infection and/or antibodies to infection is being recommended as essential for making public policy decisions to open-up or to continue enforcing national, state and local government rules to "shelter-in-place". However, all laboratory tests are imperfect and have estimates of sensitivity and specificity less than 100% - in some cases considerably less than 100%. That error will lead to biased prevalence estimates. If the true prevalence is low, possibly in the range of 1-5%, then testing error will lead to a constant background of bias that will most likely be larger and possibly much larger than the true prevalence itself. As a result, what is needed is a method for adjusting prevalence estimates for testing error. In this paper we outline methods for adjusting prevalence estimates for testing error both prospectively in studies being planned and retrospectively in studies that have been conducted. The methods if employed would also help to harmonize study results within countries and world-wide. Adjustment can lead to more accurate prevalence estimates and to better policy decisions. However, adjustment will not improve the accuracy of an individual test.

## MODELING

### COVID-19 EPIDEMIC DOUBLING TIME IN THE UNITED STATES BEFORE AND DURING STAY-AT-HOME RESTRICTIONS

Lurie MN, Silva J, Yorlets RR, Tao J, Chan PA.. J Infect Dis. 2020 Aug 1:jiaa491. doi: 10.1093/infdis/jiaa491. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

#### BLUF

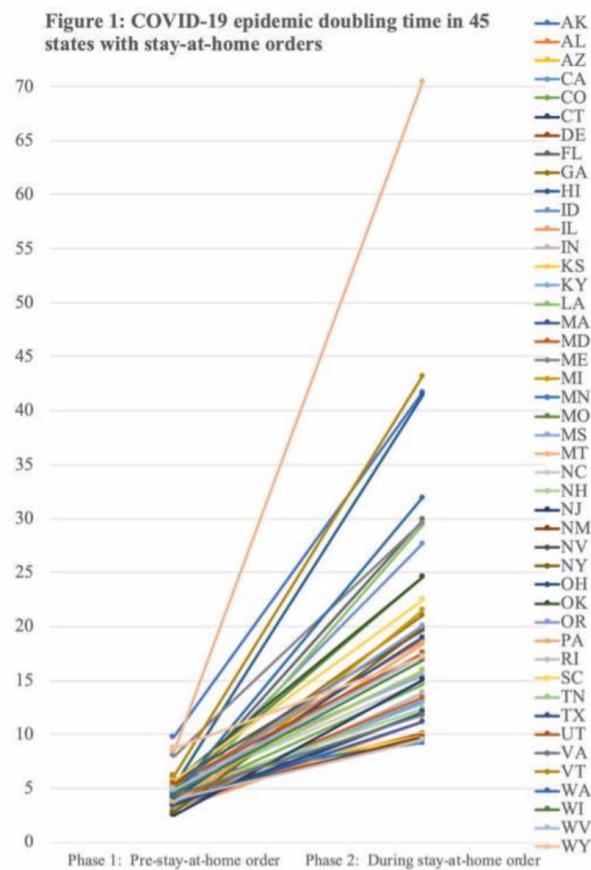
Researchers from the Brown University Department of Epidemiology and Department of Medicine examined data from the COVID-19 Data Repository at Johns Hopkins University to determine the relationship between United States state stay-at-home orders and SARS-CoV-2 doubling time in each state. They found that stay-at-home mandates correlated with virus doubling times from 2.68 days prior to mitigation efforts to 15 days after. Additionally, states without stay-at-home orders saw an increase in doubling time of 34% whereas states with stay-at-home orders saw a increase of 72%. Although limited by surveillance data, these findings support that present efforts at social distancing help control COVID-19 spread within communities.

## ABSTRACT

INTRODUCTION: COVID-19 has spread rapidly in the United States since January 2020. METHODS: We estimated mean epidemic doubling time, an important measure of epidemic growth, nationally, by state and in association with stay-at-home orders. RESULTS: Epidemic doubling time in the US was 2.68 days (95%CI:2.30-3.24) prior to widespread mitigation efforts, increasing by 82% to 15 days (95%CI:12.89-17.94) during the mitigation phase. Among states without stay-at-home orders, median increase in doubling time was 34% (95%CI:21.16-68.85) while for states with stay-at-home orders, median increase was 72.9% (95%CI:69.18-76.11). DISCUSSION: Statewide mitigation strategies were strongly associated with increased epidemic doubling time.

## FIGURES

Figure 1: COVID-19 epidemic doubling time in 45 states with stay-at-home orders



## BIAS AT WARP SPEED: HOW AI MAY CONTRIBUTE TO THE DISPARITIES GAP IN THE TIME OF COVID-19

Röösli E, Rice B, Hernandez-Boussard T.. J Am Med Inform Assoc. 2020 Aug 17:ocaa210. doi: 10.1093/jamia/ocaa210. Online ahead of print.

Level of Evidence: Other - Expert Opinion

## BLUF

A team of global health and computational biology experts from Stanford University discuss how artificial intelligence (AI) has contributed to racial disparities during the COVID-19 pandemic. Authors cite a systematic review that found high or unclear risk of bias in all (n=66) models screened with the Prediction Model Risk of Bias Assessment Tool, and are particularly wary about how these models are applied in regards to allocation of resources. Moving forward, authors propose transparency in AI algorithms used for public health and regulatory frameworks that facilitate open data transfer to facilitate the creation of an accessible international database and produce unbiased representative training data for AI algorithms.

## **ABSTRACT**

The COVID-19 pandemic is presenting a disproportionate impact on minorities in terms of infection rate, hospitalizations and mortality. Many believe Artificial Intelligence (AI) is a solution to guide clinical decision making for this novel disease, resulting in the rapid dissemination of under-developed and potentially biased models, which may exacerbate the disparities gap. We believe there is an urgent need to enforce the systematic use of reporting standards and develop regulatory frameworks for a shared COVID-19 data source to address the challenges of bias in AI during this pandemic. There is hope that AI can help guide treatment decisions within this crisis yet given the pervasiveness of biases, a failure to proactively develop comprehensive mitigation strategies during the COVID-19 pandemic risks exacerbating existing health disparities.

## **SYMPTOMS AND CLINICAL PRESENTATION**

### **ADULTS**

#### **THE EFFECT OF SMOKING ON COVID-19 SEVERITY: A SYSTEMATIC REVIEW AND META-ANALYSIS**

Reddy RK, Charles WN, Sklavounos A, Dutt A, Seed PT, Khajuria A.. J Med Virol. 2020 Aug 4. doi: 10.1002/jmv.26389. Online ahead of print.

Level of Evidence: 2 - Inception cohort studies

#### **BLUF**

This systematic review of 47 studies performed between December 1st, 2019 and June 2nd, 2020 (Figure 1) analyzed the impact of smoking on the severity of COVID-19. Authors found that:

1. Current smokers were at an increased risk of severe or critical COVID-19 but these individuals did not have increased in-hospital mortality (Figure 2C).
2. Patients with a history of smoking had an increased risk of severe COVID-19 as well as an increased in-hospital mortality, disease progression, and need for mechanical ventilation (Figure 3C).
3. The use of aggregated data prevented the authors from performing covariate analyses to determine the impact of age, gender, and other variables on outcomes for current and former smokers.

The review highlights the need for further investigation into the molecular underpinnings for the relationship between smoking and COVID-19 and emphasizes the necessity of public health interventions to promote and support smoking cessation.

## **ABSTRACT**

**BACKGROUND:** Various comorbidities represent risk factors for severe COVID-19. The impact of smoking on COVID-19 severity has been previously reported in several meta-analyses limited by small sample sizes and poor methodology. We aimed to rigorously and definitively quantify the effects of smoking on COVID-19 severity. **METHODS:** MEDLINE, Embase, CENTRAL and Web of Science were searched between December 1, 2019 and June 2, 2020. Studies reporting smoking status of hospitalised patients with different severities of disease and/or at least one clinical endpoint of interest (disease progression, ICU admission, need for mechanical ventilation and mortality) were included. Data were pooled using a random effects model. This study was registered on PROSPERO: CRD42020180920. **FINDINGS:** We analysed 47 eligible studies reporting on 32,849 hospitalised COVID-19 patients, with 8417 (25.6%) reporting a smoking history, comprising 1501 current smokers, 5676 former smokers and 1240 unspecified smokers. Current smokers had an increased risk of severe COVID-19 (RR 1.80, 95% CI 1.14-2.85;  $p=0.012$ ), and severe or critical COVID-19 (1.98, 1.16-3.38;  $p=0.012$ ). Patients with a smoking history had a significantly increased risk of severe COVID-19 (1.31, 1.12-1.54;  $p=0.001$ ), severe or critical COVID-19 (1.35, 1.19-1.53;  $p<0.0001$ ), in-hospital mortality (1.26, 1.20-1.32;  $p<0.0001$ ), disease progression (2.18, 1.06-4.49;  $p=0.035$ ), and need for mechanical ventilation (1.20, 1.01-1.42;  $p=0.043$ ). **CONCLUSIONS:** Patients with any smoking history are vulnerable to severe COVID-19 and worse in-hospital outcomes. In the absence of current targeted therapies, preventative and supportive strategies to reduce morbidity and mortality in current and former smokers are crucial. This article is protected by copyright. All rights reserved.

## FIGURES

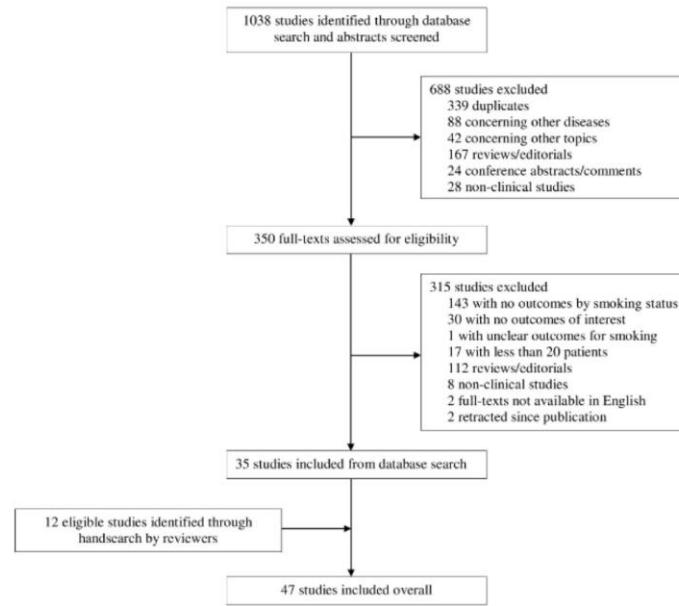


Figure 1. Flow diagram of selection of included studies.

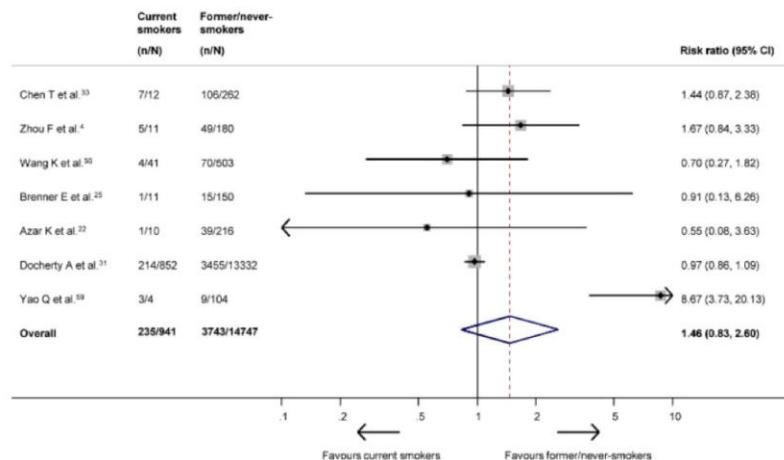


Figure 2C. Forest plot showing the effect of current smoking on mortality.

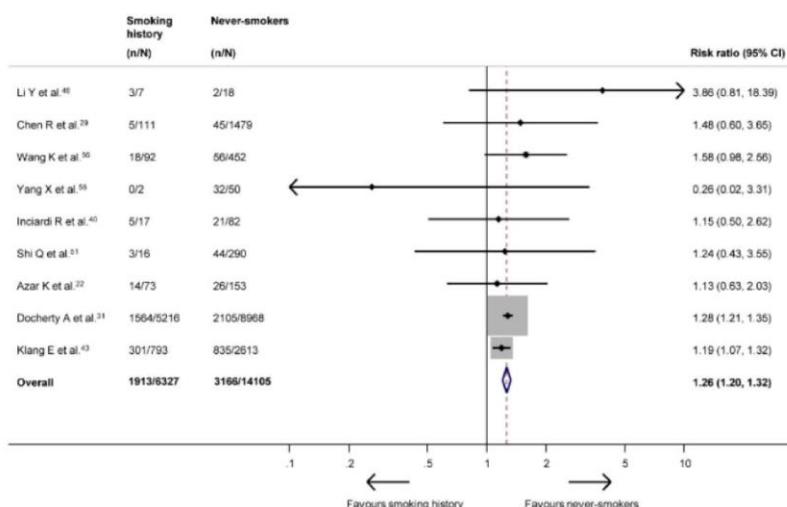


Figure 3C. Forest plot showing the effect of a smoking history on mortality.

## DYSPLASTIC CHANGES OF PERIPHERAL BLOOD CELLS IN COVID-19 INFECTION

Akcabelen YM, Gurlek Gokcebay D, Yarali N.. Turk J Haematol. 2020 Aug 19. doi: 10.4274/tjh.galenos.2020.2020.0342. Online ahead of print.

Level of Evidence: 5 - Case report

### BLUF

Pediatric hematologist/oncologists at the University of Health Sciences Ankara City Hospital in Ankara, Turkey discuss a case report of a 16-year-old female who presented initially with cough, dyspnea and anosmia, then subsequently tested positive for SARS-CoV-2 via real-time polymerase chain reaction (RT-PCR). Her peripheral blood smear revealed many giant platelets, vacuolated monocytes, and dysplastic neutrophils (Figure 1). Authors present this case to contribute to literature suggesting that dysplastic changes may be a feature of pediatric COVID-19.

### FIGURES

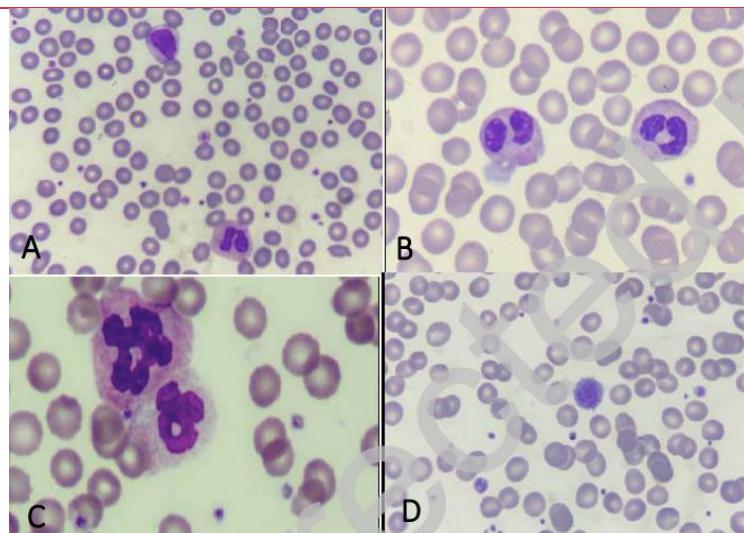


Figure 1. Dysplastic changes in peripheral blood (May-Grunewald-Giemsa stain; 100×), A: A reactive lymphocyte and pseudo Pelger-Huet anomaly of the neutrophil, B: Pseudo PelgerHuet anomaly of neutrophils, C: Lobulation anomaly of the neutrophils, D: A giant platelet.

## UNDERSTANDING THE PATHOLOGY

### AUTOPSY FINDINGS AND VENOUS THROMBOEMBOLISM IN PATIENTS WITH COVID-19: A PROSPECTIVE COHORT STUDY

Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schröder AS, Burdelski C, de Heer G, Nierhaus A, Frings D, Pfefferle S, Becker H, Bredereke-Wiedling H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Püschel K, Kluge S.. Ann Intern Med. 2020 Aug 18;173(4):268-277. doi: 10.7326/M20-2003. Epub 2020 May 6.

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

#### BLUF

Complete autopsies (including postmortem computed tomography [PCT], histopathologic and virologic analyses; Figures 1,3) of 12 deceased COVID-19 positive patients in Germany found deep vein thrombosis (DVT) in 7 patients (58%) despite low suspicion for DVT prior to death, and 4 of those patients ultimately died due to pulmonary embolisms. These findings suggest pathophysiology of COVID-19 coagulopathy may be implicated in mortality, and authors advocate for continued research regarding anti-thrombotic therapy in COVID-19 management.

#### SUMMARY

Additional key study findings include:

1. The most common comorbidities were coronary heart disease (50%) and asthma or chronic obstructive pulmonary disease (25%) (Table 1).
2. Histological analysis showed diffuse alveolar damage in 8 patients (67%) (Figure 3).
3. PCT showed reticular infiltration and severe bilateral density (Figure 1).

#### ABSTRACT

**Background:** The new coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused more than 210 000 deaths worldwide. However, little is known about the causes of death and the virus's pathologic features. **Objective:** To validate and compare clinical findings with data from medical autopsy, virtual autopsy, and virologic tests. **Design:** Prospective cohort study. **Setting:** Autopsies performed at a single academic medical center, as mandated by the German federal state of Hamburg for patients dying with a polymerase chain reaction-confirmed diagnosis of COVID-19. **Patients:** The first 12 consecutive COVID-19-positive deaths. **Measurements:** Complete autopsy, including postmortem computed tomography and histopathologic and virologic analysis, was performed. Clinical data and medical course were evaluated. **Results:** Median patient age was 73 years (range, 52 to 87 years), 75% of patients were male, and death occurred in the hospital ( $n = 10$ ) or outpatient sector ( $n = 2$ ). Coronary heart disease and asthma or chronic obstructive pulmonary disease were the most common comorbid conditions (50% and 25%, respectively). Autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom venous thromboembolism was not suspected before death; pulmonary embolism was the direct cause of death in 4 patients. Postmortem computed tomography revealed reticular infiltration of the lungs with severe bilateral, dense consolidation, whereas histomorphologically diffuse alveolar damage was seen in 8 patients. In all patients, SARS-CoV-2 RNA was detected in the lung at high concentrations; viremia in 6 of 10 and 5 of 12 patients demonstrated high viral RNA titers in the liver, kidney, or heart. **Limitation:** Limited sample size. **Conclusion:** The high incidence of thromboembolic events suggests an important role of COVID-19-induced coagulopathy. Further studies are needed to investigate the molecular mechanism and overall clinical incidence of COVID-19-related death, as well as possible therapeutic interventions to reduce it. **Primary Funding Source:** University Medical Center Hamburg-Eppendorf.

## FIGURES

Case Number	Age, y	Sex	Preexisting Medical Conditions	Treatment	BMI, kg/m <sup>2</sup>	Clinical Cause of Death	PMI, d	Cause of Death	Main Pathologic Findings	PMCT (Lungs)	Histology (Lungs)
1	52	Male	Obesity	CPR	38.8	Sudden cardiac death	1	PE, pneumonia	PE, DVT, pneumonia, obesity, cardiomegaly (640 g), splenomegaly (500 g), hepatomegaly (3880 g), shock organs (liver, kidneys), atherosclerosis	Diffuse bilateral pulmonary consolidations in each lobe	DAD: aPC, FB, GC, sparse HM, slight fibrosis Additional findings: Co, Thr DAD: aPC, HM, sparse LC Additional findings: focal Gra, CB, AB
2	70	Male	Parkinson disease, CHD, PAD, CKD	BSC	22.2	Respiratory failure, pneumonia	1	Pneumonia with bronchopneumonia	Pneumonia, CHD (stents in LAD and RCA, status post MI, coronary artery bypass), coagulopathies (with Parkin's syndrome), granular bronchitis, cardiomegaly (515 g), shock liver	No PMCT	
3	71	Male	AH, nicotine abuse, granulomatous pneumopathy	CA, MV	36.8	Respiratory failure, pneumonia	2	PE, pneumonia	PE, DVT, pneumonia, status post VATS (due to unspecked granuloma), CHD, anasarca, atherosclerosis	Emphysema; fine reticular pattern in each lobe; consolidations in the right lower and left lower lobes	DAD: SM, FB, aPC, HM, Additional findings: Thr
4	63	Male	T2DM, obesity, bronchial asthma	CA, MV, lysis of right ventricular thrombus, CPR	37.3	Cardiorespiratory failure, PE	1	PE, pneumonia	PE, DVT, pneumonia, obesity, cardiomegaly (605 g), ischemic colitis, shock liver	No PMCT	DAD: FB, aPC, HM, SM, Additional findings: HI, Thr
5	66	Male	CHD	CPR	25.3	Sudden cardiac death	2	Pneumonia	Pneumonia, DVT, CHD, status post MI	Consolidations in each lobe; reticular pattern in the right upper and lower lobes and in each left lobe	DAD: aPC, FB, HM, necrosis, LC Additional findings: surrounding small vessels, Thr
6	54	Female	Dementia, epilepsy, trisomy 21	BSC	29.6	Respiratory failure, aspiration pneumonia	1	Pneumonia	Pneumonia, kidney infarctions, PEG tube	Consolidations in the right upper and middle lobes and in parts of the left upper and lower lobes; ground glass opacities in the right upper and lower lobes and in the left upper lobe; reticular pattern in the right middle and lower lobes and in each left lobe	Gra, AB, Co (no DAD)
7	75	Female	Atrial fibrillation, CHD, nicotine abuse	NIV	26.3	Respiratory failure, viral pneumonia	4	Pneumonia	Pneumonia, lung emphysema, CHD, left cardiac dilatation, calcification of the mitral ring, cardiac pacemaker, atherosclerosis	Reticular pattern in each lobe; small areas of consolidation in the right lower, left upper, and left lower lobes	DAD: aPC, SM Additional findings: emphysema, Co, Gra, emphysema (no DAD)
8	82	Male	Parkinson disease, T2DM, CHD	BSC	27.8	Respiratory failure, viral pneumonia	1	Bronchopneumonia	Pneumonia, emphysema, DVT, CHD, status post ACVB, status post MI with left cardiac aneurysm, atherosclerosis	Emphysema; diffuse consolidations in each upper and lower lobe and in the left lower lobe; bilateral pleural effusion	
9	87	Female	Non-small cell lung cancer, COPD, CHD, CKD	BSC	15.4	Respiratory failure, viral pneumonia	4	Purulent bronchitis	Pneumonia, purulent bronchitis, CHD, status post MI, cachexia, bullous emphysema, NET in the lung, atherosclerosis	Emphysema; round tumor in the right lower lobe; small areas of consolidation in the right upper and lower lobes and in the left upper lobe; reticular pattern in the right upper and lower lobes and in each left lobe	Gra, AB, emphysema (no DAD) Additional findings: NET composed of small cells
10	84	Male	T2DM, AH, ulcerative colitis	BSC	20.7	Respiratory failure, viral pneumonia	5	Pneumonia, septic encephalopathy	Pneumonia, emphysema, septicemia, status post MI, atrophic kidneys	Reticular pattern in the right upper and lower lobes and in each left lobe; consolidations in the right middle and lower lobes and in each left lobe; ground glass opacities in the right upper and middle lobes and in parts of the left upper lobe; bilateral pleural effusion	Emphysema, Co, Gra, CB, fibrosis (no DAD)
11	85	Male	CHD, AH, bronchial asthma, atrial fibrillation	CA, MV, RRT	30.0	Cardiac arrest due to respiratory failure	2	Pneumonia	Pneumonia, DVT, minor PE, emphysema, CHD, cardiomegaly (650 g), atherosclerosis	Diffuse consolidations in each lobe; reticular pattern in the right middle and lower lobes and in each left lobe; ground glass opacities in the right upper and middle lobes and in the left upper lobe; bilateral pleural effusion	DAD: HM (spare), GC, aPC Additional findings: emphysema, Co, Gra
12	76	Male	Obesity	CA, MV, CPR	34.4	PE	3	PE	PE with lung infarctions, DVT, pneumonia, purulent tracheobronchitis, pneumonia, cardiomegaly (745 g), emphysema, obesity	No residual ventilation in either lung except for small areas in the right upper and middle lobes and in the left upper and lower lobes; bilateral pleural effusion	DAD: HM, aPC, fibrosis Additional findings: LC, PIC, HI, Thr, Co

Table 1. Patient characteristics and autopsy findings.

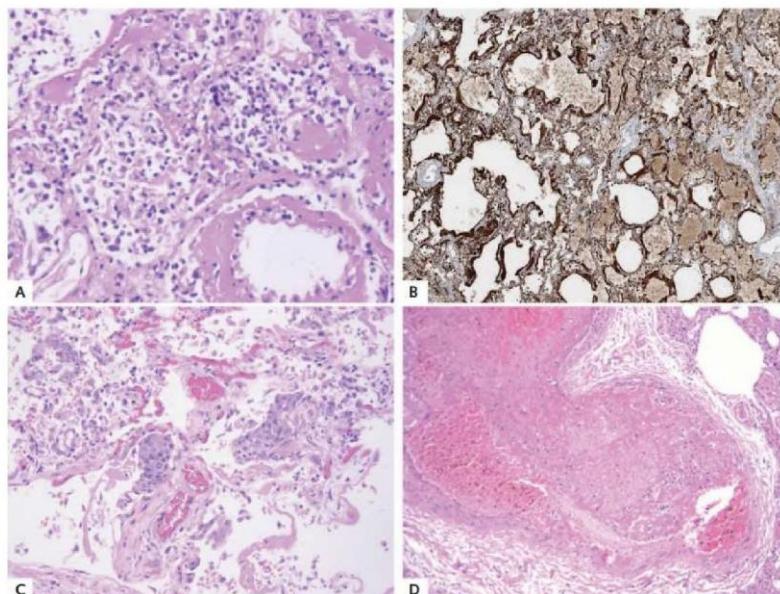


Figure 3. Histopathologic findings. A. Diffuse alveolar damage with hyaline membranes (case 4) (hematoxylin–eosin [H&E] stain; original magnification,  $\times 50$ ). B. Hyaline membranes (case 4) (cytokeratin E1/AE3 stain, original magnification  $\times 50$ ). C. Squamous metaplasia in the lung (case 5) (H&E stain; original magnification,  $\times 100$ ). D. Pulmonary embolism (case 1) (H&E stain; original magnification,  $\times 100$ ).

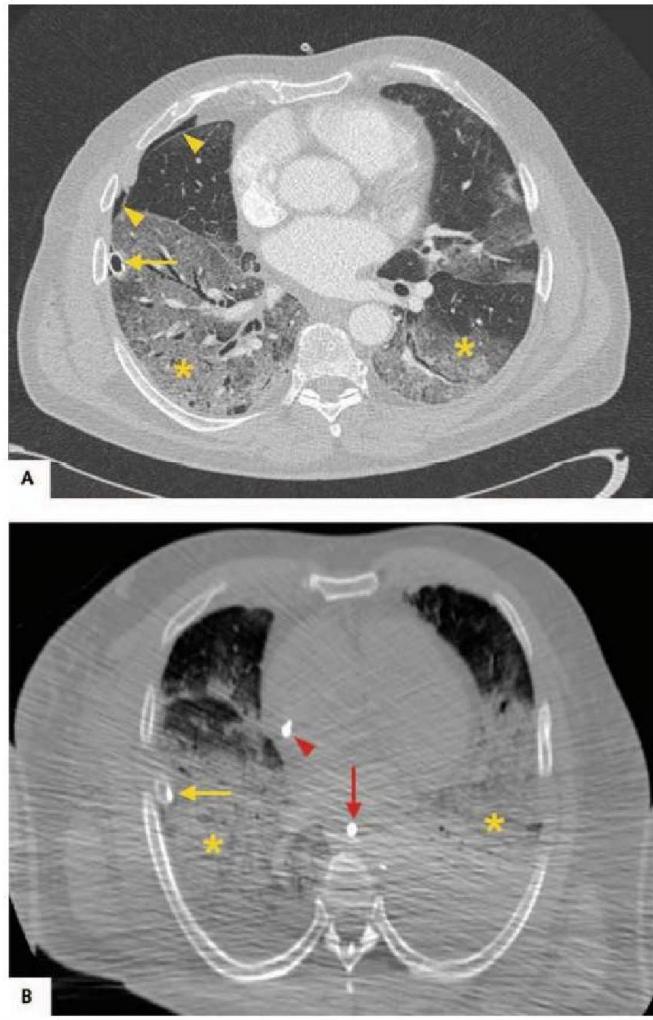


Figure 1. Antemortem versus postmortem computed tomography imaging (case 3).

Top. Contrast medium- enhanced computed tomography scan demonstrates the antemortem findings: bilateral ground glass opacities in the lower lobes of both lungs (yellow asterisks) and a chest tube (yellow arrow), which has been introduced to treat a pneumothorax (yellow arrowheads). Bottom. Computed tomography scan without contrast medium enhancement demonstrates the corresponding postmortem findings. For technical reasons, the postmortem image has a lower resolution.

To protect the staff from potential infection, bodies were scanned in a double-layer body bag with the arms positioned alongside the body. Although the findings correspond to the antemortem images, ground glass opacities in both lower lobes (yellow asterisks) and a chest tube (yellow arrow) are seen. In addition, a central venous line (red arrowhead) and gastric tube (red arrow) are visible.

# NOVEL INSIGHTS INTO THE TRANSMISSION OF SARS-COV-2 THROUGH THE OCULAR SURFACE AND ITS DETECTION IN TEARS AND CONJUNCTIVAL SECRETIONS: A REVIEW

Güemes-Villahoz N, Burgos-Blasco B, Vidal-Villegas B, Garcia-Feijoo J, Arriola-Villalobos P, Martínez-de-la-Casa JM, Diaz-Valle D, Konstas AG.. Adv Ther. 2020 Aug 18. doi: 10.1007/s12325-020-01442-7. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

## BLUF

Ophthalmologists from Spain and Greece critically appraise studies on ophthalmological transmission fo SARS-CoV-2 published before May 8, 2020 (Table 1). Authors reviewed viral ocular manifestations, ocular tropism and receptors, defense mechanism, and detection in tears/conjunctival secretions, all of which suggest that the eye plays a role in viral replication and transmission and improper eye protection particularly during aerosol creating procedures may increase the risk of transmission.

## ABSTRACT

SARS-CoV-2 is a highly transmissible virus that spreads mainly via person-to-person contact through respiratory droplets, or through contact with contaminated objects or surfaces from an infected person. At present we are passing through a phase of slow and painful understanding of the origin, epidemiological profile, clinical spectrum, and risk profile of the virus. To the best of our knowledge there is only limited and contradictory evidence concerning SARS-CoV-2 transmission through other routes. Importantly, the eye may constitute not only a potential site of virus replication but also an alternative transmission route of the virus from the ocular surface to the respiratory and gastrointestinal tract. It is therefore imperative to gain a better insight into the potential ophthalmological transmission route of the virus and establish directions on best practice and future models of care for ophthalmological patients. This review article critically evaluates available evidence on the ophthalmological mode of viral transmission and the value of earlier identification of the virus on the eye. More evidence is urgently needed to better evaluate the need for protective measures and reliable ocular diagnostic tests to diminish further pandemic spread.

## FIGURES

**Table 1 Summary of published articles presenting RT-PCR results from tears and conjunctival secretions**

From: [Novel Insights into the Transmission of SARS-CoV-2 Through the Ocular Surface and its Detection in Tears and Conjunctival Secretions: A Review](#)

References	Journal	Number of cases	RT-PCR+ in tear and conjunctival samples	Proportion of RT-PCR+	Conjunctivitis ocular symptoms	Patients with conjunctivitis and positive RT-PCR
Wu et al. [9]	JAMA Ophthalmology	28	2	7.1%	11 (39.2%)	2 (7.1%)
Zhou et al. [29]	Ophthalmology	121	3	2.5%	8 (6.6%)	1 (0.8%)
Xia et al. [5]	J. Medical Virology	30 (2 samples separated 2–3 days per eye)	1 (2 samples from the same patient)	3.3%	1 (3.33%)	1 (3.3%)
Zhang et al. [6]	MedRxiv	72	1	1.3%	2 (2.78%)	1 (1.3%)
Güemes-Villahoz et al. [28]	J. Medical Virology	36	2	5.5%	18 (50%)	1 (5.5%)

## MANAGEMENT

### ACUTE CARE

#### **HYDROXYCHLOROQUINE OR CHLOROQUINE FOR TREATMENT OR PROPHYLAXIS OF COVID-19: A LIVING SYSTEMATIC REVIEW**

Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM.. Ann Intern Med. 2020 Aug 18;173(4):287-296. doi: 10.7326/M20-2496. Epub 2020 May 27.

Level of Evidence: 2 - Systematic review of randomized trials or n-of-1 trials

#### **BLUF**

A systematic review (n= 23 studies published between December 2019 and May 2020) by authors affiliated with the University of Connecticut Health Outcomes, MedErgy HealthGroup Inc., and Universidad San Ignacio de Loyola investigates therapeutic use of hydroxychloroquine or chloroquine for adults or children with suspected COVID-19. They found that some patients on hydroxychloroquine or chloroquine exhibited only minor improvements in fevers and viral clearance (Table 1, 2), while others experienced adverse effects (namely, QTc prolongation; Table 3), suggesting data on the efficacy of these drugs in COVID-19 treatment is limited and varying.

#### **ABSTRACT**

**BACKGROUND:** Hydroxychloroquine and chloroquine have antiviral effects in vitro against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). **PURPOSE:** To summarize evidence about the benefits and harms of hydroxychloroquine or chloroquine for the treatment or prophylaxis of coronavirus disease 2019 (COVID-19). **DATA SOURCES:** PubMed (via MEDLINE), EMBASE (via Ovid), Scopus, Web of Science, Cochrane Library, bioRxiv, Preprints, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and the Chinese Clinical Trials Registry from 1 December 2019 until 8 May 2020. **STUDY SELECTION:** Studies in any language reporting efficacy or safety outcomes from hydroxychloroquine or chloroquine use in any setting in adults or children with suspected COVID-19 or at risk for SARS-CoV-2 infection. **DATA EXTRACTION:** Independent, dually performed data extraction and quality assessments. **DATA SYNTHESIS:** Four randomized controlled trials, 10 cohort studies, and 9 case series assessed treatment effects of the medications, but no studies evaluated prophylaxis. Evidence was conflicting and insufficient regarding the effect of hydroxychloroquine on such outcomes as all-cause mortality, progression to severe disease, clinical symptoms, and upper respiratory virologic clearance with antigen testing. Several studies found that patients receiving hydroxychloroquine developed a QTc interval of 500 ms or greater, but the proportion of patients with this finding varied among the studies. Two studies assessed the efficacy of chloroquine; 1 trial, which compared higher-dose (600 mg twice daily for 10 days) with lower-dose (450 mg twice daily on day 1 and once daily for 4 days) therapy, was stopped owing to concern that the higher dose therapy increased lethality and QTc interval prolongation. An observational study that compared adults with COVID-19 receiving chloroquine phosphate 500 mg once or twice daily with patients not receiving chloroquine found minor fever resolution and virologic clearance benefits with chloroquine. **LIMITATION:** There were few controlled studies, and control for confounding was inadequate in observational studies. **CONCLUSION:** Evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19 is very weak and conflicting. **PRIMARY FUNDING SOURCE:** Agency for Healthcare Research and Quality.

## FIGURES

**Table 1.** Effect of Hydroxychloroquine Reported in Controlled Studies

Study, Year (Reference)	Type	Risk of Bias	Absolute Effect of Hydroxychloroquine Versus Control (95% CI)	Strength of Evidence
<b>All-cause mortality</b>				
Chen et al, 2020 (15)	RCT	Some concerns	0/15 vs. 0/15; absolute RD, 0% (NA)	Insufficient
Barbosa et al, 2020 (21)	Cohort	Critical	4/31 vs. 1/32; absolute RD, 9.8% (-3.5% to 23.3%)	
Mahévas et al, 2020 (22)	Cohort	Moderate	3/84 vs. 4/97; absolute RD, -0.6% (-6.2% to 5.1%)	
Magagnoli et al, 2020 (23)	Cohort	Serious	27/97 vs. 18/158; absolute RD, 16.4% (6.2% to 26.6%)*	
Yu et al, 2020 (24)	Cohort	No information	9/48 vs. 238/520; absolute RD, -27% (-38.9% to -15.2%)*	
Mallat et al, 2020 (26)	Cohort	Serious	0/23 vs. 0/11 (0%); absolute RD, 0% (NA)	
Membriollo de Novales et al, 2020 (27)	Cohort	Critical	27/123 vs. 21/43; absolute RD, -26.9% (-43.5% to -10.3%)*	
Geleris et al, 2020 (29)	Cohort	Moderate	157/811 vs. 75/565; absolute RD, 6.1% (2.2% to 10%)*	
<b>Composite of intubation or death</b>				
Geleris et al, 2020 (29)	Cohort	Moderate	262/811 vs. 84/565; absolute RD, 17.4% (13.1% to 21.8%)*	Insufficient
<b>Composite of ICU admission within 7 days or death</b>				
Mahévas et al, 2020 (22)	Cohort	Moderate	16/84 vs. 21/97; absolute RD, -2.6% (-14.3% to 9.1%)	Insufficient
<b>Need for mechanical ventilation</b>				
Magagnoli et al, 2020 (23)	Cohort	Serious	12/90 vs. 25/177; absolute RD, -0.8% (-9.5% to 7.9%)	Insufficient
Mallat et al, 2020 (26)	Cohort	Serious	0/23 vs. 0/11; absolute RD, 0% (NA)	
Geleris et al, 2020 (29)	Cohort	Moderate	154/811 vs. 26/565; absolute RD, 14.4% (11.2% to 17.6%)*	
<b>Severe disease progression</b>				
Chen et al, 2020 (15)	RCT	Some concerns	1/15 vs. 0/15; absolute RD, 6.7% (-6.0% to 19.3%)	Insufficient
Chen et al, 2020 (16)	RCT	Some concerns	0/31 vs. 4/31; absolute RD, -12.9% (-24.7% to -1.1%)*	
Barbosa et al, 2020 (21)	Cohort	Critical	Respiratory support level: 0.63 points ( $\pm 0.79$ ) vs. 0.16 points ( $\pm 0.64$ ); MD, 0.47 (0.11 to 0.83)*	
Mahévas et al, 2020 (22)	Cohort	Moderate	ARDS: 24/84 vs. 23/95; absolute RD, 4.4% (-8.6% to 17.3%)	
Mallat et al, 2020 (26)	Cohort	Serious	High-flow oxygen therapy: 0/23 vs. 0/11; absolute RD, 0% (NA)	
<b>Symptom resolution</b>				
Chen et al, 2020 (15)	RCT	Some concerns	Fever: 1 vs. 1 day; MD, 0 days (NA)	Insufficient
Chen et al, 2020 (16)	RCT	Some concerns	Fever: 2.2 d ( $\pm 0.4$ ) vs. 3.2 d ( $\pm 1.3$ ); MD, -1 d (-1.5 to -0.5)*	
Tang et al, 2020 (19)	RCT	High	Cough: 2.0 d ( $\pm 0.2$ ) vs. 3.1 d ( $\pm 1.5$ ); MD, -1.1 d (-1.6 to -0.6)*	
			Composite symptom resolution: 32/64 vs. 24/55; absolute RD, 6.4% (-11.6% to 24.3%)	
<b>Progression of pulmonary lesions on CT</b>				Low
Chen et al, 2020 (15)	RCT	Some concerns	5/15 vs. 7/15; absolute RD, -13.3% (-48.1% to 21.4%)	
Chen et al, 2020 (16)	RCT	Some concerns	2/31 vs. 9/31; absolute RD, -22.6% (-40.8% to -4.4%)*	
<b>Improvement in pulmonary lesions on CT</b>				Insufficient
Chen et al, 2020 (16)	RCT	Some concerns	25/31 vs. 17/31; absolute RD, 25.8% (3.4% to 48.2%)*	
<b>Upper respiratory virologic clearance</b>				Insufficient
Chen et al, 2020 (15)	RCT	Some concerns	Day 7: 13/15 vs. 14/15; absolute RD, -6.7% (-28% to 14.7%)	
Tang et al, 2020 (19)	RCT	High	Day 14: 15/15 vs. 15/15; absolute RD, 0% (NA)	
Gautret et al, 2020 (20)	Cohort	Critical	Day 23: 53/75 vs. 56/75; absolute RD, -4% (-18.3% to 10.3%)	
Mallat et al, 2020 (26)	Cohort	Serious	Day 6: 14/20 vs. 2/16; absolute RD, 57.6% (31.8% to 83.3%)*	
			Day 14: 11/23 vs. 10/11; absolute RD, -43.1% (-69.6% to -16.5%)*	

ARDS = acute respiratory distress syndrome; CT = computed tomography; ICU = intensive care unit; MD = mean difference; NA = not applicable;

RCT = randomized controlled trial; RD = risk difference.

\* Statistically significant.

**Table 2.** Effect of Chloroquine Reported in Controlled Studies\*

Study, Year (Reference)	Type	Risk of Bias	Absolute Effect of Chloroquine Versus Control (95% CI)	Strength of Evidence
<b>All-cause mortality</b>				
Borba et al, 2020 (17, 18)	RCT	High	16/41 vs. 6/40; absolute RD, 24% (5.4% to 42.6%)*†	Insufficient
Huang et al, 2020 (28)	Cohort	Critical	0/197 vs. 0/176; absolute RD, 0% (NA)	
<b>ICU admission</b>				
Borba et al, 2020 (17, 18)	RCT	High	1/2 vs. 1/11; absolute RD, 40.9% (-30.4% to 112.3%)	Insufficient
Huang et al, 2020 (28)	Cohort	Critical	0/197 vs. 0/176; absolute RD, 0% (NA)	
<b>Need for mechanical ventilation</b>				
Borba et al, 2020 (17, 18)	RCT	High	4/20 vs. 2/19; absolute RD, 9.5% (-12.8% to 31.8%)	Insufficient
<b>Need for oxygen support</b>				
Borba et al, 2020 (17, 18)	RCT	High	3/15 vs. 1/13; absolute RD, 12.3% (-12.6% to 37.2%)	Insufficient
<b>Symptom resolution</b>				
Huang et al, 2020 (28)	Cohort	Critical	Time to normal body temperature (GM): 1.2 vs. 1.9 d; MD, -0.7 d (NR)	Insufficient
<b>Upper respiratory virologic clearance</b>				
Borba et al, 2020 (17, 18)	RCT	High	Day 4: 0/14 vs. 1/12; absolute RD, -8.3% (-24% to 7.3%)	Insufficient
Huang et al, 2020 (28)	Cohort	Critical	Day 10: 180/197 vs. 101/176; absolute RD, 34% (25.7% to 42.3%)*†	
			Day 14: 189/197 vs. 140/176; absolute RD, 16.4% (9.8% to 23%)†	

GM = geometric mean; ICU = intensive care unit; MD = mean difference; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RD = risk difference.

\* Borba et al compared high-dose versus low-dose chloroquine; Huang et al compared chloroquine versus nonchloroquine control.

† Statistically significant.

**Table 3.** Reported Harms and Adverse Events for Hydroxychloroquine and Chloroquine in Controlled Studies

Study, Year (Reference)	Type	Risk of Bias	Absolute Effect of Hydroxychloroquine/Chloroquine Versus Control, or High- Versus Low-Dose Chloroquine (95% CI)	Strength of Evidence
<b>Severe adverse events</b>				Insufficient
Chen et al, 2020 (16) Huang et al, 2020 (28)*	RCT Cohort	Some concerns Critical	0/31 vs. 0/31; absolute RD, 0% (NA) 0/197 vs. 0/176; absolute RD, 0% (NA)	
<b>Adverse events</b>				Insufficient
Chen et al, 2020 (15) Chen et al, 2020 (16) Tang et al, 2020 (19) Huang et al, 2020 (28)*	RCT RCT RCT Cohort	Some concerns Some concerns High Critical	4/15 vs. 3/15; absolute RD, 6.7% (-23.5% to 36.8%) 2/31 vs. 0/31; absolute RD, 6.5% (-2.2% to 15.1%) 21/70 vs. 7/80; absolute RD, 21.3% (8.9% to 33.6%)† 53/197 vs. 57/176; absolute RD, -5.5% (-14.8% to 3.8%)	
<b>Diarrhea</b>				Insufficient
Chen et al, 2020 (15) Tang et al, 2020 (19) Huang et al, 2020 (28)*	RCT RCT Cohort	Some concerns High Critical	2/15 vs. 0/15; absolute RD, 13.3% (-3.9% to 30.5%) 7/70 vs. 0/80; absolute RD, 10% (3% to 17%)† 6/197 vs. 11/176; absolute RD, -3.2% (-7.5% to 1.1%)	
<b>Abnormal liver function</b>				Insufficient
Chen et al, 2020 (15)	RCT	Some concerns	1/15 vs. 1/15; absolute RD, 0% (-17.9% to 17.9%)	
<b>Rash</b>				Insufficient
Chen et al, 2020 (16) Huang et al, 2020 (28)*	RCT Cohort	Some concerns Critical	1/31 vs. 0/31; absolute RD, 3.1% (-2.9% to 9.2%) 1/197 vs. 0/176; absolute RD, 0.5% (-0.5% to 1.5%)	
<b>Headache</b>				Insufficient
Chen et al, 2020 (16) Huang et al, 2020 (28)*	RCT Cohort	Some concerns Critical	1/31 vs. 0/31; absolute RD, 3.1% (-2.9% to 9.2%) 3/197 vs. 3/176; absolute RD, 0.2% (-2.7% to 2.4%)	
<b>QTc prolongation</b>				Insufficient
Mahévas et al, 2020 (22)	Cohort	Moderate	7/84 vs. 0/97; absolute RD, 8.3% (2.4% to 14.2%)†	
<b>Severe QTc prolongation (&gt;500 ms)</b>				Insufficient
Borba et al, 2020 (17, 18)‡ Mahévas et al, 2020 (22)	RCT Cohort	High Moderate	7/37 vs. 4/36; absolute RD, 7.8% (-8.5% to 24.1%) 1/84 vs. 0/97; absolute RD, 1.2% (-1.1% to 3.5%)	
<b>Ventricular tachycardia</b>				Insufficient
Borba et al, 2020 (17, 18)‡	RCT	High	2/37 vs. 0/36; absolute RD, 5.4% (-1.9% to 12.7%)	
<b>Anemia</b>				Insufficient
Chen et al, 2020 (15) Borba et al, 2020 (17, 18)‡	RCT RCT	Some concerns High	0/15 vs. 1/15; absolute RD, -6.7% (-19.3% to 6%) Decrease in hemoglobin level >3 g/dL or ≥30% from baseline: 7/24 vs. 4/18; absolute RD, 6.9% (-19.5% to 33.4%)	
<b>Elevated serum creatinine level</b>				Insufficient
Chen et al, 2020 (15) Borba et al, 2020 (17, 18)‡	RCT RCT	Some concerns High	0/15 vs. 1/15; absolute RD, -6.7% (-19.3% to 6%) Serum creatinine level ≥30% from baseline: 7/14 vs. 6/19; absolute RD, 18.4% (-15.1% to 51.9%)	

NA = not applicable; RCT = randomized controlled trial; RD = risk difference.

\* Huang et al compared chloroquine versus nonchloroquine control.

† Statistically significant.

‡ Borba et al compared high-dose versus low-dose chloroquine.

## INFERENCE FROM LONGITUDINAL LABORATORY TESTS CHARACTERIZES TEMPORAL EVOLUTION OF COVID-19-ASSOCIATED COAGULOPATHY (CAC)

Pawlowski C, Wagner T, Puranik A, Murugadoss K, Loscalzo L, Venkatakrishnan AJ, Pruthi RK, Houghton DE, O'Horo JC, Morice WG, Williams AW, Gores GJ, Halamka J, Badley Md AD, Barnathan ES, Makimura H, Khan N, Soundararajan V.. Elife. 2020 Aug 17;9:e59209. doi: 10.7554/elife.59209. Online ahead of print.

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

### BLUF

A retrospective cohort study using Electronic Health Record (EHR) data from the Mayo Clinic Health System in Rochester, Minnesota from February 15, 2020 to May 28, 2020 found COVID-19 positive patients (confirmed via polymerase chain reaction [PCR]; n=246) had higher plasma fibrinogen levels and lower platelet counts than COVID-19 negative patients (n=13,666) at time of testing but as the infection progressed COVID-19 positive patients showed declining fibrinogen and increased platelet counts (Figure 3), while 31% (n=76/246) developed at least one clot diagnosis (Table 3). Authors suggest that understanding the evolution and range of COVID-19 associated coagulopathy (CAC) may provide insight for advancement in thromboprophylaxis therapy.

### ABSTRACT

Temporal inference from laboratory testing results and triangulation with clinical outcomes extracted from unstructured EHR provider notes is integral to advancing precision medicine. Here, we studied 246 SARS-CoV-2 PCR-positive (COVIDpos) patients and propensity-matched 2,460 SARS-CoV-2 PCR-negative (COVIDneg) patients subjected to around 700,000 lab tests cumulatively across 194 assays. Compared to COVIDneg patients at the time of diagnostic testing, COVIDpos patients tended to have higher plasma fibrinogen levels and lower platelet counts. However, as the infection evolves, COVIDpos patients distinctively show declining fibrinogen, increasing platelet counts, and lower white blood cell counts. Augmented curation of EHRs suggests that only a minority of COVIDpos patients develop thromboembolism, and rarely, disseminated intravascular coagulopathy (DIC), with patients generally not displaying platelet reductions typical of consumptive coagulopathies. These temporal trends provide fine-grained resolution into COVID-19 associated coagulopathy (CAC) and set the stage for personalizing thromboprophylaxis.

## FIGURES

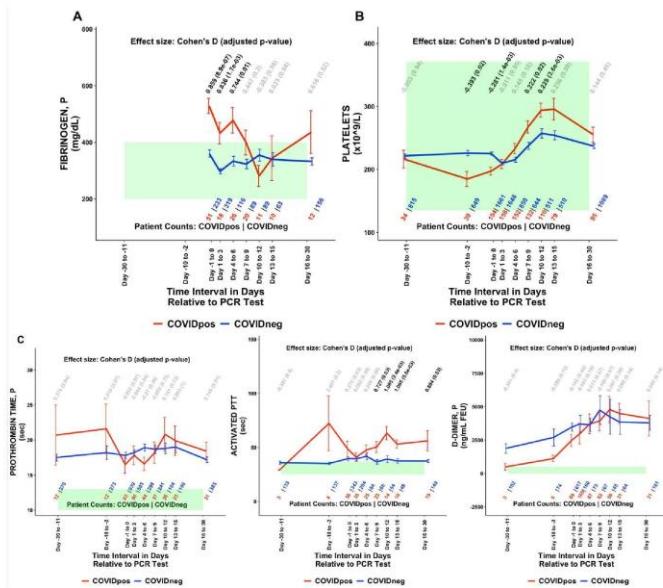


Figure 3. COVID-19 positive (COVIDpos) patients show distinctly opposite temporal trends in fibrinogen and platelet counts starting at the time of diagnosis. Longitudinal trends of COVIDpos versus COVID-19 negative (COVIDneg) (matched) patients for the following lab tests: (A) Fibrinogen, plasma, (B) Platelets, (C) Other coagulation-related tests including prothrombin time (PT), activated partial thromboplastin time (aPTT), and D-dimers. For any windows of time during which at least three patients in each cohort had test results, data is shown as mean with standard errors. The normal range for each lab test is shaded in green. Values given horizontally along the top of the plot are Cohen's D statistics comparing the COVIDpos and COVIDneg (matched) cohorts along with BH-adjusted Mann-Whitney test p-values. Significant differences (adjusted p-value less than 0.05) are shown in black, while non-significant values are shown in gray. Values given horizontally along the bottom of the plot are the numbers of patients in the COVIDpos and COVIDneg cohorts, respectively (i.e. # COVIDpos | # COVIDneg). For certain lab tests, some data points are missing because these time windows had fewer than 3 data points in the COVIDpos cohort.

Clotting Phenotype	Cohort 1: COVID <sub>pos</sub> with longitudinal data	Cohort 2: COVID <sub>pos</sub> without longitudinal data	Cohort 3: Complete COVID <sub>pos</sub> cohort
<i>Deep vein thrombosis</i>	<b>47</b> [19%]	<b>6</b> [0.30%]	<b>53</b> [2.4%]
<i>Pulmonary embolism</i>	<b>22</b> [8.9%]	<b>9</b> [0.45%]	<b>31</b> [1.4%]
<i>Myocardial infarction</i>	<b>10</b> [4.1%]	<b>8</b> [0.40%]	<b>18</b> [0.81%]
<i>Venous thromboembolism</i>	<b>7</b> [2.8%]	<b>0</b>	<b>7</b> [0.31%]
<i>Thrombotic stroke</i>	<b>2</b> [0.81%]	<b>2</b> [0.10%]	<b>4</b> [0.18%]
<i>Cerebral venous thrombosis</i>	<b>0</b>	<b>0</b>	<b>0</b>
<i>Disseminated intravascular coagulation</i>	<b>5</b> [2.0%]	<b>0</b>	<b>5</b> [0.22%]
<b>Total Unique Patients with Clot</b>	<b>76</b> [31%]	<b>25</b> [1.3%]	<b>101</b> [4.5%]
<b>Total Patients</b>	<b>246</b>	<b>1,986</b>	<b>2,232</b>

Table 3. Prevalence of thrombotic phenotypes after clinical presentation in COVIDpos patients with and without available longitudinal lab testing data. For each clotting phenotype listed, a BERT-based neural network was used to extract diagnostic sentiment from individual electronic health record (EHR) patient notes in which the phenotype (or a synonym thereof) was present. This automated curation was applied to clinical notes for each patient from Day = -1 (clinical presentation) to Day = 30 (end of the study period) relative to the PCR testing date In bold: absolute number of patients with each phenotype; in brackets: percentage of all patients in each cohort with the given specific thrombotic phenotype.

### EARLY DETECTION OF DEEP VEIN THROMBOSIS IN PATIENTS WITH CORONAVIRUS DISEASE 2019: WHO TO SCREEN AND WHO NOT TO WITH DOPPLER ULTRASOUND?

Ierardi AM, Coppola A, Fusco S, Stellato E, Aliberti S, Andrisani MC, Vespro V, Arrichiello A, Panigada M, Monzani V, Grasselli G, Venturini M, Rehani B, Peyvandi F, Pesenti A, Blasi F, Carrafiello G.. J Ultrasound. 2020 Aug 18. doi: 10.1007/s40477-020-00515-1. Online ahead of print.

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

#### BLUF

A cohort study by radiologists in Spain found an incidence of deep vein thrombosis (DVT) of 10.7% among 234 symptomatic COVID-19 patients who underwent Doppler ultrasound (DUS), with 1.6% of DVTs among moderate COVID-19 patients (1/60) and 13.8% DVTs among severely/critically ill COVID-19 patients (24/174). Further, several respiratory measures (fraction of inspired oxygen, respiratory rate, etc), heparin administration, and certain laboratory findings (interleukin 6, D-dimer, C-reactive protein, etc) were correlated with DVT (Table 3, Figures 4,5). Given these findings, the authors suggest that DUS may be a useful screening tool for early DVT identification, especially among severe COVID-19 patients.

#### ABSTRACT

**PURPOSE:** Aim of the study is to evaluate the incidence of DVT in COVID-19 patients and its correlation with the severity of the disease and with clinical and laboratory findings. **METHODS:** 234 symptomatic patients with COVID-19, diagnosed according to the World Health Organization guidelines, were included in the study. The severity of the disease was classified as moderate, severe and critical. Doppler ultrasound (DUS) was performed in all patients. DUS findings, clinical, laboratory's and therapeutic variables were investigated by contingency tables, Pearson chi square test and by Student t test and Fisher's exact test. ROC curve analysis was applied to study significant continuous variables. **RESULTS:** Overall incidence of DVT was 10.7% (25/234): 1.6% (1/60) among moderate cases, 13.8% (24/174) in severely and critically ill patients. Prolonged bedrest and intensive care unit admission were significantly associated with the presence of DVT (19.7%). Fraction of inspired oxygen, P/F ratio, respiratory rate, heparin administration, D-dimer, IL-6, ferritin and CRP showed correlation with DVT. **CONCLUSION:** DUS may be considered a useful and valid tool for early identification of DVT. In less severely affected patients, DUS as screening of DVT might be unnecessary. High rate of DVT found in severe patients and its correlation with respiratory parameters and some significant laboratory findings suggests that these can be used as a screening tool for patients who should be getting DUS.

#### FIGURES

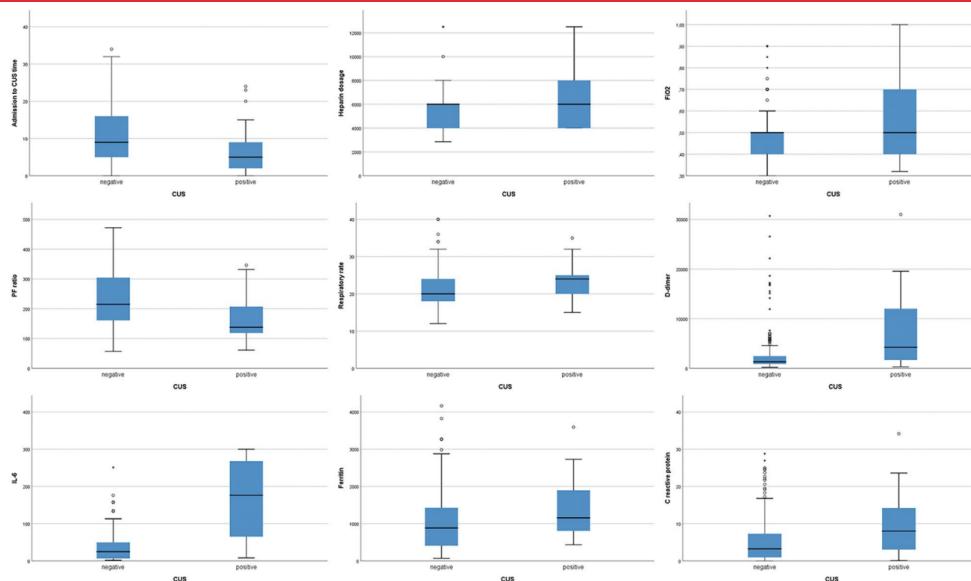


Figure 4. Boxplot for significant continuous variables

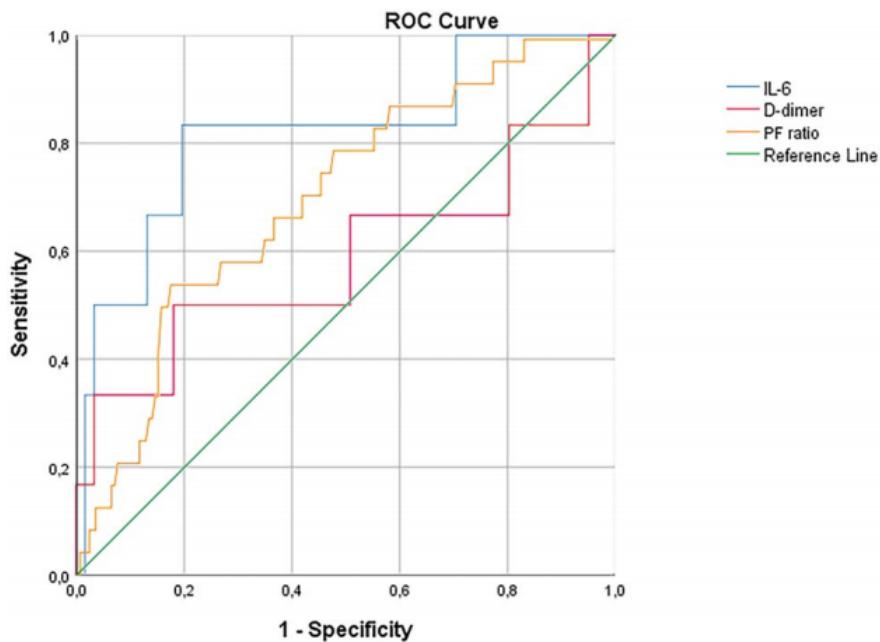


Fig. 5 ROC curve for significant continuous variables with  $\text{AUC}>0.7$

Variable	AUC	Cutoff	Sensitivity	Specificity
Admission to DUS time (days)	0.661	9.5	0.760	0.490
Heparin dosage (UI)	0.611	5350	0.619	0.470
$\text{FiO}_2$	0.638	0.525	0.478	0.768
PF ratio	0.701	292.5	0.917	0.292
Respiratory rate (breaths per minute)	0.637	19	0.880	0.314
D-dimer ( $\mu\text{g/mL}$ )	0.707	2128	0.680	0.706
IL-6 (pg/mL)	0.820	64.95	0.833	0.806
Ferritin (ng/mL)	0.663	907.5	0.708	0.515
C reactive protein (mg/L)	0.659	4.1	0.720	0.570

Table 3 ROC curve analysis for significant continuous variables at student t test

## NEUROLOGY

### NOT A STRING, NOT A TANGLE, NOT AN ANEURYSM : EMERGING PATTERN OF LARGE PARENCHYMAL BLEEDING IN YOUNGER PATIENTS ASSOCIATED WITH ABNORMAL VESSELS ON IMAGING

Nicholson P, Gao M, Radovanovic I, Mendes-Pereira V, Hodaie M, Pikula A, Krings T.. Clin Neuroradiol. 2020 Aug 19. doi: 10.1007/s00062-020-00944-9. Online ahead of print.

Level of Evidence: 4 - Case-series

#### BLUF

A prospective study conducted at Toronto Western Hospital in Ontario, Canada from April 1 to May 21, 2020 by researchers affiliated with neurology discuss 7 COVID-19 negative patients (aged 30-68 years, median=48 years) found to have "spot on a string sign" (SOAS; a peculiar spot-sign connected to a vessel) correlated with acute intracranial hemorrhage on computed tomography angiogram (CTA) brain (Figures 1, 2, 3). Authors suggest these unusual imaging findings may represent a direct effect of SARS-CoV-2 despite negative COVID-19 diagnostic tests in these patients (owing to poor sensitivity of nasopharyngeal swab testing) and urge clinicians to be vigilant for this phenomenon.

## ABSTRACT

PURPOSE: Intracerebral hemorrhage (ICH) accounts for up to 20% of all strokes, and there is a high rate of associated morbidity and mortality. Computed tomography (CT) findings, such as a spot sign have been shown to be an independent predictor of poor outcome. We have recently encountered a succession of ICH patients who presented with a peculiar imaging finding, which we term the spot on a string sign. This is a rare imaging finding, and interestingly, all these patients presented to our institution over the last few weeks. METHODS: This was a single high-volume center series of patients who presented to our institution between 1 April and 21 May 2020. All patients underwent initial non-contrast CT brain and subsequent CT angiography (CTA). We also present laboratory and clinical data. Our primary measure was the presence of the spot on a string sign on the CTA. We also report the clinical course of these patients. RESULTS: In this study seven large-volume ICH patients with this imaging sign were identified, with a median age of 48 years (range 30-68 years). All had tested negative for coronavirus disease 19 (COVID-19). CONCLUSION: We have described an unusual imaging finding in a cohort of younger patients with large-volume ICH, all of whom presented in a 2-month period to a high-volume neurovascular unit. The cause of these ICH presentations and associated imaging findings are unclear, but we encourage other clinicians to be aware of and vigilant for this rare phenomenon, especially in younger patients with such a bleeding pattern.

## FIGURES

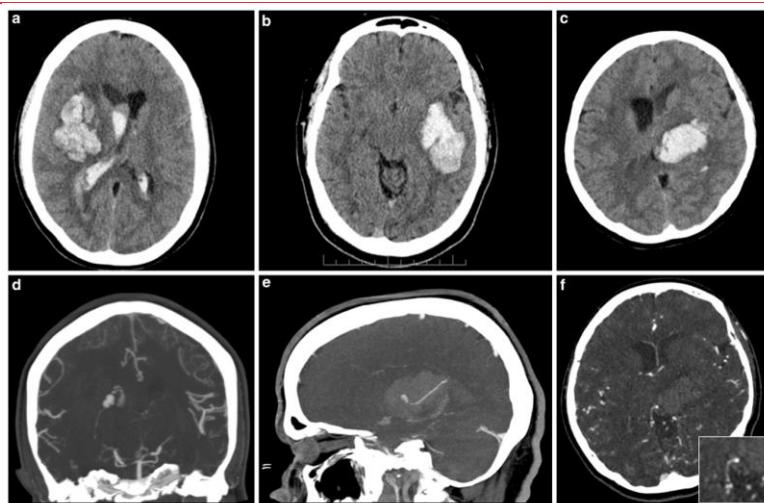


Figure 1. Representative images from three patients: (a, d): patient 1: 30-year-old female, axial non-contrast CT (top row) showing a right frontal parenchymal hematoma with intraventricular extension. Coronal CTA (bottom row) showing a tortuous, dilated lenticulostriatal vessel coursing to the hematoma with a focal aneurysmal portion of the vessel distally, giving a spot on a string (SOAS) sign. (b, e): Patient 2: 42-year-old male, axial non-contrast CT (top row) showing a left temporal parenchymal hematoma, ventricular extension is not shown. Sagittal CTA (bottom row) showing a dilated distal MCA branch coursing into the hematoma with a SOAS sign. (c, f): Patient 5: 54-year-old female, axial non-contrast CT (top row) showing a large parenchymal hematoma centered on the left thalamus. Axial CTA (bottom row) showing a SOAS sign arising from a perforator artery arising from the right posterior cerebral artery.

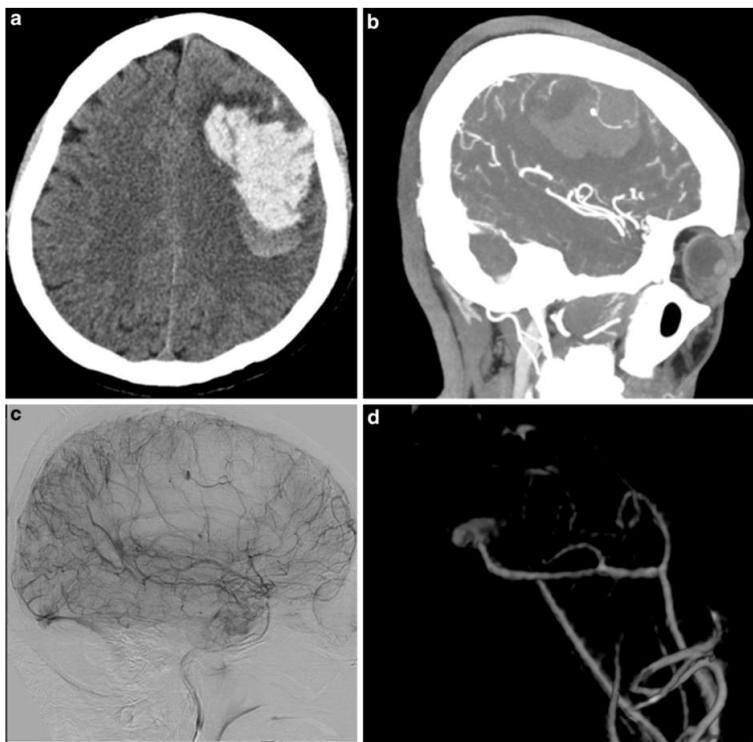


Figure 2. Images from patient 3, clockwise from top left: (a) non-contrast CT showing a large left frontal hematoma with some layering of blood products within the hematoma. (b) CTA showing a left MCA branch with a SOAS sign coursing toward the hematoma. (c) Digital subtraction angiogram showing an aneurysmal dilatation of superior division branch of the left MCA, corresponding to the abnormal vessel seen on the CTA. (d) Volume-rendered 3-D reconstruction of the abnormal vessel, showing more clearly the aneurysmal “blown out” appearance of the vessel. This corresponded to the vessel wall disruption seen on the pathological specimen following surgical resection (not shown).

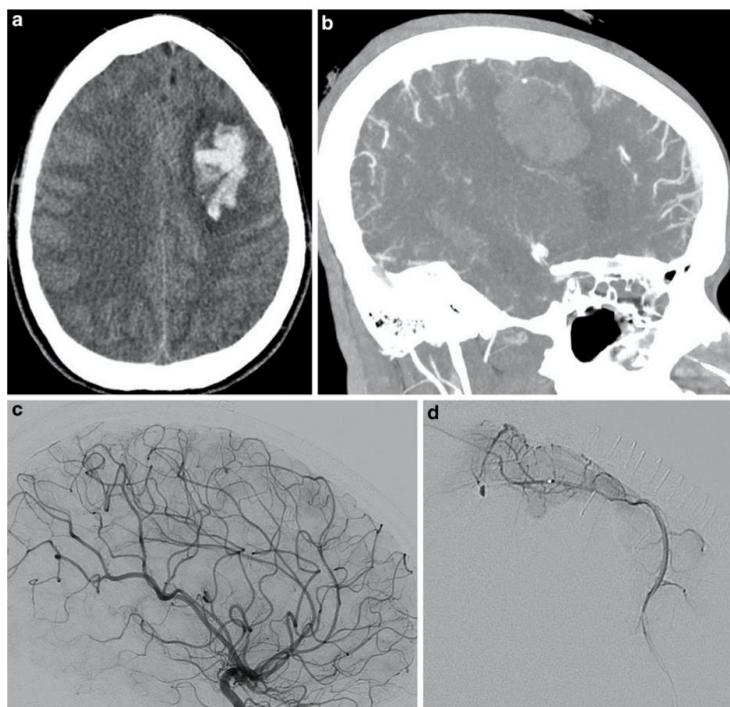


Figure 3. Images from patient 6, clockwise from top left: a non- contrast CT showing a left frontal parenchymal hematoma. There was also intraventricular extension (not shown). b Sagittal maximal intensity projection (MIP) from CTA showing a spot on a string (SOAS) sign coursing along the edge of the hematoma. c, d Left ICA injection, lateral view (c), and magnified microcatheter injection s(d) of the left callosomarginal artery in the same projection, showing the aneurysmal segment of the vessel more distally, with some contrast medium stagnation within it.

## MEDICAL SUBSPECIALTIES

### HEMATOLOGY AND ONCOLOGY

#### STUDIES ON HEMOSTASIS IN COVID-19 DESERVE CAREFUL REPORTING OF THE LABORATORY METHODS, THEIR SIGNIFICANCE AND THEIR LIMITATIONS

Hardy M, Douxfils J, Bareille M, Lessire S, Gouin-Thibault I, Fontana P, Lecompte T, Mullier F.. *J Thromb Haemost*. 2020 Aug 13. doi: 10.1111/jth.15061. Online ahead of print.

Level of Evidence: Other - Expert Opinion

#### BLUF

Authors from several institutions in Belgium, including the Namur Thrombosis and Hemostasis Center (NTHC), discuss and critique the report of Nougier et al. 2020, which studied the thrombin generation and fibrinolysis profiles of COVID-19 patients on prophylactic heparin. The authors pose several methodological approaches (illustrated below) that Nougier et al. 2020 and similar studies on hemostasis in COVID-19 should follow, highlighting the importance of reporting all study methods and potential limitations to readers.

#### SUMMARY

The authors posed the following while reviewing the observational study of Nougier et al. 2020:

- The importance in specifying the type of heparin used (UFH or LMWH) as heparin plasma levels exist between heparin testing kits. For instance, the addition of dextran sulphate leads to an overestimation of heparin levels through displacement of heparin from plasma proteins (AT, APR, PF4)
- Unfractionated and Low molecular weight heparin (UFH and LMWH respectively) must be differentiated as they have different effects on laboratory tests.
- Be aware of predisposing conditions such as antithrombin (AT) deficiency. Anti-Xa kits containing exogenous AT can also lead to an overestimation of heparin levels where AT deficiency exists.
- Determination of thrombin generation (TG) must be considered relative to the heparin dose used, and the presence or absence of dextran factored in.
- Heparin resistance and 'lab resistance' to heparin must be considered when accounting for normal TG in the face of treatment with therapeutic levels of heparin. Lab resistance to heparin is a failure to achieve therapeutic targets via aPTT or anti-Xa levels despite treatment and is due to low AT levels, high PF4 levels on heparinases or high Factor VIII or fibrinogen levels which can shorten aPTT without an effect on the anti-Xa assay.
- Hardy et al.'s 2020 own study on anti-Xa kits and UFH versus LMWH treatment found a good correlation in anti-Xa levels with both reagents (Pearson's correlation coefficient = 0.98 for both UFH and LMWH samples) suggesting that regardless of different mechanisms of action, both heparin preparations appear equally effective, despite a detected overestimation of Xa levels where dextran sulphate is present (Figure 1).
- The intrinsic limitations of tests should be considered when choosing tests, such as the presence of dextran sulphate in the testing materials versus those without it.
- Pre-analytic steps of laboratory tests such as timing of blood collection, centrifugation conditions etc must be considered prior to testing.
- For accurate assessment of results, researchers must be transparent about the laboratory methods used in testing.

## ABSTRACT

We read with much interest the recent observational study of Nougier et al., which aimed at studying thrombin generation (TG) and fibrinolysis profiles of COVID-19 patients admitted to an intensive care unit (ICU) or to an internal medicine ward and receiving various schemes of prophylactic heparin.[1] They reported that thrombin potential remained within normal range despite heparin and that fibrinolysis was decreased in relation with increased plasminogen activator inhibitor 1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) antigen plasma levels. Using the rotational thromboelastometry (ROTEM) delta device with EXTEM reagents and the addition of 0.625 microg/mL tPA (referred to as 'TEM-tPA'), they reported decreased clot lysis in COVID-19 patients, which was more pronounced in patients who presented a thrombotic event, compared to event-free patients.

## FIGURES

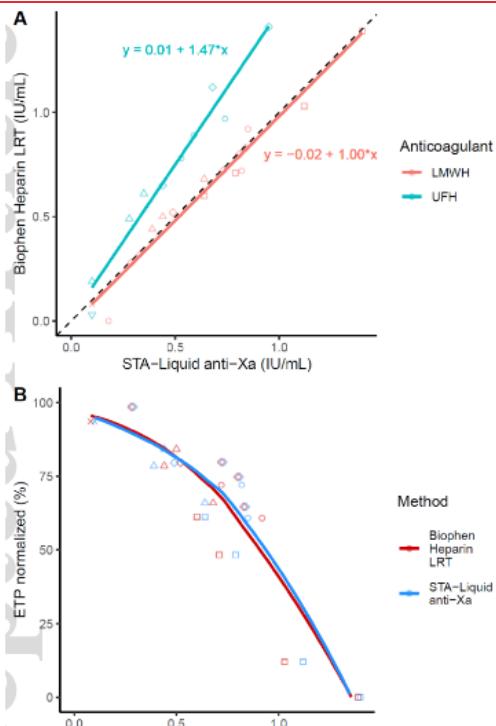


Figure 1: Correlation between anti-Xa levels as measured with two different chromogenic anti-Xa assays and the endogenous thrombin potential (ETP) in plasma samples from patients treated with heparin. Panel A represents the correlation between the 2 chromogenic anti-Xa assays depending on the type of heparin in the sample. The Biophen Heparin LRT overestimates the anti-Xa level of UFH samples compared to the STA-Liquid anti-Xa. Panel B represents the correlation between the anti-Xa levels in LMWH samples and the ETP. A progressive inhibition of TG is observed as measured anti-Xa levels increase. TG was studied with the ST-Genesia device using the STG-DrugScreen reagent and results were normalized using a reference plasma provided with STG-DrugScreen reagent. Each subject is represented by a different symbol

## ADJUSTING PRACTICE DURING COVID-19

### FOR HEALTHCARE PROFESSIONALS

#### THE USE OF BONE CONDUCTION HEADSETS TO IMPROVE COMMUNICATION DURING THE COVID-19 PANDEMIC

Lim ZJ, Claydon J.. Emerg Med Australas. 2020 Aug 14. doi: 10.1111/1742-6723.13611. Online ahead of print.

Level of Evidence: Other - Opinion

#### BLUF

In this letter to the editor, emergency department physicians in Australia discuss the benefits of using bone-conduction headsets to facilitate communication from staff caring for COVID-19 patients in negative pressure rooms. Authors state these headsets allow secure communication (compared to radios), do not need to be adjusted once placed, are easily decontaminated, but may be prohibitive due to cost.

### ACUTE CARE

#### NEUROLOGY

#### MANAGEMENT OF PATIENTS WITH NEUROMUSCULAR DISORDERS AT THE TIME OF THE SARS-COV-2 PANDEMIC

Costamagna G, Abati E, Bresolin N, Comi GP, Corti S.. J Neurol. 2020 Aug 17. doi: 10.1007/s00415-020-10149-2. Online ahead of print.

Level of Evidence: Other - Guidelines and Recommendations

#### BLUF

Members of the Neuroscience Section at the University of Milan in Italy propose guidelines for care of patients with neuromuscular disorders (NMD) during the SARS-CoV-2 pandemic. They recommend outpatient care, minimizing immune-compromising medications and in-person interactions, and maintenance of regular follow-up by utilizing telehealth (Figure 2). Additionally they suggest providers caring for NMD patients admitted to the hospital with SARS-CoV-2 consider which medications have NMD side effects (Table 3) and consult neurologists for all such patients. The authors suggest these measures can optimize outcomes for this group at increased risk for severe disease course (Table 2).

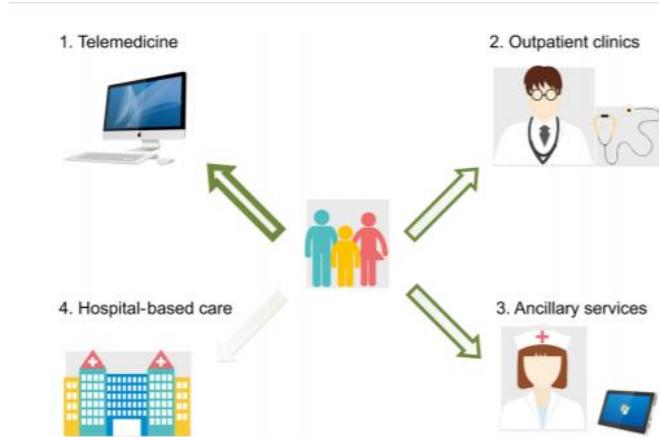
#### ABSTRACT

The novel Coronavirus disease-19 (COVID-19) pandemic has posed several challenges for neuromuscular disorder (NMD) patients. The risk of a severe course of SARS-CoV-2 infection is increased in all but the mildest forms of NMDs. High-risk conditions include reduced airway clearance due to oropharyngeal weakness and risk of worsening with fever, fasting or infection. Isolation requirements may have an impact on treatment regimens administered in hospital settings, such as nusinersen, glucosidase alfa, intravenous immunoglobulin, and rituximab infusions. In addition, specific drugs for SARS-CoV2 infection under investigation impair neuromuscular function significantly; chloroquine and azithromycin are not recommended in myasthenia gravis without available ventilatory support and prolonged prone positioning may influence options for treatment. Other therapeutics may affect specific NMDs (metabolic, mitochondrial, myotonic diseases) and experimental approaches for Coronavirus disease 2019 may be offered "compassionately" only after consulting the patient's NMD specialist. In parallel, the reorganization of hospital and outpatient services may change the management of non-infected NMD patients and their caregivers, favouring at-distance approaches. However, the literature on the validation of telehealth in this subgroup of patients is scant. Thus, as the first wave of the pandemic is progressing, clinicians and researchers should address these crucial open issues to ensure adequate caring for NMD patients. This manuscript summarizes available evidence so far and provides guidance for both general neurologists and NMD specialists dealing with NMD patients in the time of COVID-19.

## FIGURES

**Table 2** Additional risk factors increasing the risk of developing severe COVID-19 disease

Kyphoscoliosis
Highly-active immune-mediated neuromuscular disease
Mild respiratory muscle weakness
Other medical comorbidities:
• Pulmonary diseases
• Liver diseases
• Neutropenia/lymphopenia
• Renal diseases/impairment
Older age
Pregnancy (possible)
Concomitant additional neurologic diseases
Dependence from caregivers in hygiene, mobilization and feeding



**Fig. 2** The four pillars of neuromuscular disorder centres and their function during the SARS-CoV-2 pandemic. This figure displays the four main organizational milestones that could improve the care of neuromuscular disorder (NMD) patients during the pandemic. The prominent use of telemedicine approaches (wide green arrow), if possible, can help to avoid unnecessary hospital visits for NMD patients. Ancillary services performed as much as possible with virtual platforms, such as pulmonary assessments, fluoroscopic swallowing studies, and neuropsychological evaluations, and outpatient clinics represent valuable alternatives to hospital visits (medium-width green arrows). NMD patients' visits in hospital settings, particularly if dedicated to COVID patients, should be proposed more sporadically, (narrow-width green arrow), be preferred for low-risk NMD patients, and be provided following strict safety measures (see “The role of neuromuscular centre” section for more details)

## GASTROENTEROLOGY

### A PERSPECTIVE GASTROINTESTINAL ENDOSCOPY INFECTION CONTROL STRATEGY AGAINST COVID-19: WORKFLOW AND SPACE MANAGEMENT FOR THE OPERATION OF ENDOSCOPIC CENTERS

Onoyama T, Isomoto H.. Dig Endosc. 2020 Aug 5. doi: 10.1111/den.13804. Online ahead of print.

Level of Evidence: Other - Guidelines and Recommendations

#### BLUF

Physicians from Tottori University in Japan adapted a Chinese gastrointestinal endoscopy COVID-19 infection control strategy to minimize healthcare provider risk of viral exposure when performing endoscopy procedures. The proposed workflow involves the following recommendations:

- Pre-screening patients with patient history, imaging, and RT-PCR
- Only performing endoscopy on low-risk or urgent patients
- Installing particulate air filtration and negative pressure systems in rooms for urgent COVID-19 patients
- Establishing one-way walkways to avoid cross-contamination of endoscopy instruments.

The authors explain that these recommendations, if implemented, could protect healthcare workers and patients alike from nosocomial COVID-19 exposure while waiting for, recovering from, and during endoscopic GI procedures.

#### ABSTRACT

All endoscopic centers should establish infection control strategies (ICS) tailored to individual resources based upon updated national and academic guidance for COVID-19 without superseding local advisories and institutional guidelines<sup>1</sup>. Endoscopic administrators have to customize control measures and adjust with the rapidly evolving local and global pandemic and prepare for the upcoming resurgence due to relaxation of social distancing norms. In this regard, Zhang et al. have reported their stringent ICS in Peking Union Medical College Hospital (PUMCH) based on the guidance of the Chinese Society of Digestive Endoscopy and have shared their experiences from the pandemic and the subsequent recovery<sup>2</sup>.

#### FIGURES

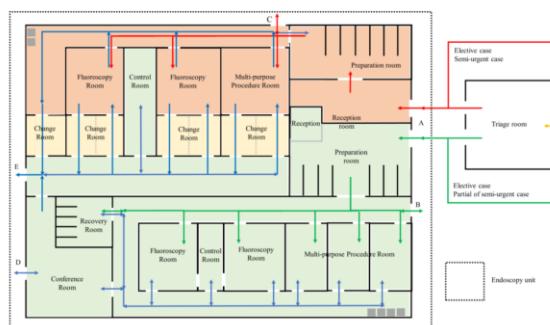


Figure 1: The workflow of the endoscopy unit is depicted. The outpatient flow is shown with orange arrows, confirmed/suspected COVID-19 patient flow with red arrows, and low-risk patient flow with green arrows. The medical staff flow is shown with blue arrows. The automated endoscope reprocessor is shown with a gray box. The endoscopic unit is separated into three zones: contaminated zones (red zones), clean zones (green zones), and buffer zones (yellow zones). Only urgent and partial semi-urgent cases with low-risk COVID-19 enter the endoscopy unit through another entrance A following the triage room. Entrance B is for inpatients with low-risk of COVID-19. Additionally, this entrance is used as an exit for low-risk patients leaving the endoscopic unit. Entrance C is for in-patients with confirmed/suspected COVID-19 and is used as an exit for confirmed/suspected COVID-19 patients. Entrance D is for the medical staff. Exit E is for the medical staff who worked in the contaminated zone. The buffer zones for changing rooms before entering the contaminated zones are for the medical staff to wear and remove PPE.

# R&D: DIAGNOSIS & TREATMENTS

## CURRENT DIAGNOSTICS

### RISK FACTORS OF SEVERE CASES WITH COVID-19: A META-ANALYSIS

Ou M, Zhu J, Ji P, Li H, Zhong Z, Li B, Pang J, Zhang J, Zheng X.. Epidemiol Infect. 2020 Aug 12:1-23. doi: 10.1017/S095026882000179X. Online ahead of print.

Level of Evidence: 1 - Systematic review of cross sectional studies with consistently applied reference standard and blinding

#### BLUF

A meta-analysis of 40 studies conducted across 31 provinces in China of severe and critically-ill COVID-19 patients (n=5,872) between February 8, 2020 and April 2, 2020 found severe disease was associated with older age (weighted mean difference [WMD]=10.69; Figure 2), higher lactate dehydrogenase (LDH; WMD=137.4; Figure 6), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), D-dimer and procalcitonin (PCT), as well as significantly decreased platelet count (WMD= -18.63) and lymphopenia (Table 2). Authors suggest these laboratory markers and age could be useful for early detection and prediction of worsening illness in COVID-19 patients.

#### FIGURES

This is an Accepted Manuscript for Epidemiology & Infection as part of the Cambridge Coronavirus Collection.

Table 1. Basic characteristics of included studies of COVID-19 patients in China

First author	Publication date in 2020	n(mild/severe or survival-non-survival)	male (%)	Single- or multi-centre *	Study population	Age <sup>b</sup> yr	Follow-up	Quality score <sup>c</sup>
Deng Y <sup>[1]</sup>	Mar 20	109/116	32	multi	survival and non-survival COVID-19 patients	43.8(18.6±19)	Jan 1 to Feb 21	5
Zhou F <sup>[2]</sup>	Mar 11	137/54	62	multi	survival and non-survival COVID-19 patients	56 (46-67)	As of Jan 21	6
Yang XB <sup>[3]</sup>	Feb 24	20/32	67	single	survival and non-survival COVID-19 patients	59.7(13.3)	Dec 2,2019 to Jan 23,2020	7
Chen T <sup>[4]</sup>	Mar 26	161/113	62	single	survival and non-survival COVID-19 patients	62(44-70)	As of Feb 28	7
Chen KB <sup>[5]</sup>	Mar 12	282/181	53	single	mild and severe COVID-19 patients	15-90	As of Feb 06	7
Xiong KH <sup>[6]</sup>	Feb 27	107/36	51	single	mild, severe and critically ill COVID-19 patients	45.1±1.0	Jan 23 to Feb 8	9
Wang D <sup>[7]</sup>	Feb 08	102/36	54	single	mild and severe COVID-19 patients	56 (42-68)	Jan 1 to Jan 28	7
Yuan J <sup>[8]</sup>	Mar 06	19/231	47	single	mild and severe COVID-19 patients	46.5±16	Jan 24 to Feb 23	9
Fang XW <sup>[9]</sup>	Feb 25	55/24	57	single	mild and severe COVID-19 patients	45.1±6.6	Jan 22 to Feb 18	6
Liu M <sup>[10]</sup>	Feb 17	26/4	33	single	mild and severe COVID-19 patients	35±8	Jan 10 to Jan 31	6
Zhong SH <sup>[11]</sup>	Mar 26	51/11	65	single	mild,severe and critically ill COVID-19 patients	51.8±13.5	Jan 21 to Feb 10	6
Guan W <sup>[12]</sup>	Feb 06	926/173	58	multi	mild and severe COVID-19 patients	47.0	NR	9
Qian GQ <sup>[13]</sup>	Mar 17	82/9	42	multi	mild and severe COVID-19 patients	50.3±5.37	Jan 20 to Feb 11	9
Huang CL <sup>[14]</sup>	Feb 15	28/13	73	single	mild and severe COVID-19 patients	49.4±1.9	As of Jan 2	7
Li KH <sup>[15]</sup>	Feb 29	58/25	53	single	mild and severe COVID-19 patients	45.5±12.3	Jan 10 to Feb	7
Wan SX <sup>[16]</sup>	Mar 21	95/40	53	single	mild and severe COVID-19 patients	47.0±6.55	Jan 23 to Feb 8	6
Gao J <sup>[17]</sup>	Mar 17	28/15	60	single	mild and severe COVID-19 patients	45.7±7.4±5.14	Jan 23 to Feb 2	6
Zhang JZ <sup>[18]</sup>	Feb 23	82/58	51	single	mild and severe COVID-19 patients	57.0	Jan 16 to Feb 3	7
Chen J <sup>[19]</sup>	Mar 13	10/63	55	single	mild and severe COVID-19 patients	15.7±6.5±5.9	Jan 10 to Feb	8
Chen YD <sup>[20]</sup>	Mar 17	48/23	47	single	mild,severe and critically ill COVID-19 patients	41.6±13.6	As of Feb 21	7

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LI D <sup>[21]</sup>	Mar 26	63/17	50	single	mild and severe COVID-19 patients	47.6±9.5	Jan 20 to Feb 27	7
LI L <sup>[22]</sup>	Apr 2	40/6	46	single	mild and severe COVID-19 patients	NR	Jan 21 to Feb 16	6
LI D <sup>[23]</sup>	Apr 2	18/44	52	single	mild,severe and critically ill COVID-19 patients	49.6±7.59±5.1	Jan 31 to Feb 25	6
Liu SJ <sup>[24]</sup>	Apr 2	196/146	54	single	mild,severe and critically ill COVID-19 patients	NR	Jan 23 to Feb 12	7
Zhang W <sup>[25]</sup>	Apr 2	56/18	47	single	mild,severe and critically ill COVID-19 patients	52.7±19	Jan 21 to Feb 11	7
Xiong J <sup>[26]</sup>	Mar 07	58/31	46	single	mild,severe and critically ill COVID-19 patients	53.1±6.9	Jan 17 to Feb 20	7
Liu Z <sup>[27]</sup>	Mar 27	84/7	62	single	mild,severe and critically ill COVID-19 patients	NR	Jan 25 to Feb 18	6
Gao W <sup>[28]</sup>	Mar 31	57/33	48	single	mild,severe and critically ill COVID-19 patients	51.7±18.6	Jan 10 to Feb	7
Xie HS <sup>[29]</sup>	Apr 2	51/28	56	single	COVID-19 patients in Wuhan Jinyintan Hospital	60.4±8.6	Feb 2 to Feb 23	7
Zhang YJ <sup>[30]</sup>	Apr 2	84/33	40	single	mild and severe COVID-19 patients	43.9±15.6±5.1	As of Feb 22	7
Liu W <sup>[31]</sup>	Feb 28	67/11	49	multi	mild and severe COVID-19 patients	38.3±31.3	Dec 30 to Jan 15	7
Shi YL <sup>[32]</sup>	Feb 27	150/14	45	single	mild,severe and critically ill COVID-19 patients	NR	Jan 10 to Feb	8
Shi JH <sup>[33]</sup>	Mar 12	38/16	57	single	mild,severe and critically ill COVID-19 patients	62.5 (50.5±8.5)	Feb 9 to Feb 29	6
Peng YD <sup>[34]</sup>	Mar 2	96/16	47	single	mild and severe COVID-19 patients	62.0±5.67	Jan 20 to Feb 15	7
Li MY <sup>[35]</sup>	Mar 20	53/13	44	single	mild and severe COVID-19 patients	16.82	Jan 20 to Feb 10	7
Chen MM <sup>[36]</sup>	Feb 27	23/25	30	single	mild and severe COVID-19 patients	43.8±6.9	Jan 24 to Feb 8	6
Wang Q <sup>[37]</sup>	Feb 24	13/22	50	single	mild and severe COVID-19 patients	43.4±15.7±7.1	Jan 26 to Feb 5	8
Li D <sup>[38]</sup>	Mar 5	20/10	60	single	mild and severe COVID-19 patients	21.72	Jan 22 to Feb 8	6
Ling F <sup>[39]</sup>	Mar 18	27/12	46	single	mild and severe COVID-19 patients	48.7±16.6±5.14	Jan 20 to Feb 10	6
Bin YF <sup>[40]</sup>	Feb 29	45/9	56	single	mild and severe COVID-19 patients	53.9±17.1	Jan 29 to Feb 16	6

\* All studies were retrospective cohort studies.

<sup>b</sup> Reported as range, mean ± SD, or median (interquartile range). NR, not reported.

<sup>c</sup> Score based on the Newcastle-Ottawa Scale guidelines<sup>[44]</sup>.

Figure 2. Meta-analysis of the difference in the average age between COVID-19 patients with mild or severe disease. WMD, weighted mean difference.

**Table 2.** Meta analysis of different laboratory parameters in COVID-19 patients

Laboratory parameters	No. studies	No. patients	Heterogeneity		Model	Meta analysis	
			P	I <sup>2</sup>		WMD (95%CI)	P
<b>Severe vs. Mild disease</b>							
Age, yr	29	4,306	< 0.001	83.4%	Random	10.69(7.83,13.54)	< 0.001
WBC, $\times 10^9/L$	32	4,736	< 0.001	83.2%	Random	0.93 (-0.51,1.36)	< 0.001
LBC, $\times 10^9/L$	31	4,456	< 0.001	65.1%	Random	-0.35 (-0.41,-0.30)	< 0.001
PLT, $\times 10^9/L$	17	3,211	< 0.001	78.5%	Random	-18.63 (-30.86,-6.40)	0.003
PCT, ng/ml	23	3,087	< 0.001	89.8%	Random	0.07 (0.05,0.10)	< 0.001
D-dimer, $\mu g/ml$	18	2,169	< 0.001	66.3%	Random	0.38 (0.24,0.52)	< 0.001
CRP, mg/L	24	2,964	< 0.001	93.5%	Random	42.7 (31.12,54.28)	< 0.001
LDH, U/L	17	1,792	< 0.001	77.7%	Random	137.4 (105.46,169.34)	< 0.001
ALT, U/L	22	2,440	< 0.001	71.0%	Random	5.12 (0.82,9.42)	0.020
AST, U/L	22	2,452	< 0.001	74.7%	Random	8.51 (5.01,12.01)	< 0.001
Cr, $\mu mol/ml$	17	1,922	0.026	61.6%	Random	4.57 (0.64,8.50)	0.023
<b>Death vs. survival</b>							
Age, yr	4	742	0.002	79.2%	Random	18.68(14.15,23.21)	< 0.001
WBC, $\times 10^9/L$	3	690	0.024	73.3%	Random	4.14 (2.87,5.41)	< 0.001
LBC, $\times 10^9/L$	4	742	0.188	37.4%	Random	-0.43 (-0.5,-0.35)	< 0.001
PLT, $\times 10^9/L$	2	243	0.001	90.9%	Random	-12.94(-92.78,66.89)	0.751
D-dimer, $\mu g/ml$	2	465	0.881	0.0%	Random	8.34(6.14,10.64)	< 0.001
LDH, U/L	2	465	< 0.001	97.6%	Random	139.3 (-188.05,466.7)	0.404
ALT, U/L	3	690	0.033	70.6%	Random	7.23 (2.25,12.2)	0.004
AST, U/L	2	499	0.003	88.6%	Random	16.68(7.48,25.89)	< 0.001

CI, confidence interval; WMD, weighted mean difference

Table 2. Meta analysis of different laboratory parameters in COVID-19 patients.

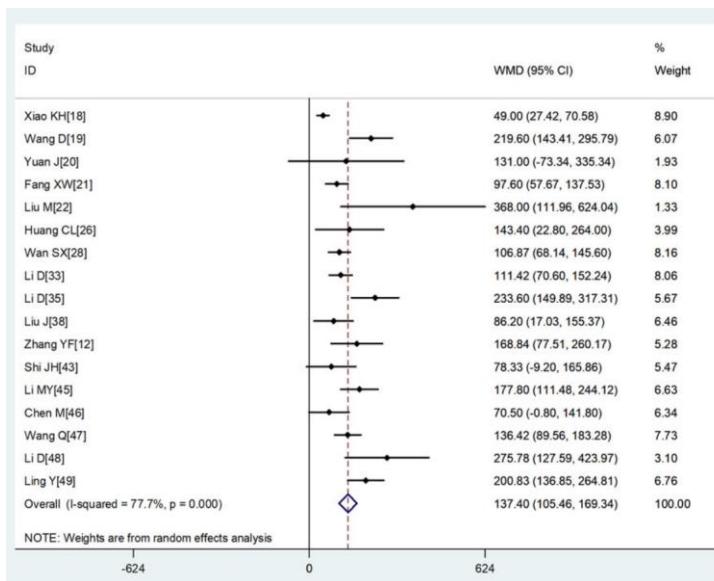


Figure 6. Meta-analysis of the difference in the lactate dehydrogenase between COVID-19 patients with mild or severe disease. WMD, weighted mean difference.

## DIAGNOSTIC VALUE OF IMAGING MODALITIES FOR COVID-19: SCOPING REVIEW

Aljondi R, Alghamdi S.. J Med Internet Res. 2020 Aug 19;22(8):e19673. doi: 10.2196/19673.

Level of Evidence: 3 - Review / Literature Review

### BLUF

Radiologists from the University of Jeddah in Saudi Arabia conducted a review of 50 articles published in 2020 examining the diagnostic value of each different imaging modalities (chest x-ray, computed tomography (CT), ultrasound, and nuclear medicine) commonly used in the diagnosis and evaluation of a patient with COVID-19. The chest x-ray and CT scan were found to be the most commonly used imaging modalities, with the chest CT being the most accurate and sensitive of all modalities in the initial diagnosis of COVID-19, although other modalities in the study are still important in evaluating disease progression. Overall, the authors conclude that early and accurate imaging and diagnosis of COVID-19 can effectively control its disease progression.

## SUMMARY

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### CT scan (Figure 2)

- most common features in COVID-19 pneumonia: peripheral ground-glass opacities (GGOs) and consolidation in the lower and middle lung regions, usually bilaterally distributed and with multi-lober involvement.
- uncommon features: pneumothorax, pleural effusion, lymphadenopathy, pericardial effusion, and lung cavitation
- advantages: early characterization of lung lesions, assessment of disease severity, and improvement of lung lesions during treatment; most sensitive modality
- disadvantages: low specificity for COVID-19 pneumonia and other viral pneumonia caused by SARS and MERS; poses increased risk of transmission to other patients or healthcare workers so thorough cleaning is required to equipment leading to prolonged downtime

### Chest X-ray (Figure 3)

- most common features: consolidation and GGOs with bilateral involvement and/or peripheral distribution
- uncommon features: pleural effusions, lung cavitation, and pneumothorax
- advantages: cost-effectiveness, widespread availability, can be used in an emergency or intensive care units to minimize infection risk
- disadvantages: limited sensitivity for COVID-19 in early stages; lack of specificity and diagnostic accuracy for COVID-19 pneumonia vs. pneumonia due to SARS and MERS

### Combined positron emission tomography/computed tomography (PET/CT) (Figure 4)

- limited studies on its role in the diagnosis of COVID-19
- advantages: sensitivity in detecting, diagnosing, and monitoring pathophysiological changes in inflamed and infected lung lesions
- disadvantages: not for routine use in emergency settings; not recommended for use in clinical practice during the pandemic due to the increased risk of infection transmission

### Ultrasound

- most common features: thickened pleural lines with irregularities, B-lines in various patterns, small peripheral consolidations, absence of pleural effusions, and appearance of A-lines during recovery
- advantages: gives similar results to chest CT and it is superior to standard chest radiography; could aid the rapid diagnosis and management of COVID-19 pneumonia and its progression toward ARDS; can be used in the emergency department or in the intensive care unit for scanning COVID-19 patients due to its portability, safety, absence of radiation, ease of use, repeatability, and low cost; play a crucial role in the diagnosis and monitoring of pregnant women with COVID-19
- disadvantages: aerated lungs may block transmission of ultrasonography, preventing the detection of deep lesions within the lung

## ABSTRACT

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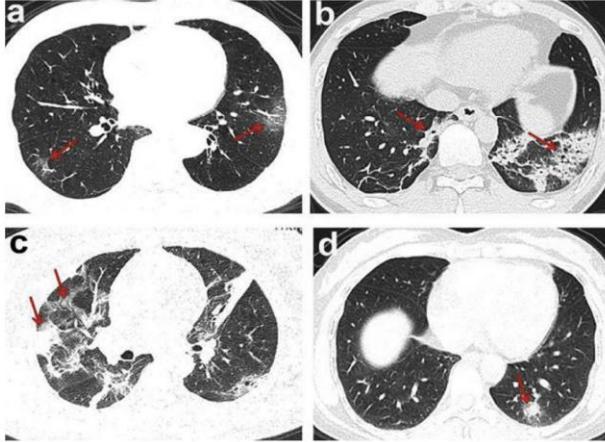
**BACKGROUND:** Coronavirus disease 2019 (COVID-19) is a serious infectious disease resulting in severe respiratory illness. This pandemic represents a serious public health risk. Therefore, early and accurate diagnosis is essential to control disease progression. Radiological examinations play a crucial role in early identification and management of infected patients.

**OBJECTIVE:** This study aimed to identify the diagnostic value of different imaging modalities used for diagnosis of COVID-19.

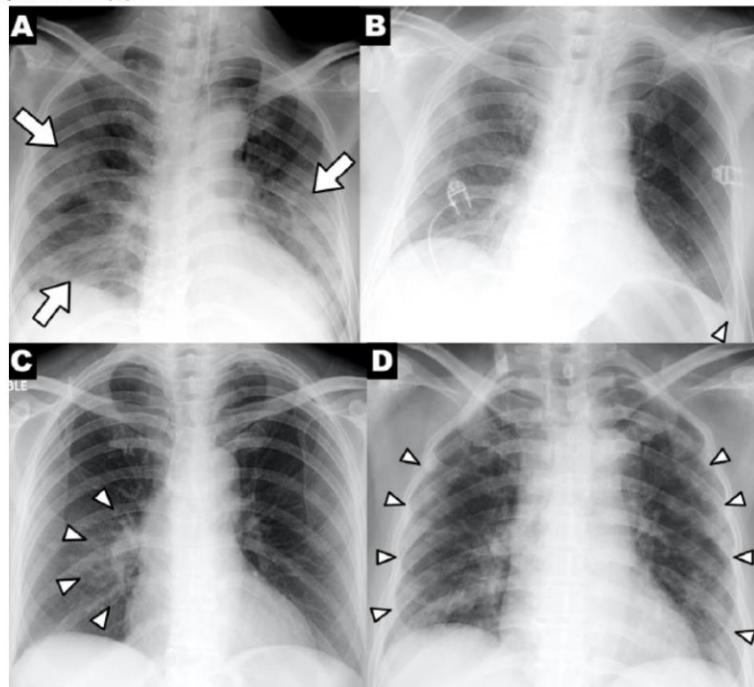
**METHODS:** A comprehensive literature search was conducted using the PubMed, Scopus, Web of Science, and Google Scholar databases. The keywords diagnostic imaging, radiology, respiratory infection, pneumonia, coronavirus infection and COVID-19 were used to identify radiology articles focusing on the diagnosis of COVID-19 and to determine the diagnostic value of various imaging modalities, including x-ray, computed tomography ultrasound, and nuclear medicine for identification and management of infected patients. **RESULTS:** 50 articles were identified in the literature search. Studies that investigated the diagnostic role and imaging features of patients with COVID-19, using either chest CT, lung ultrasound, chest x-ray, or PET/CT scan, were discussed. Of these imaging modalities, chest x-ray and CT scan are commonly used for diagnosis and management of COVID-19 patients, with chest CT scan being more accurate and sensitive in identifying COVID-19 at early stages. Only a few studies have investigated the role of ultrasound and PET/CT scan in diagnosing COVID-19. **CONCLUSIONS:** Chest CT scan remains the most sensitive imaging modality in initial diagnosis and management of suspected and confirmed patients with COVID-19. Other diagnostic imaging modalities could add value in evaluating disease progression and monitoring of critically ill COVID-19 patients. **CLINICALTRIAL:**

## FIGURES

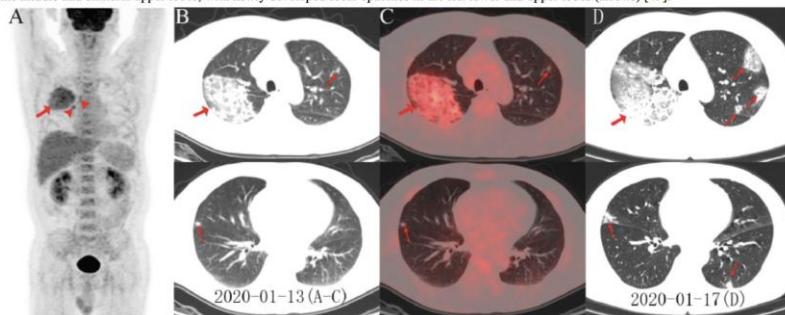
**Figure 2.** Chest computed tomography findings in patients with coronavirus disease [63]. (a) Ground-glass opacities, (b) consolidations, (c) consolidations with ground-glass opacities, (d) solid nodules.



**Figure 3.** Chest x-ray findings in a patient with coronavirus disease. (A) Patchy consolidations, (B) pleural effusion, (C) perihilar distribution, (D) peripheral distribution [18].



**Figure 4.** Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) imaging findings in a patient with coronavirus disease. (A) The PET maximum intensity projection image shows an FDG-avid mass in the right lung with a maximum standardized uptake value of 4.9, as well as increased accumulation of FDG in the right hilar lymph nodes, in the right paratracheal stripe (arrowhead), and in the bone marrow. The axial images of the low-dose CT scan (B) and the PET/CT fusion (C) show ground-glass opacities in the right upper lobe with areas of focal consolidation (arrows) and focal opacities in the right middle and left upper lobes (arrows). Follow-up CT axial images obtained 4 days later (D) show lesion progression in the middle and bilateral upper lobes, with newly developed focal opacities in the left lower and upper lobes (arrows) [49].



## DEVELOPMENTS IN TREATMENTS

### EARLY SAFETY INDICATORS OF COVID-19 CONVALESCENT PLASMA IN 5000 PATIENTS

Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, Carter RE, Klompa AM, Wiggins CC, Shepherd JR, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Johnson PW, Lesser ER, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Hodge DO, Kunze KL, Buras MR, Vogt MN, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Van Buskirk CM, Winters JL, Stubbs JR, Paneth NS, Verdun NC, Marks P, Casadevall A. *J Clin Invest.* 2020 Aug 10:140200. doi: 10.1172/JCI140200. 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

Researchers conducted an analysis of safety metrics and mortality rate in 5000 hospitalized patients between April 3rd, 2020 and May 11th, 2020 with severe or life-threatening COVID-19 who received transfusions of ABO-compatible human COVID-19 convalescent plasma that was pre-screened for SARS-CoV-2 via clinical laboratory or antibody test. Thirty-six patients (less than 1%) had severe adverse events within four hours of transfusion with a 0.08% mortality rate at the four hour mark; the seven day mortality rate for the study group was 14.9% compared to the case fatality rate of 10-20% for hospitalized COVID-19 patients (Table 2). The authors note several risks of convalescent plasma transfusion, but given the high mortality rates expected in a critically ill population, they are optimistic that this could be a viable treatment option once further efficacy studies are performed.

#### ABSTRACT

**BACKGROUND:** Convalescent plasma is the only antibody based therapy currently available for COVID 19 patients. It has robust historical precedence and sound biological plausibility. Although promising, convalescent plasma has not yet been shown to be safe as a treatment for COVID-19. **METHODS:** Thus, we analyzed key safety metrics after transfusion of ABO compatible human COVID-19 convalescent plasma in 5,000 hospitalized adults with severe or life threatening COVID-19, with 66% in the intensive care unit, as part of the US FDA Expanded Access Program for COVID-19 convalescent plasma. **RESULTS:** The incidence of all serious adverse events (SAEs) in the first four hours after transfusion was <1%, including mortality rate (0.3%). Of the 36 reported SAEs, there were 25 reported incidences of related SAEs, including mortality (n = 4), transfusion-associated circulatory overload (TACO; n = 7), transfusion-related acute lung injury (TRALI; n = 11), and severe allergic transfusion reactions (n = 3). However, only 2 (of 36) SAEs were judged as definitely related to the convalescent plasma transfusion by the treating physician. The seven-day mortality rate was 14.9%. **CONCLUSION:** Given the deadly nature of COVID 19 and the large population of critically-ill patients included in these analyses, the mortality rate does not appear excessive. These early indicators suggest that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19.

#### FIGURES

Four-hour reports	Reported (n = 36)	Related <sup>A</sup> (n = 25)	Estimate (95% CI)
Mortality	15	4	0.08% (0.03%, 0.21%)
Transfusion-associated circulatory overload	7	7	0.14% (0.07%, 0.29%)
Transfusion-related acute lung injury	11	11	0.22% (0.12%, 0.39%)
Severe allergic transfusion reaction	3	3	0.06% (0.02%, 0.18%)
Seven-day reports			
Mortality	602		14.9% (13.8%, 16.0%) <sup>B</sup>

Table 2. Serious adverse event characteristics (n = 5,000).

## SARS-COV-2 S1 IS SUPERIOR TO THE RBD AS A COVID-19 SUBUNIT VACCINE ANTIGEN

Wang Y, Wang L, Cao H, Liu C.. J Med Virol. 2020 Jul 21. doi: 10.1002/jmv.26320. Online ahead of print.  
Level of Evidence: Other - Mechanism-based reasoning

### BLUF

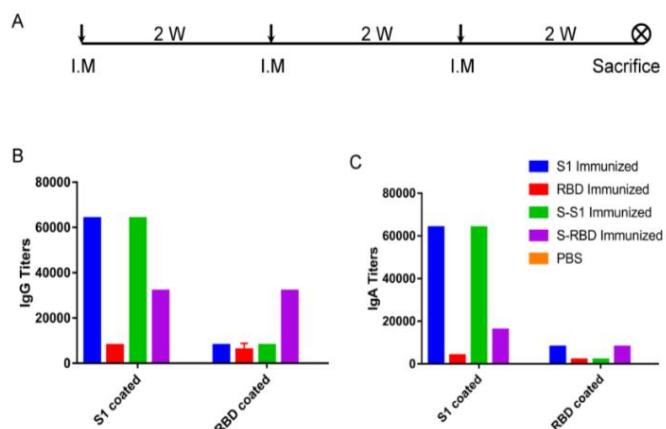
Medical biologists in Kunming, China conducted in-vitro and in-vivo mouse studies to compare the SARS-CoV-2 S1 protein to the S1 Receptor Binding Domain (RBD) as potential antigens for a vaccine and found that mice challenged with S1 proteins produced significantly greater antibody titers than when challenged with RBD antigens. These results suggest that a vaccine based on the entire S1 subunit could potentially be more effective at eliciting host immune responses than one based only on the RBD.

### ABSTRACT

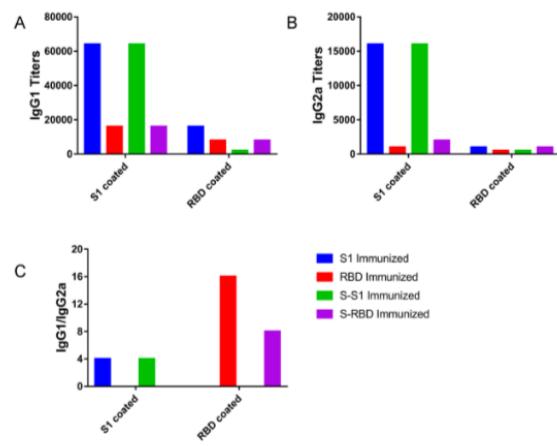
Since its emergence in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has developed into a global pandemic within a matter of months. While subunit vaccines are one of the prominent options for combating coronavirus disease 2019 (COVID-19), the immunogenicity of spike protein-based antigens remains unknown. When immunized in mice, the S1 domain induced much higher IgG and IgA antibody levels than the RBD and more efficiently neutralized SARS-CoV-2 when adjuvanted with alum. It is inferred that a large proportion of these neutralization epitopes are located in the S1 domain but outside the RBD and that some of these are spatial epitopes. This finding indicates that expression systems with posttranslational modification abilities are important to maintain the natural configurations of recombinant spike protein antigens and are critical for effective COVID-19 vaccines. Further, adjuvants prone to a Th1 response should be considered for S1-based subunit COVID-19 vaccines to reduce the potential risk of antibody-dependent enhancement (ADE) of infection. This article is protected by copyright. All rights reserved.

### FIGURES

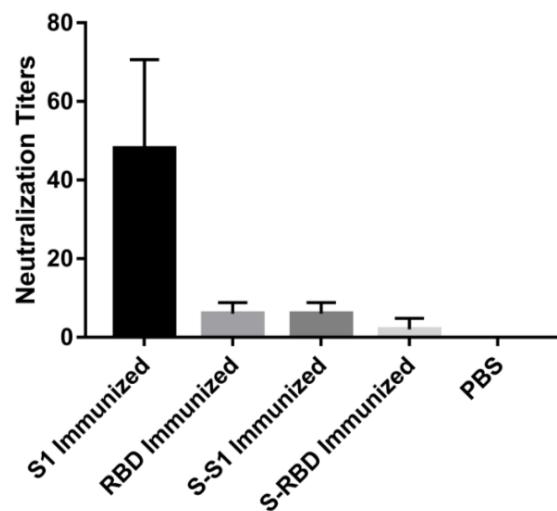
Figure 2. Immunization schedule and humoral responses of various immunogens in mice. (A) Immunization schedule. I.M.: intramuscular. W: week. (B) S1- and RBD-specific IgG titers. (C) S1- and RBD-specific IgA titers.



**Figure 3. Th1-Th2 balance analysis.** (A) S1- and RBD-specific IgG1 titers.  
 (B) S1- and RBD-specific IgG2a titers. (C) IgG1/IgG2a ratios.



**Figure 4. SARS-CoV-2 neutralization titers of serum from mice vaccinated with various immunogens.** PBS: serum from mice immunized with PBS.



# ACKNOWLEDGEMENTS

## CONTRIBUTORS

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Alisa Malyavko  
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Julia Ghering  
Kersti Bellardi  
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