

# The Daily COVID-19 Literature Surveillance Summary

**December 30, 2020**



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# COVID-19 Daily Literature Surveillance

COVID19LST



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# LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
<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			
<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

- The US Centers for Disease Control COVID-19 Response Team used data from three online CARAVAN omnibus surveys (n=858) conducted to assess parental attitudes and concerns about schools reopening during the COVID-19 pandemic and found [more white families were in favor of in-person school](#) (62.3%) compared to Hispanic families (50.2%, p=0.014) and Black families (46.0%, p=0.007), while non-white parents were more concerned about schools opening safely (98.8% very or somewhat concerned) than were white families (86.0%, p=0.012). Authors suggest socioeconomic differences and structural inequities may drive these differing attitudes and recommend school districts consider each community's unique needs when devising school reopening plans.

## Epidemiology

- In a retrospective cohort study evaluating albumin levels in correlation with disease severity and inflammatory markers (CRP, d-dimer, and IL-6), investigators in Milan, Italy analyzed data from 207 COVID-19 patients admitted to Fatebenefratelli-Sacco Hospital and found 50.7% patients had hypoalbuminemia (serum albumin <30 g/L), and that [albumin levels were significantly inversely correlated with increased severity of disease and worse outcomes](#) at day 30, as well as inversely correlated with inflammatory markers. The results suggest hypoalbuminemia and urinary protein wasting may be useful biomarkers on admission to determine disease severity.
- A cohort study by an international team of researchers compares [COVID-19 outcomes in pregnant women \(n=1549\) vs non-pregnant women](#) of reproductive age (n=19,825) from the Mexican National Registry of Coronavirus database and found that pregnant women had higher odds of death (OR 1.65, 95% CI 1.30-2.09), pneumonia (OR 1.99, 95% CI 1.81-2.19) and ICU admission (OR 2.25, 95% CI 1.86-2.71) than non-pregnant women, but similar odds of intubation (OR 0.93, 95% CI 0.70-1.25). Authors note additional research is required to understand potential mechanisms of this increased risk, and determine the external validity of this cohort of patients.

## Understanding the Pathology

- Microbiologists and infectious disease specialists from Anhui Medical University and the Anhui and Fuyang Centers for Disease Control in China [analyzed SARS-CoV-2 IgM and IgG antibody responses using indirect ELISA](#) in serum from 165 patients and found spike protein IgM and IgG was detectable in 12.5% of hospitalized patients on day 1 of infection, IgM peaked at 22-28 days and was undetectable in 30% and 79% of patients at three and seven months, respectively, and IgG peaked at four months and declined rapidly at seven months. Authors suggest their analysis can help guide SARS-CoV-2 diagnosis and vaccine development via an improved understanding of the human humoral response in COVID-19.

## Transmission & Prevention

- A review of current data on COVID-19 transmission and vaccine efficacy by otolaryngologists from Harvard Medical School and Johns Hopkins School of Medicine illustrates how COVID-19 mRNA vaccines generate immunogenicity by creating IgG antibodies against the SARS-CoV-2 virus, however IgG antibodies, while preventing patients from clinically getting sick with COVID-19, do [not stop the virus from replicating in the upper airway](#) -- as this requires secretory IgA antibodies -- suggesting that transmission precautions should still be widely practiced even after vaccination.
- An international group of researchers discuss possible explanations for why the [household secondary attack rates \(HSAR\) in Asian countries such as Singapore and China \(12% and 11% respectively\) are significantly lower than in the US \(30-50%\)](#). Authors attribute this difference to self-isolation protocols in Asia, such as the Chinese "fangcang shelter hospitals," which provide COVID-19 positive individuals with a healthcare facility where they can quarantine until no longer infectious. Conversely, the strategy in the US and Europe centers around home quarantining, leading to higher rates of secondary infections. While significant cultural and structural differences exist that would prevent the US from successfully implementing a similar self-isolation protocol to those seen in the Asian countries highlighted, further research is needed to identify areas for improvement in current US public health policies.

## Management

- A multicenter retrospective study conducted by French physicians at the Cochin Hospital utilized demographic data, clinical symptomatology, and results of lab tests from 605 patients with clinical suspicion of COVID-19 to create a [pre-test probability score of SARS-CoV-2 infection](#) (the PARIS score) and found that fever, myalgias, lymphopenia, and elevated CRP had the highest positive predictive value, though no clinical variable was individually significant. The high-probability PARIS score had a positive predictive value of 93%, while the low-probability score had a negative predictive value of 98%. This study adds to the existing body of evidence by providing an evidenced-based prediction tool that can easily be incorporated into clinical practice, however further external validation is still needed.
- A systematic review by South Korean radiologists found the incidence of pulmonary embolism (PE) and deep vein thrombosis (DVT) in patients with COVID-19 were 16.5% and 14.8% respectively, and that only 42% of PE patients had evidence of DVT. Additionally, data revealed that D-dimer levels of 500 and 1000 micrograms/L showed high sensitivity (96% and 91%, respectively) but low specificity (10% and 24%) for detecting PE. These findings suggest that [coagulopathy in COVID-19 may be more severe than typical illness](#) (estimated rates of PE and DVT in critically-ill hospitalized patients 6-10%) and possibly occur via a distinct mechanism of localized endothelialitis instead of lower extremity DVT.

## R&D: Diagnosis & Treatments

- This industry-sponsored phase 3 randomized controlled trial involving 389 hospitalized patients with COVID-19 pneumonia found that [patients who received IV tocilizumab had faster recovery rates and less chance of progression to mechanical ventilation or death](#) after 28 days compared to the placebo group (12% vs 19.3%, hazard ratio 0.56, 95% CI 0.33-0.97, p=0.04), suggesting that this IL-6 inhibitor may be an effective treatment to reduce hospital days and ventilator use in COVID-19. Importantly, this trial was conducted in 6 countries and included over 80% minority populations, who are known to have disproportionately worse outcomes and less inclusion in clinical trials compared to their white counterparts. However, there was no significant difference in overall all-cause mortality, and the current cost of this brand name biologic may be prohibitive for wide scale use in these populations.
- A group of hematology and immunology experts illustrate how [SARS-CoV-2 directed T-cell immunotherapy may be a feasible method for prevention and early treatment of COVID-19 in immunocompromised patients](#) by demonstrating how in-vitro expansion of SARS-CoV-2 specific T-cells in convalescent plasma donors can be directed to recognize and elicit a robust T-cell immune response to common viral antigens. Specifically, they found increased interferon- $\gamma$  production (representative of "polyfunctional T-cell response") to SARS-CoV-2 spike protein, membrane protein, and nucleocapsid peptide in 12 (26%), 27 (59%), and 10 (22%) convalescent donors (respectively), as well as in 2 of 15 unexposed controls. The authors propose that this adaptive immune response is critical for developing effective long-term immunity, and may be beneficial for immunocompromised patients with blood disorders or bone marrow transplants.

## Mental Health & Resilience Needs

- Scientists from the Center for Disease Control studied emergency department (ED) visits from January 6, 2019 - September 6, 2020 and found an [increase in the proportion of ED visits related to abuse and neglect in children and adolescents](#) during the COVID-19 pandemic despite a lower number of ED visits overall, and those visits were more likely to result in hospitalization than in 2019. This suggests that the social and economic effects of the pandemic (loss of income and increased stress related to parental child care, increased substance use, and mental health conditions) may be the cause of this increase, and the authors suggest strengthening families' economic support, ensuring family-friendly work policies, and modifying early home visitation practices to improve the safety of children and adolescents.

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## CLIMATE

## DISPARITIES

### RACIAL AND ETHNIC DIFFERENCES IN PARENTAL ATTITUDES AND CONCERNs ABOUT SCHOOL REOPENING DURING THE COVID-19 PANDEMIC - UNITED STATES, JULY 2020

Gilbert LK, Strine TW, Szucs LE, Crawford TN, Parks SE, Barradas DT, Njai R, Ko JY.. MMWR Morb Mortal Wkly Rep. 2020 Dec 11;69(49):1848-1852. doi: 10.15585/mmwr.mm6949a2.

Level of Evidence: 3 - Local non-random sample

#### BLUF

The US Centers for Disease Control COVID-19 Response Team used data from three online CARAVAN omnibus surveys ( $n=858$ ) conducted from July 8-12, 2020 to assess parental attitudes and concerns about schools reopening during the COVID-19 pandemic (Table 1). They found more white families were in favor of in-person school (62.3%) compared to Hispanic families (50.2%,  $p=0.014$ ) and Black families (46.0%,  $p=0.007$ ) while non-white parents were more concerned about schools opening safely (98.8% very or somewhat concerned) than were white families (86.0%,  $p=0.012$ ) (Tables 2, 3). Authors suggest socioeconomic differences and structural inequities may drive these differing attitudes and recommend school districts consider each community's unique needs when devising school reopening plans.

#### ABSTRACT

In light of the disproportionate risk of hospitalization and death attributable to coronavirus disease 2019 (COVID-19) among racial and ethnic minority groups, parental attitudes and concerns regarding school reopening were assessed by race and ethnicity using data from three online CARAVAN omnibus surveys conducted during July 8-12, 2020, by ENGINE Insights.\* Survey participants included 858 parents who had children and adolescents in kindergarten through grade 12 (school-aged children) living in their household. Overall, 56.5% of parents strongly or somewhat agreed that school should reopen this fall, with some differences by race/ethnicity: compared with 62.3% of non-Hispanic White (White) parents, 46.0% of non-Hispanic Black or African American (Black) parents ( $p = 0.007$ ) and 50.2% of Hispanic parents ( $p = 0.014$ ) agreed that school should reopen this fall. Fewer White parents (62.5%) than Hispanic (79.5%,  $p = 0.026$ ) and non-Hispanic parents of other racial/ethnic groups (66.9%,  $p = 0.041$ ) were supportive of a mask mandate for students and staff members. Understanding parental attitudes and concerns is critical to informing communication and messaging around COVID-19 mitigation. Families' concerns also highlight the need for flexible education plans and equitable resource provision so that youth education is not compromised.

## FIGURES

**TABLE 2. Parental attitudes and concerns about risks and benefits of school reopening during the COVID-19 pandemic and impacts of COVID-19 on student academic and health-related outcomes, by race/ethnicity — ENGINE Insights, United States, 2020**

Return

Question and response	Racial/Ethnic group, % (95% CI)				
	Overall*	White, non-Hispanic*	Black, non-Hispanic*	Hispanic or Latino*	Other, <sup>†</sup> non-Hispanic*
<b>How much do you agree or disagree with the following?</b>					
<b>Schools should reopen for all students in the fall</b>					
Strongly/Somewhat agree	56.5 (52.8–60.3)	62.3 (57.7–66.9)	46.0 (35.0–57.0) <sup>§</sup>	50.2 (41.5–58.8) <sup>§</sup>	52.6 (39.1–66.1)
<b>I would rather homeschool my child until a COVID-19 vaccine is available</b>					
Strongly/Somewhat agree	73.3 (70.0–76.6)	69.8 (65.5–74.2)	75.6 (66.2–85.0)	82.4 (75.8–88.9) <sup>§</sup>	64.7 (51.6–77.8) <sup>¶</sup>
<b>The overall experience of being in school is more important for students, despite ongoing COVID-19 concerns around the country</b>					
Strongly/Somewhat agree	61.8 (58.1–65.5)	67.6 (63.2–72.0)	56.5 (45.4–67.7)	53.9 (45.3–62.5) <sup>§</sup>	53.4 (39.9–67.0) <sup>§</sup>
<b>Even if measures are put in place, I am concerned about students following through and fully complying with social distancing and mask wearing mandates</b>					
Strongly/Somewhat agree	85.7 (83.1–88.4)	85.2 (81.9–88.6)	91.9 (86.6–97.2) <sup>¶</sup>	80.6 (73.6–87.5)	96.9 (92.5–100.0) <sup>§,¶</sup>
<b>Thinking about this upcoming school year, how concerned are you about the following?</b>					
<b>The quality of your children's education being negatively impacted by the COVID-19 pandemic</b>					
Very/Somewhat concerned	89.4 (87.1–91.8)	90.9 (88.2–93.7)	89.3 (82.9–95.8)	84.9 (78.8–91.0)	93.4 (87.6–99.2)
<b>School reopening safely in the fall</b>					
Very/Somewhat concerned	87.8 (85.4–90.3)	86.0 (82.7–89.3)	93.5 (88.6–98.3) <sup>§</sup>	86.0 (80.1–91.8)	98.8 (96.3–100.0) <sup>§,¶</sup>
<b>The potential disruption to your daily routines if virtual (at-home) learning becomes necessary</b>					
Very/Somewhat concerned	77.4 (74.1–80.6)	78.6 (74.5–82.5)	78.8 (70.0–87.6)	71.8 (63.9–79.6)	84.7 (75.2–94.2)
<b>Your child contracting COVID-19 as a result of attending school</b>					
Very/Somewhat concerned	86.3 (83.7–88.9)	84.1 (80.6–87.6)	92.6 (87.4–97.8) <sup>§</sup>	85.5 (79.4–91.6)	95.6 (90.6–100.0) <sup>§,¶</sup>
<b>Your child bringing COVID-19 home as a result of attending school</b>					
Very/Somewhat concerned	86.3 (83.8–88.9)	84.5 (81.0–87.9)	92.7 (87.3–98.2) <sup>§</sup>	86.2 (80.4–92.0)	89.4 (80.9–98.0)

**Abbreviations:** CI = confidence interval; COVID-19 = coronavirus disease 2019.

\* Weighted.

<sup>†</sup> Other, non-Hispanic includes participants who identified as American Indian/Alaska Native, Asian, multiracial, and other.

<sup>§</sup> p≤0.05 compared with White, non-Hispanic.

<sup>¶</sup> p<0.05 compared with Hispanic.

**TABLE 3. Parental attitudes and concerns about school reopening strategies and mask mandates, by race/ethnicity — ENGINE Insights, United States, 2020**

Return

Questions and responses	Racial/Ethnic group, % (95% CI)				
	Overall*	White, non-Hispanic*	Black, non-Hispanic *	Hispanic or Latino*	Other, <sup>†</sup> non-Hispanic*
<b>In light of the COVID-19 pandemic, how comfortable would you be with the following?</b>					
<b>Your children's school(s) reopening at full capacity in the fall</b>					
Very comfortable/Somewhat comfortable	52.7 (48.9–56.4)	57.1 (52.4–61.8)	43.0 (32.0–53.9) <sup>§</sup>	53.3 (44.7–61.9)	32.5 (20.1–44.9) <sup>§,¶</sup>
<b>Your children's school(s) reopening at 50% capacity in the fall, with the other 50% dedicated to virtual learning</b>					
Very comfortable/Somewhat comfortable	66.2 (62.6–69.8)	67.9 (63.5–72.4)	58.2 (47.1–69.3)	67.1 (59.0–75.2)	64.8 (52.1–77.6)
<b>Your children's school(s) reopening in the fall exclusively with virtual learning</b>					
Very comfortable/Somewhat comfortable	69.7 (66.2–73.2)	69.1 (64.7–73.6)	73.3 (63.7–82.9)	69.8 (61.8–77.9)	66.7 (53.9–79.6)
<b>When school resumes in the fall, do you believe wearing masks/facial coverings should be mandated for everyone (both students and staff)?</b>					
Yes, at all times	68.3 (64.8–71.8)	62.5 (57.9–67.1)	73.1 (63.4–82.7)	79.5 (72.7–86.4) <sup>§</sup>	66.9 (54.2–79.5) <sup>§</sup>

**Abbreviations:** CI = confidence interval; COVID-19 = coronavirus disease 2019.

\* Weighted.

<sup>†</sup> Other, non-Hispanic includes participants who identified as American Indian/Alaska Native, Asian, multiracial, and other.

<sup>§</sup> p≤0.05 compared with White, non-Hispanic.

<sup>¶</sup> p<0.05 compared with Hispanic.

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**TABLE 1. Characteristics of respondents with school-aged children (kindergarten [K]–grade 12) — ENGINE Insights, United States, 2020**

[Return](#)

Characteristic	Unweighted no. (weighted %)
Total	858 (100)
<b>Parent's race/ethnicity</b>	
White, non-Hispanic	571 (55.6)
Black, non-Hispanic	88 (13.2)
Hispanic, non-Hispanic	140 (24.4)
Other, non-Hispanic *	59 (6.7)
<b>Parent's sex</b>	
Female	377 (51.1)
<b>Child's grade level<sup>t</sup></b>	
K–4	428 (50.2)
5–8	412 (46.1)
9–12	295 (35.6)
<b>Household region<sup>s</sup></b>	
Northeast	153 (15.4)
Midwest	160 (19.9)
South	346 (41.1)
West	199 (23.6)
<b>Education</b>	
Less than high school	225 (38.0)
Some college or technical school	161 (20.4)
Bachelor's degree or higher	472 (41.6)

\* Other, non-Hispanic includes participants who identified as American Indians and Alaska Natives, Asians, multiracial persons, and other.

<sup>t</sup> These totals sum to >100% because some parents had more than one school-aged child living in the household.

<sup>s</sup> Northeast: Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont; Midwest: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin; South: Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia; West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming.

## EPIDEMIOLOGY

### SYMPTOMS AND CLINICAL PRESENTATION

#### ADULTS

#### ROLE OF SERUM ALBUMIN AND PROTEINURIA IN PATIENTS WITH SARS-COV-2 PNEUMONIA

Bassoli C, Oreni L, Ballone E, Foschi A, Perotti A, Mainini A, Casalini G, Galimberti L, Meroni L, Antinori S, Milazzo L.. Int J Clin Pract. 2020 Dec 17:e13946. doi: 10.1111/ijcp.13946. Online ahead of print.

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

#### BLUF

In this retrospective cohort study, investigators from various institutions in Milan, Italy analyzed data from 207 COVID-19 patients admitted to Fatebenefratelli-Sacco Hospital in Milan, Italy, evaluating albumin levels in correlation with disease severity and inflammatory markers (CRP, d-dimer, and IL-6). The results revealed 50.7% patients had hypoalbuminemia (serum albumin <30 g/L), and that albumin levels were significantly inversely correlated with increased severity of disease and worse outcomes at day 30 (Figure 1), as well as inversely correlated with inflammatory markers (Figure 2). The results suggest hypoalbuminemia and urinary protein wasting may be useful biomarkers on admission to determine disease severity.

#### ABSTRACT

**BACKGROUND:** Hypoalbuminemia is frequently observed in patients with SARS-CoV-2 infection although its underlying mechanism and relationship with clinical outcome still need to be clarified. **METHODS:** We retrospectively evaluated in patients with COVID-19 hospitalized at the Fatebenefratelli-Sacco Hospital in Milan, the prevalence of hypoalbuminemia, its association with the severity of COVID-19, with the levels of C-reactive protein, d-dimer and interleukin-6 and with clinical outcome over a follow-up period of 30 days. Urinalysis was evaluated in a subgroup of patients. **RESULTS:** Serum albumin levels < 30 g/L were found in 105/207 (50.7%) patients at hospital admission. Overall, the median albumin value was 29.5 g/L (IQR 25-32.8). A negative association was found between albumin levels and severity of COVID-19 ( $p<0.0001$ ) and death ( $p=0.003$ ). An inverse correlation was observed between albumin and both C-reactive protein and D-dimer at hospital admission ( $r = -0.487$  and  $r = -0.479$ , respectively;  $p< 0.0001$ ). Finally, a positive correlation was found between albumin levels and eGFR ( $r= 0.137$ ;  $p=0.049$ ). Proteinuria was observed in 75% of patients with available data and it did not differ between patients with hypoalbuminemia and those with albumin  $\geq 30$  g/L (81% and 67%, respectively;  $p=0.09$ ). **CONCLUSION:** In patients with COVID-19 hypoalbuminemia is common and observed in quite an early stage of pulmonary disease. It is strictly associated with inflammation markers and clinical outcome. The common finding of proteinuria, even in the absence of creatinine increase, indicates protein loss as a possible biomarker of local and systemic inflammation worthwhile to evaluate disease severity in COVID-19.

#### FIGURES

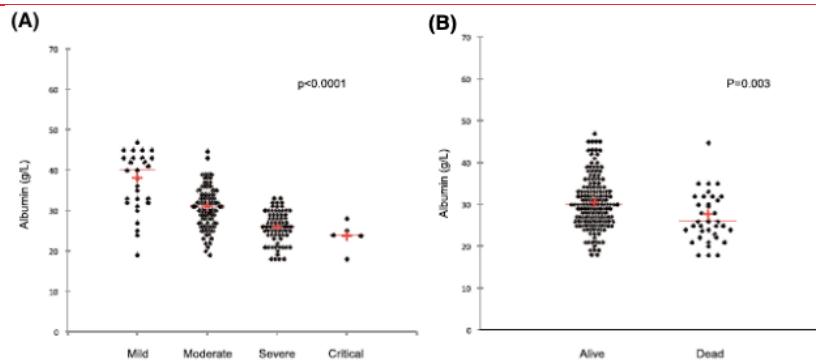


Figure 1. Serum albumin levels at hospitals admission in patients with COVID-19 pneumonia according with disease severity (A) and according with clinical outcome (B).

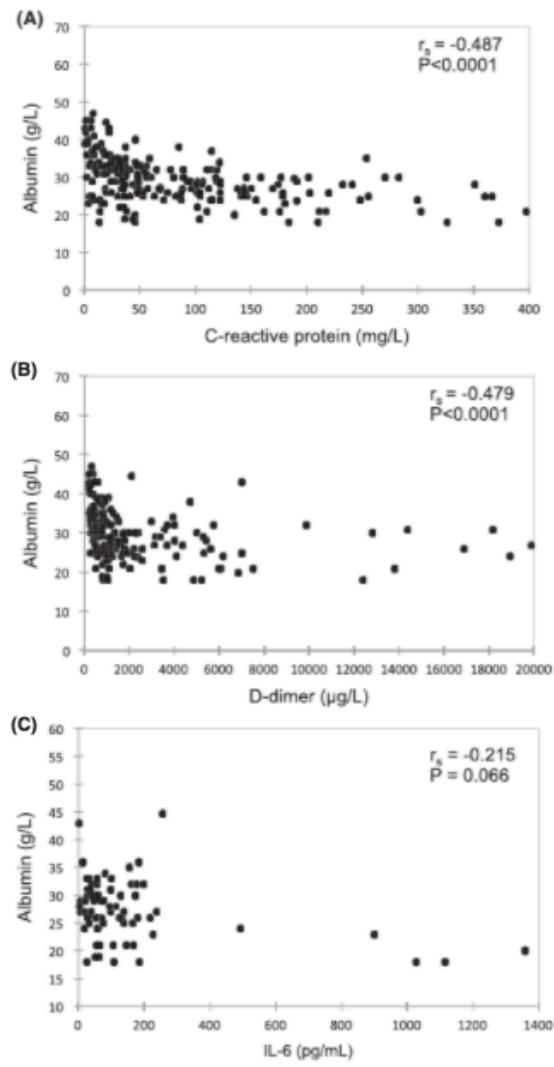


Figure 2. Spearman coefficient correlation between serum albumin at admission and C-reactive protein (A) levels, D-dimer levels (B), and serum IL-6 levels (C) at hospital admission in patients with COVID-19 pneumonia.

## PREGNANT PERSONS

### PREGNANT WOMEN WITH SARS-COV-2 INFECTION ARE AT HIGHER RISK OF DEATH AND SEVERE PNEUMONIA: PROPENSITY SCORE-MATCHED ANALYSIS OF A NATIONWIDE PROSPECTIVE COHORT STUDY (COV19MX)

Martinez-Portilla RJ, Sotiriadis A, Chatzakis C, Torres-Torres J, Espino Y Sosa S, Sandoval-Mandujano K, Castro-Bernabe DA, Medina-Jimenez V, Monarrez-Martin JC, Figueras F, Poon LC.. Ultrasound Obstet Gynecol. 2020 Dec 15. doi: 10.1002/uog.23575. Online ahead of print.

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

#### BLUF

A cohort study by an international team of researchers compares COVID-19 outcomes in pregnant women (n=1549) vs non-pregnant women of reproductive age (n=19,825) from the Mexican National Registry of Coronavirus database. Results indicate that pregnant women had higher odds of death (OR 1.65, 95% CI 1.30-2.09), pneumonia (OR 1.99, 95% CI 1.81-2.19) and ICU admission (OR 2.25, 95% CI 1.86-2.71) than non-pregnant women, but similar odds of intubation (OR 0.93, 95% CI 0.70-1.25). Authors note additional research is required to understand potential mechanisms of this increased risk, and determine the external validity of this cohort of patients.

## **ABSTRACT**

**BACKGROUND:** Limited, unmatched data reported low complication rates in pregnant women with COVID-19. This study compared COVID-19-related outcomes in pregnant women versus non-pregnant women after adjusting for potential risk factors for severe outcomes. **METHODS:** Data were obtained from the COVID-19 National Data Registry of Mexico, which is an ongoing prospective cohort of people of any age with clinically suspected SARS-CoV-2 infection and admitted to 475 monitoring hospitals. This study included pregnant and non-pregnant women of reproductive age (15-49 y) with COVID-19 confirmed by reverse transcription polymerase chain reaction. To adjust for underlying risk factors, propensity score matching was conducted for chronic obstructive pulmonary disease, asthma, smoking, hypertension, cardiovascular disease, obesity, diabetes, and age. The primary outcome was death. Secondary outcomes were pneumonia, intubation, and intensive care unit (ICU) admission. **RESULTS:** The initial sample comprised of 5183 pregnant and 175,908 non-pregnant COVID-19 patients. The crude (unmatched) rates of death, pneumonia, intubation, and ICU admission in pregnant and non-pregnant women were 1.5% vs. 1.5%, 9.9% vs. 6.5%, 8.1% vs. 9.9%, 13.0% vs. 6.9%, respectively. After propensity score matching (5183 pregnant- and 5183 non-pregnant matched women), pregnant women had higher odds of death (odds ratio [OR] 1.65, 95% CI 1.30-2.09), pneumonia (OR 1.99, 95% CI 1.81-2.19) and ICU admission (OR 2.25, 95% CI 1.86-2.71) than non-pregnant women, but similar odds of intubation (OR 0.93, 95% CI 0.70-1.25). **CONCLUSIONS:** After adjusting for background demographic and medical factors, pregnancy is a risk factor for death, intubation and ICU admission in SARS-CoV-2-infected women of reproductive age. This article is protected by copyright. All rights reserved.

# UNDERSTANDING THE PATHOLOGY

## NEUTRALIZING SARS-COV-2

Poeschla E.. eLife. 2020 Dec 15;9:e64496. doi: 10.7554/eLife.64496.

Level of Evidence: 5 - Expert Opinion

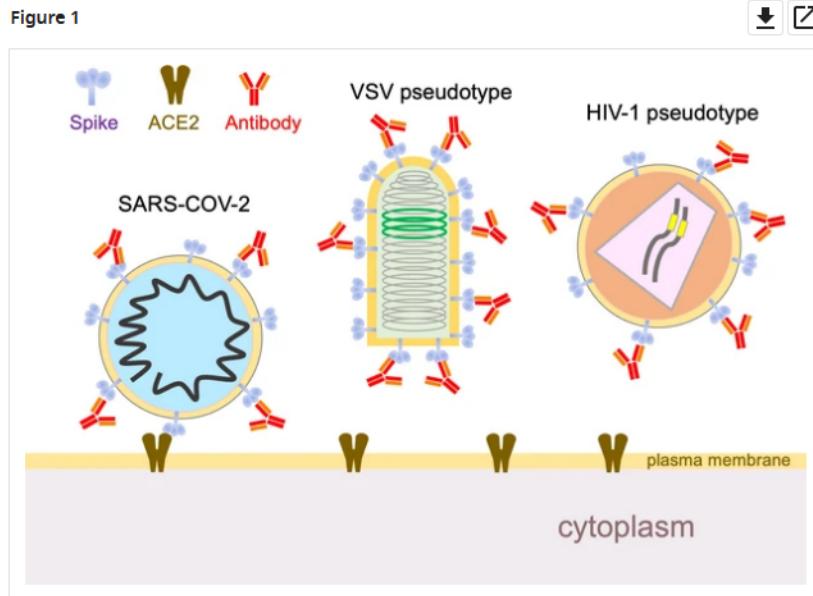
### BLUF

An infectious disease physician from University of Colorado discusses new findings from a paper by Weisblum, et al. (2020) that discusses how SARS-CoV-2 may become resistant to antibodies targeting spike protein receptors that are used during convalescent plasma treatment. Resistance emerged after only 2-3 passages, but the mutations blocking a monoclonal antibody did not confer resistance to plasma antibodies from the same individual (Figure 1). The author suggests these findings indicate combined therapies, much like those used for HIV, may be necessary to prevent SARS-CoV-2 resistance and are an important consideration in the proper design of vaccines.

### ABSTRACT

Experiments with hybrid viruses are illuminating how SARS-CoV-2 can escape neutralizing antibodies.

### FIGURES



#### Using hybrid viruses to study SARS-CoV-2 escape from neutralizing antibodies.

The surface of the SARS-CoV-2 virion (left) contains spike proteins (pale blue) that bind to ACE2 receptors (brown), which leads to membrane fusion and entry into the cell. Neutralizing antibodies (red) can stop this happening by binding to the spike proteins, so viruses undergo reciprocal evolution to escape such antibodies. To better understand how viruses evolve to become resistant to different kinds of antibodies, Weisblum et al. developed two hybrid viruses that could be studied in the laboratory. The first was a hybrid rabies family virus (VSV, middle) that carries the SARS-CoV-2 spike protein rather than the normal envelope protein in its outer lipid envelope. This hybrid is replication-competent, carries a GFP transgene (green), and can be used for experiments in which it undergoes serial passage and selection in the presence of convalescent plasma or monoclonal antibodies. The second hybrid was an HIV-1 vector pseudotyped with the spike protein. This hybrid is replication-defective, carries a luciferase transgene (yellow), and completes a single cycle of infection. VSV: vesicular stomatitis virus.

## EVALUATION OF SERUM IGM AND IGG ANTIBODIES IN COVID-19 PATIENTS BY ENZYME LINKED IMMUNOSORBENT ASSAY

Zhou C, Bu G, Sun Y, Ren C, Qu M, Gao Y, Zhu Y, Wang L, Sun L, Liu Y.. J Med Virol. 2020 Dec 17. doi: 10.1002/jmv.26741. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

### BLUF

Microbiologists and infectious disease specialists from Anhui Medical University and the Anhui and Fuyang Centers for Disease Control in China analyzed SARS-CoV-2 IgM and IgG antibody responses in serum from 165 patients collected between January 20 and February 28, 2020 using indirect ELISA (Figure 1). They found spike protein IgM and IgG was detectable in 12.5% of hospitalized patients on day 1 of infection. IgM peaked at 22-28 days and was undetectable in 30% and 79% of patients at three and seven months, respectively, while IgG peaked at four months and declined rapidly at seven months (Figures 2 and 3). Authors suggest their analysis can help guide SARS-CoV-2 diagnosis and vaccine development via an improved understanding of the human humoral response in COVID-19.

### ABSTRACT

**OBJECTIVE:** SARS-CoV-2 is sweeping the world since the end of 2019. The titer change of antibodies against SARS-CoV-2 needs to be further clarified, the clinical and preventive value of antibodies still needs to be further investigated. **METHOD:** An ELISA was established by coating with SARS-CoV-2 recombinant spike protein and used to detect serum IgM and IgG antibodies against SARS-CoV-2 in COVID-19 patients to evaluate the pattern of changes of antibodies. **RESULTS:** The specificity of the ELISA for detection SARS-CoV-2 IgM and IgG were 96% (144/150) and 100% (150/150), respectively. The sensitivity of ELISA was 100% (150/150) for IgM, and 99.3% (149/150) for IgG. SARS-CoV-2-SP-IgM and SP-IgG antibodies could be detected on day 1 of hospitalization in 12.5% patients, and SP-IgM began to decrease after reaching its peak at around 22-28 days, and become negative at month 3 in 30% patients and negative at month 7 in 79% of these patients after onset; IgG reached its peak around day 22-28 and kept at a high level within the longest observation period for 4 months, it dropped very sharply at 7 months. The positive rates of SP-IgM and SP-IgG were higher than those of RT-qPCR on day 7 and 4. **CONCLUSION:** The established indirect ELISA has good specificity and sensitivity. IgM and IgG against SARS-CoV-2 appeared almost simultaneously in the early stage, and the level of IgG antibodies couldn't maintain a high plateau in the observation period of 7 months. Our data will help develop the diagnosis and vaccine of SARS-CoV-2. This article is protected by copyright. All rights reserved.

### FIGURES

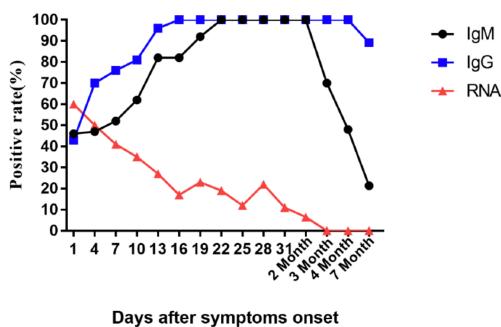


Figure 1: "Specificity and sensitivity of indirect enzyme-linked immunosorbent assay for IgM and IgG antibodies. HBV, HCV, tuberculosis and respiratory diseases has no cross reaction with IgM, RA have cross reaction with IgM (20% 26/30). HBV, HCV, RA, tuberculosis and respiratory diseases has no cross reaction with IgG".

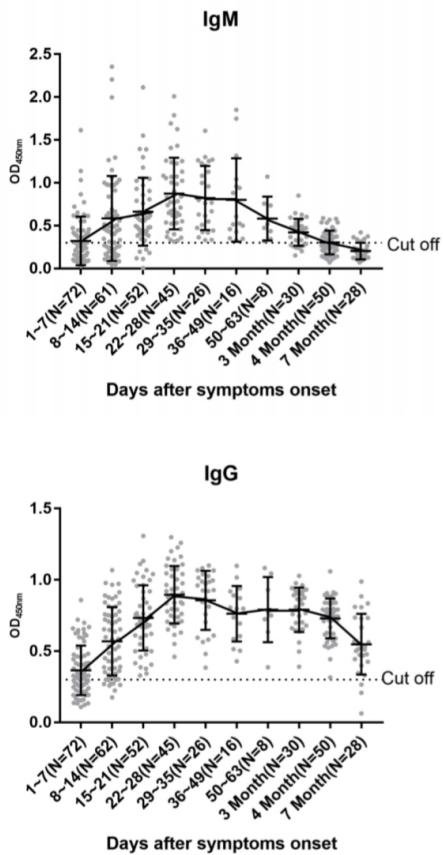


Figure 3: "IgM and IgG antibody responses against SARS-CoV-2 from the first day to four months after symptom onset. IgM becomes negative after 3 months of onset. IgG maintains high platform levels even at 4 months of disease onset but decreased in the 7th month ( $P=0.0013$ ,  $P < 0.01$ ). Line chart show mean and standard deviation, all data is displayed as symbol, Numbers of sample (N) are shown underneath".

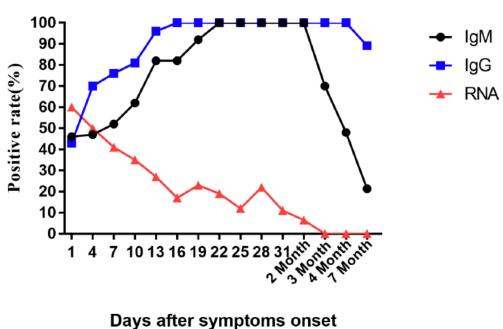


Figure 2. Graph of positive rates of RNA, IgM and IgG days after symptom onset. The positive IgM and IgG assays were higher than RT-qPCR, 7 and 4 days after the onset of the disease, respectively. RNA has 763 data from 107 patients. The results of IgM and IgG were testing by 390 sample from 165 patients. RNA was tested using throat swab or sputum sample.

# IN ANIMAL MODELS

## DEXAMETHASONE VS. COVID-19: AN EXPERIMENTAL STUDY IN LINE WITH THE PRELIMINARY FINDINGS OF A LARGE TRIAL

Hosseinzadeh MH, Shamshirian A, Ebrahimzadeh MA.. Int J Clin Pract. 2020 Dec 17:e13943. doi: 10.1111/ijcp.13943. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

### BLUF

Following the RECOVERY trial, researchers from the Mazandaran University of Medical Sciences in Iran conducted a mechanism-based study on the in-vivo effects of dexamethasone vs propranolol in different mouse models of hypoxia (asphyxic, circulatory, and hemic hypoxia). They found that dexamethasone conferred protection from both asphyxic and hemic hypoxia, while propranolol conferred protection against all 3 models of hypoxia to a slightly greater extent than dexamethasone. The authors propose that propranolol may be beneficial in the treatment of COVID-19 related hypoxia. However, this model simply shows a potential benefit of sympathetic inhibition during hypoxic states, but fails to account for the myriad other physiologic factors that occur during infection and immune response.

### ABSTRACT

**BACKGROUND:** The preliminary report of the RECOVERY large randomized controlled trial indicated a promising survival effect for dexamethasone therapy of coronavirus disease 2019 (COVID-19). This study aimed to investigate the anti-hypoxic activities of dexamethasone to understand a possible mechanism of its action in hypoxia-induced lethality through experimental models of hypoxia. **METHODS:** In this investigation, 84 Male BALB/c mice were randomly divided into groups of seven (12 groups). Treatment groups received 10 days of dexamethasone intraperitoneal injection at both human dose (~ 0.1 mg/kg) and the animal doses (~ 1 mg/kg). Control negative and positive groups were treated with 10 ml/kg of normal saline and 30 mg/kg of propranolol, respectively. Three experimental models of hypoxia; asphyctic, circulatory, and hemic were applied in this study. **RESULTS:** The findings showed that dexamethasone significantly prolonged the latency for death in the asphyctic model concerning the control group in both human ( $P<0.0001$ ) and animal dose ( $P<0.0001$ ). The results were also highly significant for both doses in the hemic model ( $P<0.001$ ). In the circulatory model, although a small increase was observed in death prolongation, results were not statistically significant for both doses in this model ( $P>0.05$ ). **CONCLUSIONS:** This experimental in vivo investigation demonstrated an excellent protective effect for ten days of dexamethasone treatment against hypoxia, especially in asphyctic and hemic models. In addition to promising dexamethasone outcomes, using propranolol as the positive control illustrated a very substantial anti-hypoxic effect even much better than dexamethasone in all models. It seems that propranolol would be a safe, potential, and prudent choice to invest in treating COVID-19 patients.

## TRANSMISSION & PREVENTION

### DEVELOPMENTS IN TRANSMISSION & PREVENTION

#### COVID-19 VACCINES MAY NOT PREVENT NASAL SARS-COV-2 INFECTION AND ASYMPTOMATIC TRANSMISSION

Bleier BS, Ramanathan M Jr, Lane AP.. Otolaryngol Head Neck Surg. 2020 Dec 15:194599820982633. doi: 10.1177/0194599820982633. Online ahead of print.

Level of Evidence: 5 - Expert Opinion

#### BLUF

A review of current data on COVID-19 transmission and vaccine efficacy by otolaryngologists from Harvard Medical School and Johns Hopkins School of Medicine illustrates how COVID-19 mRNA vaccines generate immunogenicity by creating IgG antibodies against the SARS-CoV-2 virus. However IgG antibodies, while preventing patients from clinically getting sick with COVID-19, do not stop the virus from replicating in the upper airway -- as this requires secretory IgA antibodies -- suggesting that transmission precautions should still be widely practiced even after vaccination.

#### ABSTRACT

Current COVID-19 vaccine candidates are administered by injection and designed to produce an IgG response, preventing viremia and the COVID-19 syndrome. However, systemic respiratory vaccines generally provide limited protection against viral replication and shedding within the airway, as this requires a local mucosal secretory IgA response. Indeed, preclinical studies of adenovirus and mRNA candidate vaccines demonstrated persistent virus in nasal swabs despite preventing COVID-19. This suggests that systemically vaccinated patients, while asymptomatic, may still become infected and transmit live virus from the upper airway. COVID-19 is known to spread through respiratory droplets and aerosols. Furthermore, significant evidence has shown that many clinic and surgical endonasal procedures are aerosol generating. Until further knowledge is acquired regarding mucosal immunity following systemic vaccination, otolaryngology providers should maintain precautions against viral transmission to protect the proportion of persistently vulnerable patients who exhibit subtotal vaccine efficacy or waning immunity or who defer vaccination.

## PREVENTION IN THE COMMUNITY

#### QUESTIONING COVID-19 SURFACE STABILITY AND FOMITE SPREADING IN THREE AEROMEDICAL CASES: A CASE SERIES

Horoho S, Musik S, Bryant D, Brooks W, Porter IM.. Mil Med. 2020 Dec 17:usaa548. doi: 10.1093/milmed/usaa548. Online ahead of print.

Level of Evidence: 4 - Case-series

#### BLUF

Physicians from the US Navy evaluated three cases of PCR-confirmed COVID-19 at the Naval Air Squadron in Jacksonville, Florida. They conducted contact tracing (Table 1) and found transmission likely occurred at a public restaurant in case 1 and squadron convenience store, beach, shopping center, or restaurant in cases 2 and 3. Military personnel (n=195) who contacted surfaces or equipment touched by cases 2 or 3 were tested, and only one individual tested positive for SARS-CoV-2. Authors conclude that despite laboratory-based evidence that SARS-CoV-2 persists on surfaces, these cases suggest fomite transmission may be less concerning than previously thought, and further studies are needed to clarify the role of fomite transmission in real-world scenarios.

## ABSTRACT

It is well established that coronavirus disease 2019 is primarily transmitted through respiratory droplets, and there is mounting research speculation that it may also be transmitted via fomites. Several studies have shown that the virus can persist on both porous and nonporous surfaces for hours to days, depending upon the material. This article examines three cases of polymerase chain reaction-proven severe acute respiratory syndrome coronavirus 2 infection with several additional individuals meeting CDC close contact criteria. In 1 case, 195 downstream contacts were all tested to prevent a mass outbreak in a deployment posture. Analysis of these contacts yielded only a single positive test, which could be reasonably ascribed to respiratory droplet transmission. While these cases and their contacts ultimately represent a small sample size, we suggest fomite spread may not be a significant means of transmission for severe acute respiratory syndrome coronavirus 2 in real-world operational scenarios.

## FIGURES

**TABLE I.** Summary of Case Series Demographics and Symptoms

	Case 1	Case 2	Case 3
Age/gender	22/female	20/male	19/male
Symptoms	Congestion, headache, cough, myalgia, dyspnea, and left rib pain	Headache and subjective fever	Burning sensation in chest, headache, congestion, anosmia, and ageusia
Exposure	Public restaurant	Geedunk, public beach, restaurant, and shopping center	Geedunk, public beach, restaurant, and shopping center
CDC close contacts	9	203	203
Downstream positives	1	0	0

## DIFFERENTIAL HOUSEHOLD ATTACK RATES MIRROR THE ABILITY TO CONTROL COVID-19

Cook AR, Dickens BL, Wilder-Smith A.. Clin Infect Dis. 2020 Dec 11:ciaa1842. doi: 10.1093/cid/ciaa1842. Online ahead of print.

Level of Evidence: 5 - Expert Opinion

## BLUF

An international group of researchers discuss possible explanations for why the household secondary attack rates (HSAR) in Asian countries such as Singapore and China (12% and 11% respectively) are significantly lower than in the US (30-50%). The authors attribute this difference to self-isolation protocols in Asia, such as the Chinese "fangcang shelter hospitals," which provide COVID-19 positive individuals with a healthcare facility where they can quarantine until no longer infectious. Conversely, the strategy in the US and Europe centers around home quarantining, leading to higher rates of secondary infections (Figure 1). While significant cultural and structural differences exist that would prevent the US from successfully implementing a similar self-isolation protocol to those seen in the Asian countries highlighted, further research is needed to identify areas for improvement in current US public health policies.

## FIGURES

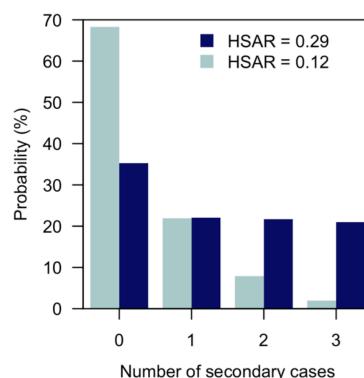


Figure 1. Number of additional infections in households of four members with a single index case, when the household secondary attack rate (HSAR) is 0.29 (based on Ref [1]) or 0.12 (based on Ref [3]). Probabilities are from a chain-binomial model [7]. The average number of secondary cases in the HSAR=0.29 case is 1.3; for HSAR=0.12 it is 0.4.

## MANAGEMENT

### ACUTE CARE

#### PRE-TEST PROBABILITY FOR SARS-COV-2-RELATED INFECTION SCORE: THE PARIS SCORE

Tordjman M, Mekki A, Mali RD, Saab I, Chassagnon G, Guillo E, Burns R, Eshagh D, Beaune S, Madelin G, Bessis S, Feydy A, Mihoubi F, Doumenc B, Mouthon L, Carlier RY, Drapé JL, Revel MP.. PLoS One. 2020 Dec 17;15(12):e0243342. doi: 10.1371/journal.pone.0243342. eCollection 2020.

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

#### BLUF

A multicenter retrospective study conducted by French physicians at the Cochin Hospital utilized demographic data, clinical symptomatology, and results of lab tests from 605 patients with clinical suspicion of COVID-19 to create a pre-test probability score of SARS-CoV-2 infection (the PARIS score). These results revealed that fever, myalgias, lymphopenia, and elevated CRP (Tables 1 and 2) had the highest positive predictive value, though no clinical variable was individually significant. The high-probability PARIS score had a positive predictive value of 93%, while the low-probability score had a negative predictive value of 98% (Table 4). This study adds to the existing body of evidence by providing an evidenced-based prediction tool that can easily be incorporated into clinical practice, however further external validation is still needed.

#### ABSTRACT

**INTRODUCTION:** In numerous countries, large population testing is impossible due to the limited availability of RT-PCR kits and CT-scans. This study aimed to determine a pre-test probability score for SARS-CoV-2 infection. **METHODS:** This multicenter retrospective study (4 University Hospitals) included patients with clinical suspicion of SARS-CoV-2 infection. Demographic characteristics, clinical symptoms, and results of blood tests (complete white blood cell count, serum electrolytes and CRP) were collected. A pre-test probability score was derived from univariate analyses of clinical and biological variables between patients and controls, followed by multivariate binary logistic analysis to determine the independent variables associated with SARS-CoV-2 infection. **RESULTS:** 605 patients were included between March 10th and April 30th, 2020 (200 patients for the training cohort, 405 consecutive patients for the validation cohort). In the multivariate analysis, lymphocyte ( $<1.3 \text{ G/L}$ ), eosinophil ( $<0.06 \text{ G/L}$ ), basophil ( $<0.04 \text{ G/L}$ ) and neutrophil counts ( $<5 \text{ G/L}$ ) were associated with high probability of SARS-CoV-2 infection but no clinical variable was statistically significant. The score had a good performance in the validation cohort (AUC = 0.918 [CI: [0.891-0.946]; STD = 0.014] with a Positive Predictive Value of high-probability score of 93% (95%CI: [0.89-0.96]). Furthermore, a low-probability score excluded SARS-CoV-2 infection with a Negative Predictive Value of 98% (95%CI: [0.93-0.99]). The performance of the score was stable even during the last period of the study (15-30th April) with more controls than infected patients. **CONCLUSIONS:** The PARIS score has a good performance to categorize the pre-test probability of SARS-CoV-2 infection based on complete white blood cell count. It could help clinicians adapt testing and for rapid triage of patients before test results.

## FIGURES

	<b>Patients</b>	<b>Controls</b>	<b>p-value</b>
n	100	100	
Age	65 [24]	60 [31]	0.14
Sex (M:F)	65:35	45:55	0.005
<i>Clinical characteristics</i>			
Cough	79	66	0.04
Fever	90	63	<0.001
Temperature at ER	37.7 [1.4]	37 [0.7]	0.28
Shortness of breath	70	69	0.88
Saturation	95% [6]	96% [4]	0.03
Diarrhea	22	14	0.14
Myalgia	34	17	0.006
Headaches	16	18	0.71
Anosmia	11	5	0.12
Agueusia	14	4	0.01
Time from onset	6d [5]	5d [5]	0.12
<i>Comorbidities</i>			
Comorbidities	61	70	0.18
Diabetes	19	19	1
Hypertension	32	21	0.08
Renal failure	7	6	0.77
Pulmonary disease <sup>a</sup>	17	43	<0.001
Immunodeficiency/ autoimmune disease	13	23	0.07
<i>Including: HIV</i>	2	5	0.25
<i>Treatments</i>			
Steroids	4	7	0.35
Chemotherapy	2	3	0.65
<i>Blood tests</i>			
Hemoglobin (g/dL)	13.70 [2.50]	13.20 [2.10]	0.31
Lymphocytes (G/L)	0.87 [0.48]	1.96. [1.18]	<0.001
Neutrophils (G/L)	4.29 [3.06]	6.47 [4.55]	<0.001
Eosinophils (G/L)	0.00 [0.01]	0.10 [0.19]	<0.001
Basophils (G/L)	0.01 [0.03]	0.04 [0.01]	<0.001
Monocytes (G/L)	0.44 [0.33]	0.70 [0.46]	<0.001
Platelets (G/L)	195.00 [91.75]	253.00 97.25]	<0.001
Sodium (mmol/L)	136.00 [5.00]	137.00 [4.25]	0.008
Potassium (mmol/L)	4.0 [0.50]	4.00 [0.40]	0.97
Chloride (mmol/L)	97.00 [4.00]	98.50 [5.00]	0.001
Bicarbonate (mmol/L)	24.00 [3.83]	24.00 [4.03]	0.82
Total protein (g/L)	71.80 [6.80]	74.00 [7.00]	0.07
Creatinine ( $\mu$ mol/L)	82.00 [33.50]	78.00 [31.50]	0.39
CRP (mg/L)	62.2 [78.20]	11.1 [67.40]	<0.001

<sup>a</sup>Pulmonary disease: asthma, COPD or restrictive syndrome; Results are presented as median [interquartile range]; G/L =  $10^9$ / Liter.

Table 1. Characteristics of patients with SARS-CoV-2 infection (confirmed with both PCR and CT) and controls.

	<b>Patients</b>	<b>Controls</b>	<b>B</b>	<b>Exp(B)/OR</b>	<b>p-value</b>
Basophils<0.04G/L	92	41	1.89	6.59	0.001
Eosinophils <0.06G/L	91	36	1.92	6.81	0.001
Lymphocytes<1.3G/L	89	24	2.56	12.88	<0.001
Neutrophils<5G/L	64	30	2.00	7.73	<0.001

OR: Odd-Ratio; Nagelkerke R<sup>2</sup> = 0.70; Hosmer-Lemeshow goodness of fit statistic: p = 0.83.

Table 2. Binary logistic regression using descending wald model.

<b>PARIS score</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>PPV</b>	<b>NPV</b>	<b>N</b>
0	1	0	0.64	NA	40
1	1	0.28	0.71	1	39
2	0.99	0.53	0.79	0.98	46
3	0.92	0.72	0.85	0.83	60
4	0.79	0.90	0.93	0.70	120
5	0.38	0.99	0.99	0.47	100

PPV = Positive Predictive Value; NPV = Negative Predictive Value; N: Number of Patients.

Table 4. Performance in the validation cohort depending on the value of the PARIS score (performance for a score to the value).

## CRITICAL CARE

### PULMONARY EMBOLISM AND DEEP VEIN THROMBOSIS IN COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Suh YJ, Hong H, Ohana M, Bompard F, Revel MP, Valle C, Gervaise A, Poissy J, Susen S, Hékimian G, Artifoni M, Periard D, Contou D, Delaloye J, Sanchez B, Fang C, Garzillo G, Robbie H, Yoon SH.. Radiology. 2020 Dec 15:203557. doi: 10.1148/radiol.2020203557. Online ahead of print.

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

#### BLUF

A systematic review by South Korean radiologists found the incidence of pulmonary embolism (PE) and deep vein thrombosis (DVT) in patients with COVID-19 were 16.5% and 14.8% respectively, and that only 42% of PE patients had evidence of DVT. Additionally, data revealed that D-dimer levels of 500 and 1000 micrograms/L showed high sensitivity (96% and 91%, respectively) but low specificity (10% and 24%) for detecting PE. These findings suggest that coagulopathy in COVID-19 may be more severe than typical illness (estimated rates of PE and DVT in critically-ill hospitalized patients 6-10%) and possibly occur via a distinct mechanism of localized endothelialitis instead of lower extremity DVT.

#### ABSTRACT

**Background** The association of pulmonary embolism (PE) with deep vein thrombosis (DVT) in patients with coronavirus disease 2019 (COVID-19) remains unclear, and the diagnostic accuracy of D-dimer tests for PE is unknown. **Purpose** To conduct meta-analysis of the study-level incidence of PE and DVT and to evaluate the diagnostic accuracy of D-dimer tests for PE from multicenter individual patient data. **Materials and Methods** A systematic literature search identified studies evaluating the incidence of PE or DVT in patients with COVID-19 from January 1, 2020, to June 15, 2020. These outcomes were pooled using a random-effects model and were further evaluated using metaregression analysis. The diagnostic accuracy of D-dimer tests for PE was estimated on the basis of individual patient data using the summary receiver operating characteristic curve. **Results** Twenty-seven studies with 3342 patients with COVID-19 were included in the analysis. The pooled incidence rates of PE and DVT were 16.5% (95% CI: 11.6, 22.9;  $I^2 = 0.93$ ) and 14.8% (95% CI: 8.5, 24.5;  $I^2 = 0.94$ ), respectively. PE was more frequently found in patients who were admitted to the intensive care unit (ICU) (24.7% [95% CI: 18.6, 32.1] vs 10.5% [95% CI: 5.1, 20.2] in those not admitted to the ICU) and in studies with universal screening using CT pulmonary angiography. DVT was present in 42.4% of patients with PE. D-dimer tests had an area under the receiver operating characteristic curve of 0.737 for PE, and D-dimer levels of 500 and 1000 mug/L showed high sensitivity (96% and 91%, respectively) but low specificity (10% and 24%, respectively). **Conclusion** Pulmonary embolism (PE) and deep vein thrombosis (DVT) occurred in 16.5% and 14.8% of patients with coronavirus disease 2019 (COVID-19), respectively, and more than half of patients with PE lacked DVT. The cutoffs of D-dimer levels used to exclude PE in preexisting guidelines seem applicable to patients with COVID-19. RSNA, 2020 Supplemental material is available for this article. See also the editorial by Woodard in this issue.

## FIGURES

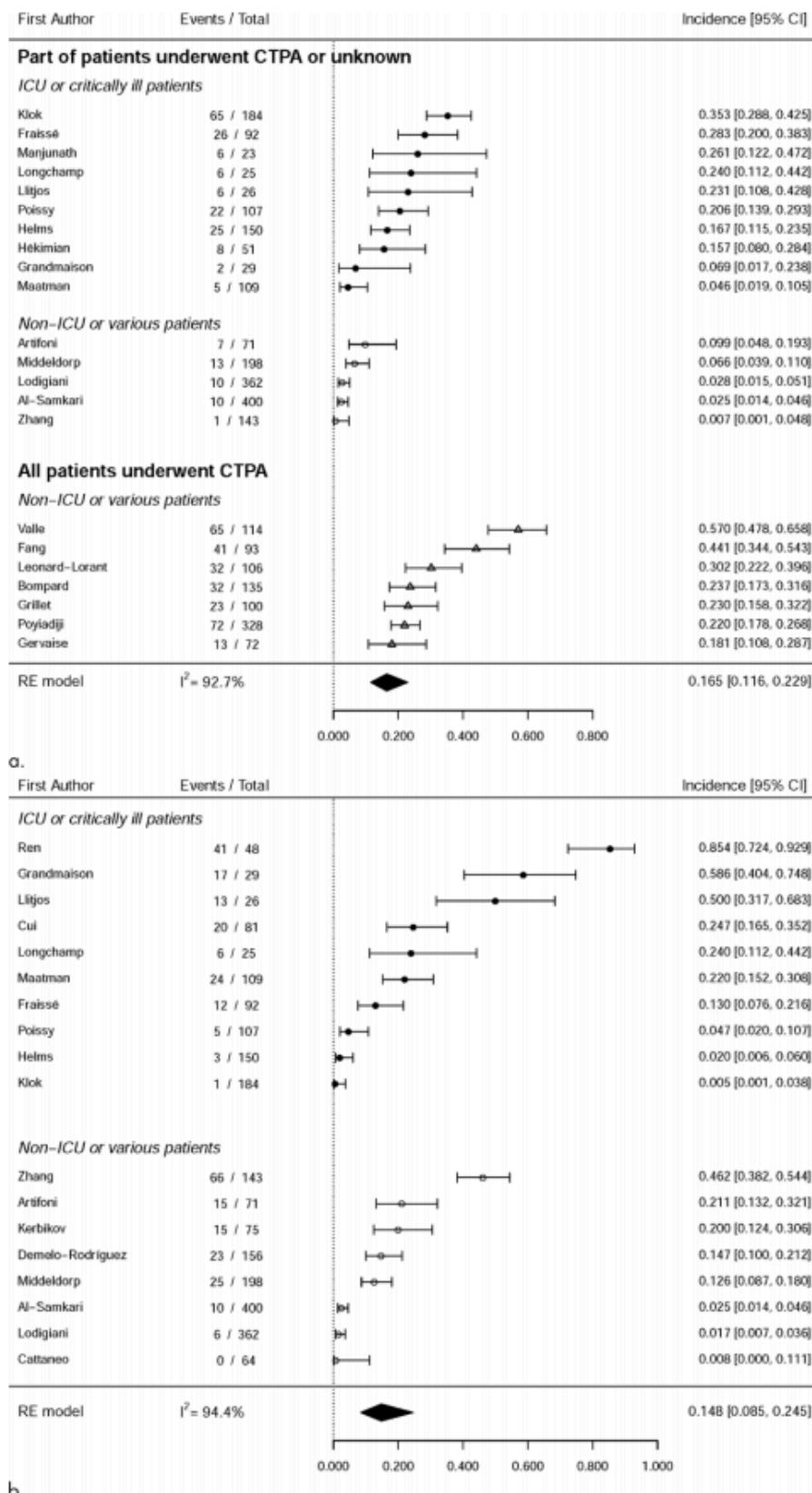


Figure 2 a,b: Forest plots show pooled incidence rates of (a) pulmonary embolism (PE) ( $n = 22$ ) and (b) deep vein thrombosis (DVT) ( $n = 18$ ) in patients with coronavirus disease 2019. The estimated overall incidence rates of PE and DVT were 16.5% (95% CI: 11.6, 22.9) and 14.8% (95% CI: 8.5, 24.5), respectively. Significant inter-study heterogeneity was seen in all groups. CTPA = CT pulmonary angiography, ICU = intensive care unit, RE = random effects.

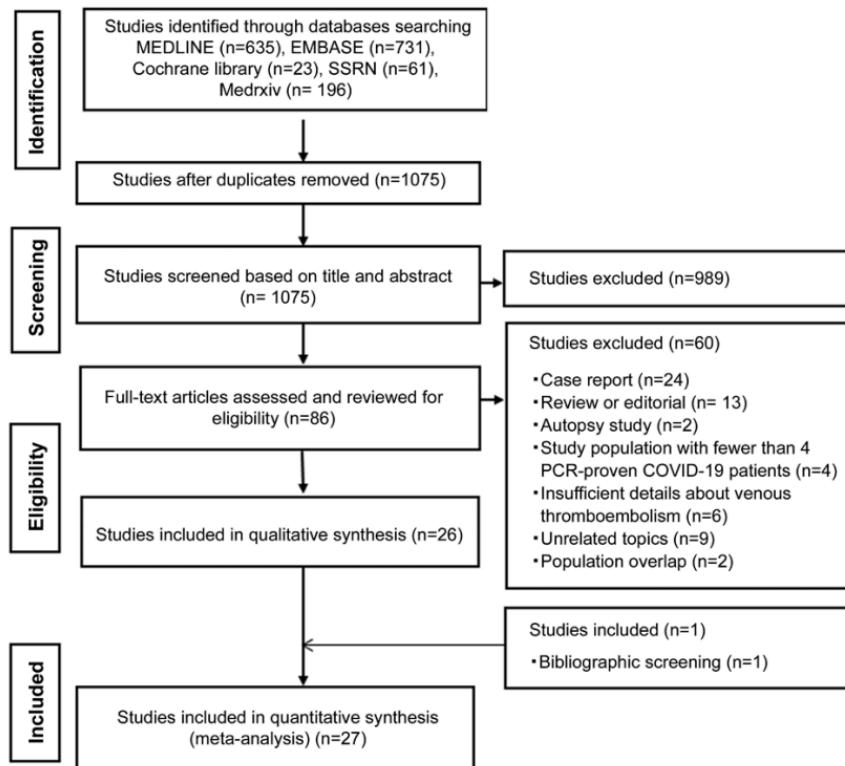


Figure 1: Flowchart of the literature review process. COVID-19 = coronavirus disease 2019, PCR = polymerase chain reaction.

Parameter	Incidence (%)	Heterogeneity*
PE		
Overall	16.5 (11.6, 22.9)	NA
Study design		
Retrospective ( <i>n</i> = 20)	15.5 (10.4, 22.6)	<.001, 0.93
Prospective ( <i>n</i> = 2)	25.1 (11.1, 47.2)	<.001, 0.93
Study population <sup>†</sup>		
Non-ICU or various ( <i>n</i> = 12)	10.5 (5.1, 20.2)	<.001, 0.95
ICU or critically ill patients ( <i>n</i> = 18)	24.7 (18.6, 32.1)	<.001, 0.82
Anticoagulation		
None or unknown ( <i>n</i> = 2)	21.0 (15.6, 27.8)	0.43, <0.001
Yes ( <i>n</i> = 20)	16.0 (10.8, 23.0)	<.001, 0.93
Proportion of patients undergoing CT pulmonary angiography		
Part of patients or unknown ( <i>n</i> = 15)	11.3 (6.7, 18.4)	<.001, 0.92
All patients ( <i>n</i> = 7)	30.2 (21.0, 41.3)	<.001, 0.91
DVT		
Overall	14.8 (8.5, 24.5)	NA
Study design		
Retrospective ( <i>n</i> = 15)	18.8 (10.5, 31.5)	<.001, 0.95
Prospective ( <i>n</i> = 3)	3.0 (0.4, 19.5)	<.001, 0.91
Study population <sup>†</sup>		
Non-ICU or various ( <i>n</i> = 8)	7.4 (3.2, 16.2)	<.001, 0.93
ICU or critically ill patients ( <i>n</i> = 13)	21.2 (11.1, 36.8)	<.001, 0.93

Note.—Numbers in parentheses are 95% CIs. DVT = deep vein thrombosis, ICU = intensive care unit, NA = nonapplicable, PE = pulmonary embolism.

\* Values indicate the *P* value for Cochran *Q* test and *I*<sup>2</sup>.

<sup>†</sup> When applicable, data were separately extracted for patients admitted to the ICU and those who were not from studies of disease of various levels of severity and were presented as different subgroups.

Table 2: Pooled Incidence of PE and DVT according to Study Characteristics

# A POSSIBLE INCREASED RISK OF METAMIZOLE-ASSOCIATED NEUTROPENIA AMONG COVID-19 PATIENTS

Lerman TT, Sagi M, Shafir Y, Sheena L, Cohen E, Goldberg E, Krause I.. Br J Clin Pharmacol. 2020 Dec 17. doi: 10.1111/bcp.14703. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

## BLUF

A group of physicians from Israel describe a series of 3 patients with COVID-19 who were treated with metamizole and subsequently developed severe neutropenia. This paper raises concerns that COVID-19 could increase the risk of metamizole-induced neutropenia, and may change WHO standards of treatment.

## SUMMARY

Metamizole is an analgesic and anti-pyretic which is currently banned in the United States.

Case 1: 33-year-old female admitted after her fifth delivery without any complications. She took metamizole for abdominal cramps after delivery. On admission, she had a positive COVID-19 test and an absolute neutrophil count of 700 cells/ul. She discontinued metamizole and after 2 days had a spontaneous recovery of her neutrophil count.

Case 2: 53-year-old female with a history of migraines, smoking and a warm autoimmune hemolytic anemia. On the third day of hospitalization, after extensive testing for liver illnesses and testing positive for COVID-19, she became febrile and received metamizole. On day 10, after receiving 1g metamizole PO, she became severely neutropenic with an absolute neutrophil count of 300 cells/ul that decreased to 0. Though the drug was discontinued, her neutrophil count never recovered and the patient died of complications of COVID-19.

Case 3: 53-year-old male with severe mental retardation and Barrett's esophagus presented 10 days after a positive COVID-19 test result with diffuse interstitial opacities with right sided predominance. He received 1g IV metamizole due to high grade fever. Upon admission, his leukocyte count was 1,600 cells/ul with an absolute neutrophil count of 1,500 cells/ul. By day 2 of hospitalization, his leukocytes had decreased to 1,000 cells/ul and neutrophils to 900 cells/ul without any other significant cell changes.

## ABSTRACT

Metamizole is commonly used as analgesic and antipyretic drug. The use of metamizole is prohibited in several countries due to its rare side effect of neutropenia and even agranulocytosis. Among the many symptoms of COVID-19 fever and diffuse pain predominant and therefore it can be assumed that metamizole may be widely used in the current epidemic period. So far, there have been no reports on the safety of metamizole in COVID-19 patients. We describe a series of 3 patients who developed severe neutropenia under metamizole treatment raising a concern of a possible increased risk of this side effect among COVID-19 patients.

## R&D: DIAGNOSIS & TREATMENTS

### DEVELOPMENTS IN TREATMENTS

#### TOCILIZUMAB IN PATIENTS HOSPITALIZED WITH COVID-19 PNEUMONIA

Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, Cameron ML, Garcia-Diaz J, Chávez V, Mekebеб-Reuter M, Lima de Menezes F, Shah R, González-Lara MF, Assman B, Freedman J, Mohan SV.. N Engl J Med. 2020 Dec 17. doi: 10.1056/NEJMoa2030340. Online ahead of print.

Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

#### BLUF

This industry-sponsored phase 3 randomized controlled trial involving 389 hospitalized patients with COVID-19 pneumonia found that patients who received IV tocilizumab had faster recovery rates and less chance of progression to mechanical ventilation or death after 28 days compared to the placebo group (12% vs 19.3%, hazard ratio 0.56, 95% CI 0.33-0.97, p=0.04; as shown in Figure 2), suggesting that this IL-6 inhibitor may be an effective treatment to reduce hospital days and ventilator use in COVID-19. Importantly, this trial was conducted in 6 countries and included over 80% minority populations, who are known to have disproportionately worse outcomes and less inclusion in clinical trials compared to their white counterparts. However, there was no significant difference in overall all-cause mortality, and the current cost of this brand name biologic may be prohibitive for wide scale use in these populations.

#### ABSTRACT

**BACKGROUND:** Coronavirus disease 2019 (Covid-19) pneumonia is often associated with hyperinflammation. Despite the disproportionate incidence of Covid-19 among underserved and racial and ethnic minority populations, the safety and efficacy of the anti-interleukin-6 receptor antibody tocilizumab in patients from these populations who are hospitalized with Covid-19 pneumonia are unclear. **METHODS:** We randomly assigned (in a 2:1 ratio) patients hospitalized with Covid-19 pneumonia who were not receiving mechanical ventilation to receive standard care plus one or two doses of either tocilizumab (8 mg per kilogram of body weight intravenously) or placebo. Site selection was focused on the inclusion of sites enrolling high-risk and minority populations. The primary outcome was mechanical ventilation or death by day 28. **RESULTS:** A total of 389 patients underwent randomization, and the modified intention-to-treat population included 249 patients in the tocilizumab group and 128 patients in the placebo group; 56.0% were Hispanic or Latino, 14.9% were Black, 12.7% were American Indian or Alaska Native, 12.7% were non-Hispanic White, and 3.7% were of other or unknown race or ethnic group. The cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was 12.0% (95% confidence interval [CI], 8.5 to 16.9) in the tocilizumab group and 19.3% (95% CI, 13.3 to 27.4) in the placebo group (hazard ratio for mechanical ventilation or death, 0.56; 95% CI, 0.33 to 0.97; P = 0.04 by the log-rank test). Clinical failure as assessed in a time-to-event analysis favored tocilizumab over placebo (hazard ratio, 0.55; 95% CI, 0.33 to 0.93). Death from any cause by day 28 occurred in 10.4% of the patients in the tocilizumab group and 8.6% of those in the placebo group (weighted difference, 2.0 percentage points; 95% CI, -5.2 to 7.8). In the safety population, serious adverse events occurred in 38 of 250 patients (15.2%) in the tocilizumab group and 25 of 127 patients (19.7%) in the placebo group. **CONCLUSIONS:** In hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival. No new safety signals were identified. (Funded by Genentech; EMPACTA ClinicalTrials.gov number, NCT04372186.).

## FIGURES

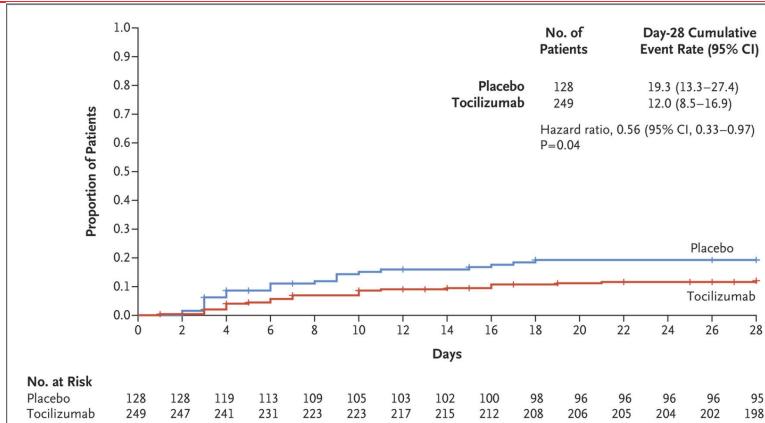


Figure 2. Time to Mechanical Ventilation or Death by Day 28 in the Modified Intention-to-Treat Population.

The cumulative proportion of patients was estimated with the Kaplan-Meier method and compared in the two groups with the use of the stratified log-rank test. The stratified Cox proportional-hazards model was used to estimate the hazard ratio and 95% confidence interval. Data on patients who did not receive mechanical ventilation or who died on or before day 28 were censored at day 28 or the date of the last available follow-up, whichever occurred first.

## SARS-COV-2-SPECIFIC T CELLS ARE RAPIDLY EXPANDED FOR THERAPEUTIC USE AND TARGET CONSERVED REGIONS OF THE MEMBRANE PROTEIN

Keller MD, Harris KM, Jensen-Wachspress MA, Kankate VV, Lang H, Lazarski CA, Durkee-Shock J, Lee PH, Chaudhry K, Webber K, Datar A, Terpilowski M, Reynolds EK, Stevenson EM, Val S, Shancer Z, Zhang N, Ulrey R, Ekanem U, Stanojevic M, Geiger A, Liang H, Hoq F, Abraham AA, Hanley PJ, Cruz CR, Ferrer K, Dropulic L, Gangler K, Burbelo PD, Jones RB, Cohen JI, Bolland CM.. Blood. 2020 Dec 17;136(25):2905-2917. doi: 10.1182/blood.2020008488.

Level of Evidence: 5 - Mechanism-based reasoning

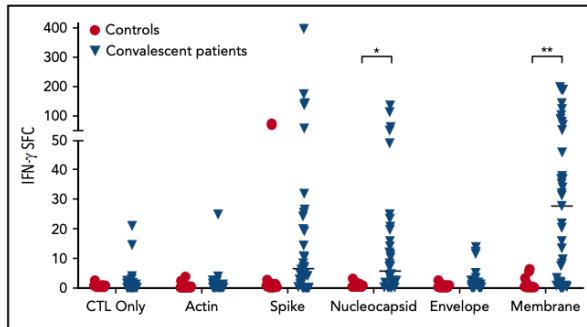
## BLUF

A group of hematology and immunology experts illustrate how SARS-CoV-2 directed T-cell immunotherapy may be a feasible method for prevention and early treatment of COVID-19 in immunocompromised patients. This study demonstrates how in-vitro expansion of SARS-CoV-2 specific T-cells in convalescent plasma donors can be directed to recognize and elicit a robust T-cell immune response to common viral antigens (Figures 1-3). Specifically, they found increased interferon- $\gamma$  production (representative of "polyfunctional T-cell response") to SARS-CoV-2 spike protein, membrane protein, and nucleocapsid peptide in 12 (26%), 27 (59%), and 10 (22%) convalescent donors (respectively), as well as in 2 of 15 unexposed controls. The authors propose that this adaptive immune response is critical for developing effective long-term immunity, and may be beneficial for immunocompromised patients with blood disorders or bone marrow transplants.

## ABSTRACT

T-cell responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been described in recovered patients, and may be important for immunity following infection and vaccination as well as for the development of an adoptive immunotherapy for the treatment of immunocompromised individuals. In this report, we demonstrate that SARS-CoV-2-specific T cells can be expanded from convalescent donors and recognize immunodominant viral epitopes in conserved regions of membrane, spike, and nucleocapsid. Following in vitro expansion using a good manufacturing practice-compliant methodology (designed to allow the rapid translation of this novel SARS-CoV-2 T-cell therapy to the clinic), membrane, spike, and nucleocapsid peptides elicited interferon-gamma production, in 27 (59%), 12 (26%), and 10 (22%) convalescent donors (respectively), as well as in 2 of 15 unexposed controls. We identified multiple polyfunctional CD4-restricted T-cell epitopes within a highly conserved region of membrane protein, which induced polyfunctional T-cell responses, which may be critical for the development of effective vaccine and T-cell therapies. Hence, our study shows that SARS-CoV-2 directed T-cell immunotherapy targeting structural proteins, most importantly membrane protein, should be feasible for the prevention or early treatment of SARS-CoV-2 infection in immunocompromised patients with blood disorders or after bone marrow transplantation to achieve antiviral control while mitigating uncontrolled inflammation.

## FIGURES



**Figure 1. T-cell recognition of SARS-CoV-2 viral antigens.**

Specificity of the expanded cells in response to SARS-CoV-2 antigens from convalescent patients ( $n = 46$ ) and unexposed controls ( $n = 15$ ) was assayed by IFN- $\gamma$  ELISpot assay (bars = median). Unstimulated T cells (control [CTL] only) and stimulation with actin were used as negative controls. Results are presented as spot-forming units (SFC) per  $1 \times 10^3$  cells. Specificity was defined as  $\geq 20$  spots per well with significance above background (actin) via 2-tailed Student  $t$  test.  
\* $P = .0008$ , \*\* $P = 6.24 \times 10^{-6}$ .

**Table 2. Identified class 2 epitopes in membrane, nucleocapsid, and spike proteins and predicted HLA restrictions**

Peptide sequence	Amino acid location	Subject	HLA-DRB1	HLA-DRB3	HLA-DRB4	HLA-DRB5	HLA-DQA1	HLA-DQB1	HLA-DPA1	HLA-DPB1
<b>Membrane</b>										
LRGHLRIAGHHLGRC	144-159	6 10 13 18	07:01, <b>11:04</b> 07:01, <b>11:01</b> <b>11:04</b> , 15:02 <b>11:04</b> , 15:01	02:02 02:02 02:02 02:02	01:03 01:01 01:01, 01:03 01:01		01:02 01:03, 05:01 01:02, 05:01 01:02, 05:01	03:01, 03:03 02:02, 03:01 03:01, 06:01 03:01, 06:02	01:03, 02:01 01:03, 03:01 01:03, 02:01 01:03, 02:01	03:01, 03:03 04:01, 11:01 02:01, 14:01 04:01, 14:01
LRIAGHHLGRCDIKD	148-163	6 13	07:01, 11:04 11:04, 15:02	02:02 02:02	01:03 01:01, 01:03	01:02 01:02	03:01, 05:01 03:01, 05:01 03:01, 05:01	01:03, 03:03 01:03, 02:01 01:03, 03:01	03:01, 02:01 03:01, 03:03 04:01, 11:01	
SRTLSYYKLGASQRV	173-188	10 13 17 18 21 23	07:01, 11:01 11:04, 15:02 12:01, 15:01 11:04, 15:01 03:02, 16:02 01:01, 03:01	02:02 02:02 02:02 02:02 01:01 01:01	01:01 01:01, 01:03 01:01 01:01, 01:03 01:01, 01:03 01:01, 01:03	01:02, 05:01 02:02 01:02, 04:01 01:01, 05:01 01:02, 05:01 01:01	02:01, 03:01 03:01, 06:01 03:01, 06:02 04:02, 05:02 02:02, 02:02 01:03, 01:03	01:03, 02:01 01:03, 02:01 01:03, 02:01 02:01, 14:01 02:01, 14:01 02:01, 02:01		
SYYKLGASQRVAGDS	177-192	10 17 21 23	<b>07:01</b> , 11:01 12:01, 15:01 03:02, 16:02 <b>01:01</b> , 03:01	02:02 02:02 01:02 01:01	01:01 01:01 01:01, 01:03 01:01, 01:03	01:01 02:02, 05:01 01:02, 04:01 02:02	02:01, <b>05:01</b> 03:01, <b>05:01</b> 04:02, 05:02 02:01, 05:01	01:03, 03:01 01:03, 01:03 02:02, 02:02 01:03, 01:03	04:01, 11:01 02:01, 04:01 01:01, 01:01 02:01, 02:01	
LGASQRVAGDSGFAA	181-195	23	01:01, 03:01	01:01	01:01, 01:03			01:01, 05:01	02:01, 05:01	02:01, 02:01
<b>Nucleocapsid</b>										
KPRQKRTATKAYNVT AFFGMSRIGMVETPS	257-271 313-327	24 18	04:01, 07:01 11:04, 15:01	01:01 02:02	01:03		03:01, 05:05 01:02, 05:01	03:01, 03:02 03:01, 06:02	<b>02:01, 02:01</b> 01:03, 02:01	<b>14:01, 14:01</b> 04:01, 14:01
<b>Spike</b>										
PFFSNVTWFHAIHVS NVTWFHAIHVGTING SKHTPINLVRDLPQG PINLVRDLPQGFSAL YNYLYRLFRKSNLKP	57-71 61-75 205-219 209-223 449-463	8 8 37 21 37	03:01, 13:01 03:01, 13:01 03:01, 04:01 03:02, 16:02 <b>03:01</b> , 04:01	01:01 01:01 01:01 01:62 <b>01:01</b>	01:03 01:03 01:03 01:01, 01:03 01:03		01:03, 05:01 01:03, 05:01 03:01, 05:01 01:02, 04:01 03:01, 05:01	02:01, 06:03 02:01, 06:03 02:01, 03:02 04:02, 05:02 02:01, 03:02	01:03, 01:03 01:03, 01:03 01:03, 01:03 01:02, 02:02 01:03, 01:03	04:01, 04:01 04:01, 04:01 02:01, 03:01 01:01, 01:01 02:01, 03:01

Boldface type indicates a strong binder (< 2); italic type indicates a weak binder (2-10).

# MENTAL HEALTH & RESILIENCE NEEDS

## IMPACT ON PUBLIC MENTAL HEALTH

### TRENDS IN U.S. EMERGENCY DEPARTMENT VISITS RELATED TO SUSPECTED OR CONFIRMED CHILD ABUSE AND NEGLECT AMONG CHILDREN AND ADOLESCENTS AGED <18 YEARS BEFORE AND DURING THE COVID-19 PANDEMIC - UNITED STATES, JANUARY 2019-SEPTEMBER 2020

Swedo E, Idaikkadar N, Leemis R, Dias T, Radhakrishnan L, Stein Z, Chen M, Agathis N, Holland K. MMWR Morb Mortal Wkly Rep. 2020 Dec 11;69(49):1841-1847. doi: 10.15585/mmwr.mm6949a1.

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

#### BLUF

Scientists from the Center for Disease Control studied emergency department (ED) visits from January 6, 2019 - September 6, 2020 and found an increase in the proportion of ED visits related to abuse and neglect in children and adolescents during the COVID-19 pandemic despite a lower number of ED visits overall (Figure 1A and 1B), and those visits were more likely to result in hospitalization than in 2019. This suggests that the social and economic effects of the pandemic (loss of income and increased stress related to parental child care, increased substance use, and mental health conditions) may be the cause of this increase, and the authors suggest strengthening families' economic support, ensuring family-friendly work policies, and modifying early home visitation practices to improve the safety of children and adolescents.

#### ABSTRACT

Heightened stress, school closures, loss of income, and social isolation resulting from the coronavirus disease 2019 (COVID-19) pandemic have increased the risk for child abuse and neglect (1). Using National Syndromic Surveillance Program (NSSP) data from January 6, 2019-September 6, 2020, CDC tabulated weekly numbers of emergency department (ED) visits related to child abuse and neglect and calculated the proportions of such visits per 100,000 ED visits, as well as the percentage of suspected or confirmed ED visits related to child abuse and neglect ending in hospitalization, overall and stratified by age group (0-4, 5-11, and 12-17 years). The total number of ED visits related to child abuse and neglect began decreasing below the corresponding 2019 period during week 11 (March 15-March 22, 2020) for all age groups examined, coinciding with the declaration of a national emergency on March 13 (2); simultaneously, the proportion of these visits per 100,000 ED visits began increasing above the 2019 baseline for all age groups. Despite decreases in the weekly number of ED visits related to child abuse and neglect, the weekly number of these visits resulting in hospitalization remained stable in 2020; however, the yearly percentage of ED visits related to child abuse and neglect resulting in hospitalization increased significantly among all age groups. Although the increased proportion of ED visits related to child abuse and neglect might be associated with a decrease in the overall number of ED visits, these findings also suggest that health care-seeking patterns have shifted during the pandemic. Hospitalizations for child abuse and neglect did not decrease in 2020, suggesting that injury severity did not decrease during the pandemic, despite decreased ED visits. Child abuse is preventable; implementation of strategies including strengthening household economic supports and creating family-friendly work policies can reduce stress during difficult times and increase children's opportunities to thrive in safe, stable, and nurturing relationships and environments (3).

#### FIGURES

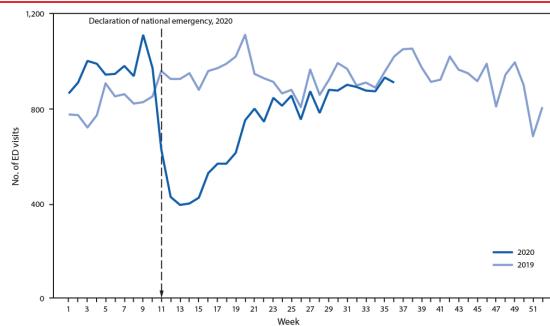


Figure 1A. Number of emergency department (ED) visits related to suspected and confirmed child abuse and neglect among children and adolescents aged <18 years, by week — National Syndromic Surveillance Program, United States, 2019–2020

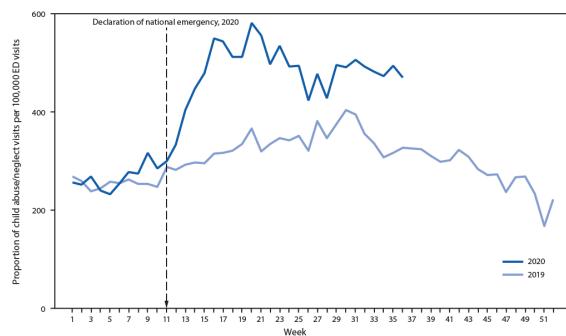


Figure 1B. Proportion of emergency department (ED) visits related to suspected and confirmed child abuse and neglect among children and adolescents aged <18 years, by week — National Syndromic Surveillance Program, United States, 2019–2020

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