

# The Daily COVID-19 Literature Surveillance Summary

**September 09, 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			
<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>

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

# EXECUTIVE SUMMARY

## Epidemiology

- Public health experts affiliated with Indiana University estimated the infection fatality ratios (IFR) of SARS-CoV2 based on antibody tests in a random sample of residents aged 12+ in Indiana. The average age of decedents was 76.9 (SD 13.1). 1099 COVID-19 deaths were recorded and the average IFR was 0.26%, but stratified IFR varied by age: >60yo IFR 1.71%, <40yo IFR 0.01%; and by race: whites IFR 0.18% and non-whites IFR 0.59%. These results from the SARS-CoV-2 population prevalence data suggest that [risk of death increases with age and varies by race](#).
- A retrospective single center study (Hospital of the University of Paris, France) of 100 adult patients with confirmed SARS-CoV-2 admitted to the ICU, 81/100 of whom had mortality-associated varying severity of [acute kidney injury](#) (AKI), found no statistically significant association between complement activation/inflammatory markers (C3, IL-6, ferritin) and AKI as defined by urinary output and the Kidney Disease Improving Global Outcomes (KDIGO) criteria after adjusting for confounders. They also reported 80% incidence of AKI during the first 7 days in ICU and found 90% of patients with AKI required mechanical ventilation. Due to its high incidence, the authors suggest AKI is an important co-morbidity to monitor and investigate in critically-ill COVID-19 patients.

## Understanding the Pathology

- Cardiologists at Johns Hopkins University School of Medicine and Harvard Medical School discuss how direct and indirect [SARS-CoV-2 triggered endothelial exocytosis](#) could be responsible for widespread thrombosis and hyper-inflammation seen in patients with severe COVID-19, proposing that endothelial exocytosis releases secretory granules containing von Willebrand factor (VWF) and P-selectin thus causing platelet aggregation and leukocyte adherence, resulting in microvascular obstruction and release of pro-inflammatory cytokines. Authors suggest better understanding the role of endothelial exocytosis by SARS-CoV-2 and underlying mechanisms could provide potential therapeutic targets for novel drug development and drug repurposing.
- This in vitro study by researchers from several medical academic centers in Germany found that SARS-CoV-2 targeted [cortical plate neurons of human central nervous system tissue models](#) (brain organoids derived from pluripotent stem cells which are comparable to complex neural epithelium), which caused changes in Tau distribution, hyperphosphorylation of Tau, and neuronal death; however, compared to respiratory and renal epithelium the virus did not appear to have a high level of replication in neuronal cells. Authors present these findings to offer insight on SARS-CoV-2 neuronal targeting mechanisms and suggest organoids may serve well as screening tools for anti-SARS-CoV-2 agents.

## Transmission & Prevention

- A case series conducted by infectious disease experts at Luigi Sacco University Hospital in Milan, Italy found that among 7 patients persistently carrying SARS-CoV-2, treatment with an Atomix Wave kit to wash their nasopharynx with 3% H2O2 solution for 14 days resulted in negative nasopharyngeal SARS-CoV-2 swabs for at least the first 48 hours (one patient tested weakly positive at 72 hours, and four tested weakly positive at day 7) and up to the full 14 days (2 patients). This study indicates that [H2O2 washes could be used to disrupt viral shedding](#), and further studies with more intensive nasopharyngeal washing are required to determine if better viral shedding suppression can be achieved to prevent transmission from long term SARS-CoV-2 carriers.
- A retrospective study in Incheon, Korea of 19,296 people self-quarantined for a mandatory 14-days (due to close contact with confirmed COVID-19 or return from overseas travel) helped identify 56 (0.3%) cases of COVID-19, 18 of which were asymptomatic, through self-reported symptoms or mandatory pre-release RT-PCR testing. These findings suggest that [mandatory diagnostics prior to release from quarantine](#) may assist in identifying asymptomatic COVID-19 cases to help control potential spread of the virus.

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# CLIMATE

## GLOBAL

### PREPARING FOR A PANDEMIC: HIGHLIGHTING THEMES FOR RESEARCH FUNDING AND PRACTICE-PERSPECTIVES FROM THE GLOBAL RESEARCH COLLABORATION FOR INFECTIOUS DISEASE PREPAREDNESS (GLOPID-R)

Norton A, Sigfrid L, Aderoba A, Nasir N, Bannister PG, Collinson S, Lee J, Boily-Larouche G, Golding JP, Depoortere E, Carson G, Kerstiens B, Yazdanpanah Y.. BMC Med. 2020 Sep 8;18(1):273. doi: 10.1186/s12916-020-01755-y.

Level of Evidence: Other - Guidelines and Recommendations

#### BLUF

A set of guidelines put forth by the Global Research Collaboration for Infectious Disease Preparedness outlined six recommendations, including utilizing cohort studies, improving research activity mapping, coordinating and collaborating between studies, finding sustainable funding and research capacity, rapidly mobilizing research funds and resources, and creating ethically centered research (Table 1) in order to ensure the facilitation of research during global pandemics.

#### FIGURES

**Table 1** COVID-19 relevant practice and ongoing priorities linked to the GloPID-R Frontiers meeting recommendations

	GloPID-R Frontiers meeting recommendations	COVID-19-relevant practice and ongoing priorities
1.	<b>Research cohorts</b> are valuable tools for building pandemic research responses.	Several cohorts including UK Biobank and a DHSS in Mozambique have already pivoted or enhanced for COVID-19. Further consideration needs to be given by funders and researchers to relevant cohorts for COVID-19 research. Newly created cohorts are being funded and need to be designed in a way in which they can evolve to address future research questions.
2.	<b>Research capacity and activity mapping</b> are essential to facilitate collaboration and improve targeting of resources.	For COVID-19, GloPID-R has collaborated with the UK Collaborative on Development Research to strengthen research mapping through the 'COVID-19 Research Project Tracker' [4], a live database of funded research projects on COVID-19 mapped to the WHO Research Roadmap for COVID-19. Several other research trackers have been established focusing on clinical research.
3.	<b>Research collaboration</b> especially between clinical trial networks and cohorts are essential to improve research outcomes.	Collaboration between cohorts and clinical trial networks is already evident through initiatives such as PREPARE, ALERRT, Pandora-ID-NET, ISARIC and other networks and was further facilitated by networking at the meeting, much of which is now enabling rapid research in the COVID-19 pandemic.
4.	<b>Sustainability</b> of funding and research capacity during inter-epidemic periods is key to ensure quality research can be initiated rapidly for epidemics and pandemics.	The COVID-19 pandemic has already shown the benefits of pre-established studies, coordination of study prioritisation and active studies, ready to recruit at the outset of an outbreak. This was the case for the RECOVERY trial and CoCIN cohort in the UK.
5.	<b>Rapid research and research funding systems</b> and <b>rapid data sharing</b> are needed to facilitate knowledge generation to improve practice within epidemics and pandemics.	The COVID-19 pandemic has resulted in greater rapid data sharing than seen before, enabling accelerated knowledge, but also highlighting the potential risks from the multitude of non-reviewed papers. This makes the GloPID-R data sharing principles of ethical, accessible, transparent, equitable, fair and quality [5] important to highlight again to guide ongoing activities and for funders to implement the GloPID-R data sharing roadmap recommendations to improve processes.
6.	<b>Ethics and social science</b> need to be core to broader epidemic pandemic and research response activities.	For COVID-19, we have certainly seen greater inclusion of ethics and social science than in any previous epidemic, and indeed, these have formed two of the priorities for the WHO 'Coordinated Global Research Roadmap for COVID-19' [6]. Research is needed to evaluate the implementation of social science research into practice, building the bridge between science and implementation through moving away from traditional silo working towards integrated, multidisciplinary practice, including social scientists, health promotion, public health and clinical practitioners.

## EPIDEMIOLOGY

### INFECTION FATALITY RATIOS FOR COVID-19 AMONG NONINSTITUTIONALIZED PERSONS 12 AND OLDER: RESULTS OF A RANDOM-SAMPLE PREVALENCE STUDY

Blackburn J, Yiannoutsos CT, Carroll AE, Halverson PK, Menachemi N.. Ann Intern Med. 2020 Sep 2. doi: 10.7326/M20-5352. Online ahead of print.

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

#### BLUF

Public health experts affiliated with Indiana University estimated the infection fatality ratios (IFR) of SARS-CoV2 based on antibody tests in a random sample of residents aged 12+ in Indiana between April 25 and 29. The average age of decedents was 76.9 (SD 13.1). 1099 COVID-19 deaths were recorded (Table) and the average IFR was 0.26%, but stratified IFR varied by age: >60yo IFR 1.71%, <40yo IFR 0.01%; and by race: whites IFR 0.18% and non-whites IFR 0.59%. These results from the SARS-CoV-2 population prevalence data suggest that risk of death increases with age and varies by race.

#### FIGURES

Table. IFR for Coronavirus Disease 2019 Among Noninstitutionalized Persons Aged ≥12 Years in Indiana

Category	Total Deaths, n	Mean Age at Death, y*	Noninstitutionalized Deaths, n†	Estimated Noninstitutionalized Infections (95% CI), n	Noninstitutionalized IFR (95% CI), %
<b>Age, y</b>					
<40	14	32.8	13	108 339 (73 041-142 095)	0.01 (0.01-0.02)
40-59	81	52.4	63	52 917 (33 963-71 546)	0.12 (0.09-0.19)
≥60	1004	79.5	419	24 493 (16 691-33 232)	1.71 (1.28-2.58)
<b>Race</b>					
White	715	78.9	250	141 026 (108 858-171 519)	0.18 (0.15-0.23)
Non-White	384	73.3	245	41 583 (17 630-71 822)	0.59 (0.34-1.41)
<b>Ethnicity</b>					
Hispanic	17	72.9	15	39 783 (10 851-73 317)	0.04 (0.02-0.14)
Non-Hispanic	1082	77.0	480	142 844 (118 830-172 653)	0.34 (0.28-0.41)
<b>Sex</b>					
Male	580	74.9	300	107 891 (64 803-169 979)	0.28 (0.18-0.47)
Female	493	79.5	169	82 096 (53 116-109 200)	0.21 (0.16-0.32)
<b>Total</b>	<b>1099</b>	<b>76.9</b>	<b>495</b>	<b>187 378 (143 881-232 883)</b>	<b>0.26 (0.21-0.35)</b>

IFR = infection fatality ratio.

\* Mean age in years at the time of death, among total deaths.

† Excludes deaths among nursing home residents.

### FINDINGS FROM A PROBABILITY-BASED SURVEY OF U.S. HOUSEHOLDS ABOUT PREVENTION MEASURES BASED ON RACE, ETHNICITY, AND AGE IN RESPONSE TO SARS-COV-2

Sauceda JA, Neilands TB, Lightfoot M, Saberi P.. J Infect Dis. 2020 Aug 29:jiaa554. doi: 10.1093/infdis/jiaa554. Online ahead of print.

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

#### BLUF

Cross sectional data from a "COVID-19 Impact Survey" conducted across the United States between April 20th and April 26th, 2020 by researchers affiliated with the Center for AIDS Prevention Studies in San Francisco, California found no significant difference between white, African American, and Latino individuals regarding 19 prevention control measures (Table 2), however African Americans and Latinos reported being less likely to use phone applications or websites to track symptoms (Table 1). Authors suggest COVID-19 disparities could be combated by use of technology for case tracking/tracing with a focus on uptake among minority populations.

## SUMMARY

Additional study findings include:

- Latinos were found to be less likely to maintain social distancing with individuals outside their household compared to whites and African Americans.
- African Americans and Latinos, as well as individuals over 60 years old, were found to be less likely to use an app on a phone or a website to read about and log symptoms.
- Individuals aged 45-59 years and 60+ years reported a lower likelihood of getting cheek or nose swab SARS-CoV-2 testing.

## ABSTRACT

We investigated individual behaviors taken by White, African American, and Latino U.S. households in response to SARS-CoV-2, and likelihood of using digital tools for symptom surveillance/reporting. We analyzed cross-sectional week one data (April 2020) of the COVID Impact Survey in a large, nationally-representative sample of U.S. adults. In general, all groups engaged in the same prevention behaviors, but Whites reported being more likely to use digital tools to report/act on symptoms and seek testing, versus African Americans and Latinos. Individual behaviors may not explain COVID-19 case disparities, and digital tools for tracking should focus on uptake among race/ethnic minorities.

## FIGURES

	Non-Latino White N= 1395	African-American N= 265	Latino N= 369	Fair	10.8	14.2	14.1
Age Categories (%)				Poor	2.7	2.2	1.4
18-29	10.3	14.2	21.4				
30-44	27.2	32.2	38.2				
45-59	25.1	24.7	21.4				
≥60	37.4	28.8	19.0				
Sex (%)							
Male	55.8	53.2	54.7	Average Number of COVID-19 Prevention			
Female	44.2	46.2	45.3	Control Measures	9.5 (3.1)	9.5 (3.2)	8.9 (3.3)
Household Size (%)				(mean, SD; Possible Range 0 to 19)			
<5 people	86.7	82.4	68.0	Mean Ratings of Using Technology-based			
≥5 people	13.3	17.6	32.0	Surveillance and Testing for COVID-19			
Household Income (%)				(1=Not likely at all, 5 = Extremely likely)			
< \$30,000	19.4	42.7	40.4	- Installing an app on your phone that	3.6 (1.4)	3.2 (1.4)	3.1 (1.4)
\$30,000 to \$49,999	18.6	19.8	20.0	asks you questions about your own			
\$50,000 to \$99,999	35.8	28.1	27.6	symptoms and provider			
≥ \$100,000	26.2	9.4	12.0	recommendations about COVID-19			
Education (%)				- Installing an app on your phone that	3.5 (1.4)	3.4 (1.4)	3.3 (1.3)
No high school	2.5	6.4	11.7	tracks your location and sends push			
High school or equivalent	17.4	18.0	25.5	notifications if you might have been			
Some college, no degree	40.2	43.8	44.4	exposed to COVID-19			
Associate degree or higher	39.9	31.8	18.4	- Using a website to log your symptoms	3.6 (1.3)	3.2 (1.3)	3.3 (1.3)
General Health (%)				and location and get recommendations			
Excellent	12.8	12.4	13.0	about COVID-19			
Very good	40.9	33.0	33.3	- Testing you for COVID-19 infection	2.7 (1.4)	2.7 (1.4)	2.7 (1.3)
Good	32.9	38.2	38.2	using a Q-tip to swab your cheek or			
				nose			
				- Testing you for immunity or resistance	2.5 (1.4)	2.9 (1.4)	2.7 (1.4)
				to COVID-19 by drawing a small			
				amount of blood			

Table 1. Characteristics of Respondents in the U.S. Household COVID-19 Impact Survey, Descriptive Statistics of Individual COVID-19 Prevention Control Measures, and Ratings of the Likelihood of Using Technology-based Surveillance and Testing for COVID-19.

	Non-Latino White	African Americans	Latino	Male (Referent Group)	Female
19 Prevention Control Measures*	% (0-no, 1 - yes)	% OR, 95% CI, p-value	% OR, 95% CI, p-value	% OR, 95% CI, p-value	%
1. Canceled a doctor appointment	36.9	31.8 0.93, .66-.131,	34.4 1.03, 0.73-1.45,	31.1 <b>0.64, 0.51-0.81,</b> <b>0.002</b>	39.5
2. Worn a face mask	80.4	83.5 0.94, 0.60-1.46,	77.2 1.03, 0.70-1.52,	79.5 0.76 0.81	80.7 0.94 0.91 0.94
3. Visited a doctor or hospital	7.4	7.1 0.98, .55-1.75,	8.9 1.07, 0.61-1.89,	6.8 0.96 0.84	7.5 0.73, 0.49-1.1, 0.19
4. Canceled or postponed work activities	39.6	38.2 0.71, 0.51-1.00,	28.2 .66, 0.47-94,	34.5 0.10 0.05	39.5 <b>0.75, 0.60-0.94,</b> <b>0.04</b>
5. Canceled or postponed school activities	21.4	17.6 0.72, .48-1.07,	18.7 1.20, 0.76-1.80	17 0.16	23.2 <b>0.54, 0.41-0.71,</b> <b>0.001</b>
6. Canceled or postponed dentist or other appointment	46.6	47.9 1.02, 0.74-1.41,	36.0 0.76, 0.55-1.06,	39 <b>0.60, 0.48-0.75,</b> <b>0.001</b>	49.4
7. Canceled outside housekeepers or caregivers	13.5	15.0 1.04, 0.67-1.62,	11.1 0.88, 0.56-1.41,	13.1 0.66	13.4 0.93, 0.68-1.3, 0.72

8. Avoided some or all restaurants	78.5	79.8 0.76, 0.51-1.14,	72.1 0.26	75.3 0.13	79.1 <b>0.60, 0.46-0.78,</b> <b>0.001</b>
9. Worked from home	42.9	55.1 0.89, 0.64-1.24,	34.1 0.57	43.7 0.41	39.7 1.24, 1.0-1.6, 0.11
10. Studied from home	19.2	18.4 1.11, 0.75-1.64,	14.9 0.86, 0.55-1.33,	17.7 0.56	18.8 <b>0.66, 0.50-0.90,</b> <b>0.03</b>
11. Canceled or postponed pleasure, social, or recreational activities	81.9	81.3 0.82, 0.54-1.25,	70.2 0.45	75.9 0.14	82.7 <b>0.52, 0.40-0.68,</b> <b>0.001</b>
12. Stockpiled food or water	35.6	35.8 0.80, 0.56-1.14,	40.1 1.31, 0.95-1.82,	35.0 0.30	37.6 0.17 <b>0.74, 0.58-0.93,</b> <b>0.03</b>
13. Avoided public or crowded places	85.3	84.3 0.64, 0.41-0.98,	82.1 0.09	81.9 0.14	86.7 <b>0.59, 0.44-0.80,</b> <b>0.04</b>
14. Prayed	51.0	49.4 0.78, 0.56-1.07,	58.0 0.20	42.4 0.87	59.9 <b>0.52, 0.42-0.65,</b> <b>0.001</b>
15. Avoided contact with high-risk people	65.1	65.9 0.98, 0.69-1.39,	63.4 0.91	59.6 0.49	69.1 <b>0.50, 0.40-0.63,</b> <b>0.001</b>
16. Washed or sanitized hands	96.3	96.3 0.91, 0.33-2.53,	94.9 0.87	94.2 0.20	97.5 <b>0.38, 0.22-0.67,</b> <b>0.005</b>
17. Kept six feet distance from those outside my household	92.9	94.8 1.04, 0.46-2.31,	89.2 0.94	91.1 <b>0.49, 0.28-0.86,</b> <b>0.04</b>	93.6 <b>0.58, 0.40-0.90,</b> <b>0.04</b>
18. Stayed home because I felt unwell	9.1	10.9 1.66, 1.02-2.69,	13.0 1.42, 0.87-2.34,	7.2 0.09	12.4 0.24 <b>0.51, 0.35-0.75,</b> <b>0.004</b>
19. Wiped packages entering my home	45.1	44.9 0.79-0.57-1.08,	46.1 1.20, 0.87-1.67,	43.2 0.21	46.9 0.36 0.05

\* Age was not associated with any COVID-19 prevention control measure and thus not shown here. Non-Latino Whites N=

1,395; Non-Latino African Americans N= 265; Latino N= 369; Male N= 908; Female N= 1,121

Table 2. A Multivariable Logistic Regression with all nineteen COVID-19 Prevention Control Measures as the Dependent Variables, Race, and Ethnicity as the Independent Variables, and Adjusted for by Age and Sex.

## SYMPTOMS AND CLINICAL PRESENTATION

### ADULTS

#### ACUTE KIDNEY INJURY IN PATIENTS WITH SARS-COV-2 INFECTION

Joseph A, Zafrani L, Mabrouki A, Azoulay E, Darmon M.. Ann Intensive Care. 2020 Sep 3;10(1):117. doi: 10.1186/s13613-020-00734-z.

Level of Evidence: 3 - Local non-random sample

### BLUF

A retrospective single center study (Hospital of the University of Paris, France) of 100 adult patients with confirmed SARS-CoV-2 admitted to the ICU from March 1 - June 1, 2020, 81/100 of whom had mortality-associated varying severity of acute kidney injury (AKI; Figure 2, Table 2), found no statistically significant association between complement activation/inflammatory markers (C3, IL-6, ferritin) and AKI as defined by urinary output and the Kidney Disease Improving Global Outcomes (KDIGO) criteria after adjusting for confounders (Figure 1). They also reported 80% incidence of AKI during the first 7 days in ICU and found 90% of patients with AKI required mechanical ventilation. Due to its high incidence, the authors suggest AKI is an important co-morbidity to monitor and investigate in critically-ill COVID-19 patients.

## ABSTRACT

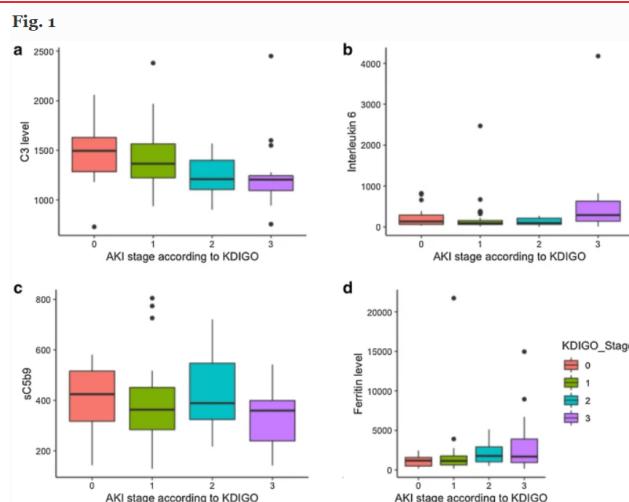
**BACKGROUND:** Acute Kidney Injury (AKI) is a frequent complication of severe SARS-CoV-2 infection. Multiple mechanisms are involved in COVID-19-associated AKI, from direct viral infection and secondary inflammation to complement activation and microthrombosis. However, data are limited in critically-ill patients. In this study, we sought to describe the prevalence, risk factors and prognostic impact of AKI in this setting.

**METHODS:** Retrospective monocenter study including adult patients with laboratory confirmed SARS-CoV-2 infection admitted to the ICU of our university Hospital. AKI was defined according to both urinary output and creatinine KDIGO criteria.

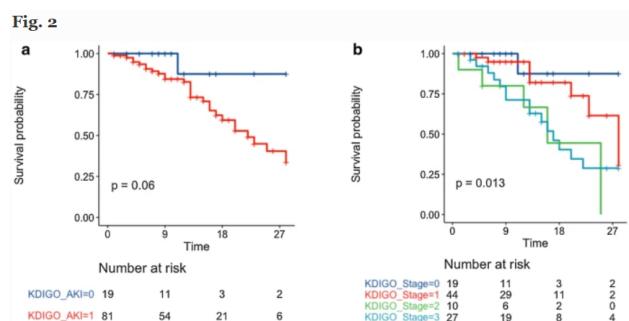
**RESULTS:** Overall, 100 COVID-19 patients were admitted. AKI occurred in 81 patients (81%), including 44, 10 and 27 patients with AKI stage 1, 2 and 3 respectively. The severity of AKI was associated with mortality at day 28 ( $p = 0.013$ ). Before adjustment, the third fraction of complement (C3), interleukin-6 (IL-6) and ferritin levels were higher in AKI patients. After adjustment for confounders, both severity (modified SOFA score per point) and AKI were associated with outcome. When forced in the final model, C3 (OR per log 0.25; 95% CI 0.01-4.66), IL-6 (OR per log 0.83; 95% CI 0.51-1.34), or ferritin (OR per log 1.63; 95% CI 0.84-3.32) were not associated with AKI and did not change the model.

**CONCLUSION:** In conclusion, we did not find any association between complement activation or inflammatory markers and AKI. Proportion of patients with AKI during severe SARS-CoV-2 infection is higher than previously reported and associated with outcome.

## FIGURES



Boxplots depicting relationship between AKI severity and C3 [ng/mL] ( $p = 0.01$ ) (a), IL-6 [ng/mL] ( $p = 0.02$ ) (b), sC5b9 [ng/mL] ( $p = 0.42$ ) (c) and ferritin levels [mg/L] ( $p = 0.03$ ) (d) levels



Kaplan-Meier curves for day-28 survival in patients with ( $n = 81$ ) and without AKI ( $n = 19$ ) (a) and with AKI stage 1 ( $n = 44$ ), 2 ( $n = 10$ ) and 3 ( $n = 27$ ) (b)

	Estimate	95% CI	p value
Model 1 (survival censored at day 28)	Hazard ratio		
Modified SOFA score at admission (per point)	1.23	1.04-1.45	0.01
Acute Kidney Injury	3.08	1.12-8.45	0.03
Model 2 (acute kidney injury)	Odds ratio		
Chronic kidney disease	3.91	0.97-26.20	0.09
Modified SOFA score at admission (per point)	1.29	1.04-1.70	0.04

Model selection was performed according to forward variable selection conditioned on  $p$  value (critical entry  $p$  value  $< 0.2$ , critical exit  $p$  value  $< 0.1$ )

Table 2. Factors associated with survival censored at day 28 (Cox Model) and risk of AKI (logistic regression)

## **COVID-19-ASSOCIATED ACUTE HAEMORRHAGIC LEUKOENCEPHALOMYELITIS**

Handa R, Nanda S, Prasad A, Anand R, Zutshi D, Dass SK, Bedi PK, Pahuja A, Shah PK, Sharma B.. Neurol Sci. 2020 Sep 2.  
doi: 10.1007/s10072-020-04703-z. Online ahead of print.

Level of Evidence: 5 - Case report

### **BLUF**

A case report by neurologists at BLK Hospital in New Delhi, India examined a 33-year-old COVID-19 positive male with acute weakness and altered sensorium who was found to have abnormal hyperintensities on brain MRI (Figures 1,2,3) and was subsequently diagnosed with acute hemorrhagic leukoencephalomyelitis secondary to COVID-19, ultimately dying from respiratory complications. Authors suggest that severe COVID-19 may manifest neurologically due to effects on the central nervous system, and clinicians should be aware of these findings to improve patient prognosis via early detection and rapid treatment.

### **SUMMARY**

Additional details of the case report as follows:

A 33 year-old male with history of kidney disease and hypertension initially presented with fever, weakness of upper and lower limbs, and altered sensorium. His interleukin (IL-6), D dimer, and S. ferritin levels were all elevated. Chest X-ray showed bilateral hilar opacities and COVID-19 nasopharyngeal PCR swab was positive. Brain MRI showed hyperintensities involving bilateral subcortical fronto-parietal lobes, splenium of corpus callosum, medulla, visualized cervical cord with petechial hemorrhages and evidence of diffusion restriction involving splenium of corpus callosum (Figures 1,2,3). Patient was diagnosed with acute hemorrhagic leukoencephalomyelitis secondary to COVID-19 and started on methylprednisolone (1 g/day for 5 days) which improved his neurological symptoms. However, his respiratory features continued to deteriorate, ventilation requirements increased, and he ultimately died on hospital day 10.

### **FIGURES**

**\*\*Please see the article for Figures.**

Figure 1. MRI FLAIR axial image showing hyperintensity in splenium of corpus callosum.

Figure 2. MRI FLAIR axial image showing confluent hyperintensities involving bilateral subcortical posterior fronto-parietal lobes.

Figure 3. MRI FLAIR axial image showing sparing of basal ganglia.

# UNDERSTANDING THE PATHOLOGY

## TARGETING TMPRSS2 IN SARS-COV-2 INFECTION

Baughn LB, Sharma N, Elhaik E, Sekulic A, Bryce AH, Fonseca R.. Mayo Clin Proc. 2020 Sep;95(9):1989-1999. doi: 10.1016/j.mayocp.2020.06.018. Epub 2020 Jul 19.

Level of Evidence: 5 - Mechanism-based reasoning

### BLUF

Geneticists and oncologists from Mayo Clinic in Minnesota and Lund University in Sweden investigated host tissue expression levels of transmembrane protease serine 2 (TMPRSS2; a protein that primes SARS-CoV-2 spike [S] protein) and angiotensin-converting enzyme 2 (ACE2; plays a key role in the virus' entry into the cell). Authors found high expression levels of TMPRSS2 in the prostate and ACE2 in the testes (Figure 1), but expression levels of TMPRSS2 and ACE2 were comparable in most non-sex specific tissues (Figure 2). This study suggests differences in ACE2 and TMPRSS2 expression levels were unlikely to result in the gender disparity seen among COVID-19 cases, but TMPRSS2 shows potential as a target for COVID-19 therapies.

### ABSTRACT

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has rapidly caused a global pandemic associated with a novel respiratory infection: coronavirus disease-19 (COVID-19). Angiotensin-converting enzyme-2 (ACE2) is necessary to facilitate SARS-CoV-2 infection, but owing to its essential metabolic roles it may be difficult to target it in therapies. Transmembrane protease serine 2 (TMPRSS2), which interacts with ACE2, may be a better candidate for targeted therapies. Using publicly available expression data, we show that both ACE2 and TMPRSS2 are expressed in many host tissues, including lung. The highest expression of ACE2 is found in the testes, whereas the prostate displays the highest expression of TMPRSS2. Given the increased severity of disease among older men with SARS-CoV-2 infection, we address the potential roles of ACE2 and TMPRSS2 in their contribution to the sex differences in severity of disease. We show that expression levels of ACE2 and TMPRSS2 are overall comparable between men and women in multiple tissues, suggesting that differences in the expression levels of TMPRSS2 and ACE2 in the lung and other non-sex-specific tissues may not explain the gender disparities in severity of SARS CoV-2. However, given their instrumental roles for SARS-CoV-2 infection and their pleiotropic expression, targeting the activity and expression levels of TMPRSS2 is a rational approach to treat COVID-19.

### FIGURES

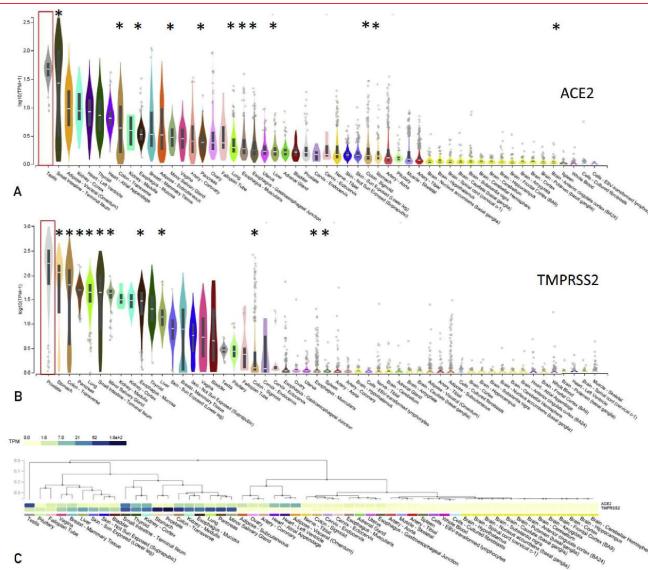


Figure 1. ACE2 and TMPRSS2 gene expression data. The data were obtained directly from the Genotype-Tissue Expression (GTEx) Project (<https://gtexportal.org>). Samples were sorted based on the median expression on a log scale using transcripts per million (TPM) unit. ACE2 (A) and TMPRSS2 (B) expression from all tissue samples available were plotted using the box plots available from the GTExPortal website with plots shown as median and 25th and 75th percentiles and dots displayed as outliers if they are above or below 1.5 times the interquartile range. Red boxes show the testes and prostate expression of ACE2 and TMPRSS2, respectively. Tissues associated with common COVID-19 symptoms are marked with an asterisk\*. In (C), a comparison of ACE2 and TMPRSS2 expression using GTEx tool multiGeneQueryPage.

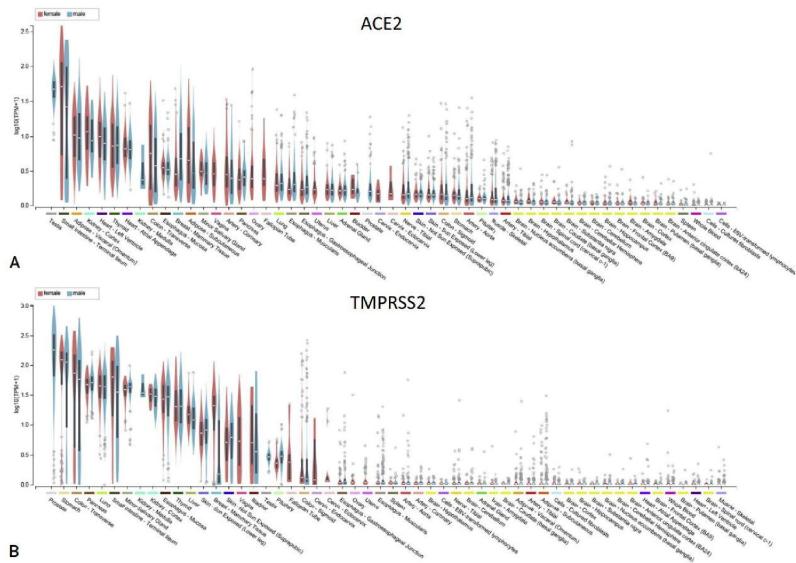


Figure 2. Sex differences in TMPRSS2 and ACE2 expression data. The data were obtained directly from the Genotype-Tissue Expression (GTEx) Project (<https://gtexportal.org>). Female subjects (pink) and male subjects (blue) were arranged based on sorting using the median expression on a log scale using transcripts per million (TPM) unit. TMPRSS2 (A) or ACE2 (B) expression from all tissues available were plotted using the box plots available from the GTExPortal website with plots shown as median and 25th and 75th percentiles with dots displayed as outliers if they are above or below 1.5 times the interquartile range.

## SEVERE COVID-19 IS A MICROVASCULAR DISEASE

Lowenstein CJ, Solomon SD.. Circulation. 2020 Sep 2. doi: 10.1161/CIRCULATIONAHA.120.050354. Online ahead of print.  
Level of Evidence: Other - Expert Opinion

### BLUF

Cardiologists at Johns Hopkins University School of Medicine and Harvard Medical School discuss how direct and indirect SARS-CoV-2 triggered endothelial exocytosis could be responsible for widespread thrombosis and hyper-inflammation seen in patients with severe COVID-19, proposing that endothelial exocytosis releases secretory granules containing von Willebrand factor (VWF) and P-selectin thus causing platelet aggregation and leukocyte adherence, resulting in microvascular obstruction and release of pro-inflammatory cytokines. Authors suggest better understanding the role of endothelial exocytosis by SARS-CoV-2 and underlying mechanisms could provide potential therapeutic targets for novel drug development and drug repurposing.

### FIGURES

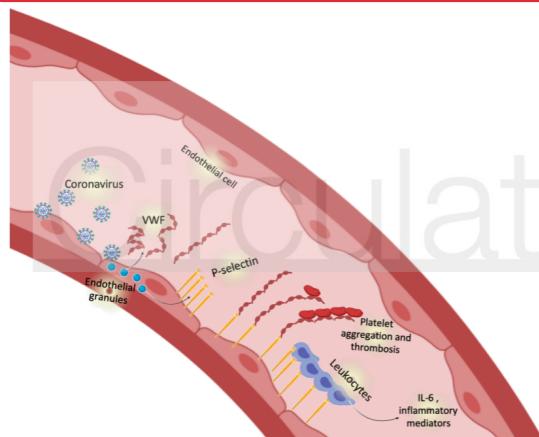


Figure. Endothelial exocytosis in COVID-19. We propose that the coronavirus SARS-CoV-2 injures endothelial cells. Endothelial cells respond to viral injury by exocytosis, mobilizing granules which release VWF and P-selectin. P-selectin plays a dual role, accelerating thrombosis by binding to platelets, and mediating vascular inflammation by interacting with leukocytes.

## SARS-COV-2 TARGETS NEURONS OF 3D HUMAN BRAIN ORGANOIDS

Ramani A, Müller L, Niklas Ostermann P, Gabriel E, Abida-Islam P, Müller-Schiffmann A, Mariappan A, Goureau O, Gruell H, Walker A, Andrée M, Hauka S, Houwaart T, Dilthey A, Wohlgemuth K, Omran H, Klein F, Wieczorek D, Adams O, Timm J, Korth C, Schaal H, Gopalakrishnan J.. EMBO J. 2020 Sep 2:e2020106230. doi: 10.15252/embj.2020106230. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

### BLUF

This in vitro study by researchers from several medical academic centers in Germany found that SARS-CoV-2 targeted cortical plate neurons of human central nervous system tissue models (brain organoids derived from pluripotent stem cells which are comparable to complex neural epithelium), which caused changes in Tau distribution, hyperphosphorylation of Tau, and neuronal death (Figure 2A-F); however, compared to respiratory and renal epithelium the virus did not appear to have a high level of replication in neuronal cells. Authors present these findings to offer insight on SARS-CoV-2 neuronal targeting mechanisms and suggest organoids may serve well as screening tools for anti-SARS-CoV-2 agents.

### ABSTRACT

COVID-19 pandemic caused by SARS-CoV-2 infection is a public health emergency. COVID-19 typically exhibits respiratory illness. Unexpectedly, emerging clinical reports indicate that neurological symptoms continue to rise, suggesting detrimental effects of SARS-CoV-2 on the central nervous system (CNS). Here, we show that a Dusseldorf isolate of SARS-CoV-2 enters 3D human brain organoids within two days of exposure. We identified that SARS-CoV-2 preferably targets neurons of brain organoids. Imaging neurons of organoids reveal that SARS-CoV-2 exposure is associated with altered distribution of Tau from axons to soma, hyperphosphorylation, and apparent neuronal death. Our studies, therefore, provide initial insights into the potential neurotoxic effect of SARS-CoV-2 and emphasize that brain organoids could model CNS pathologies of COVID-19.

### FIGURES

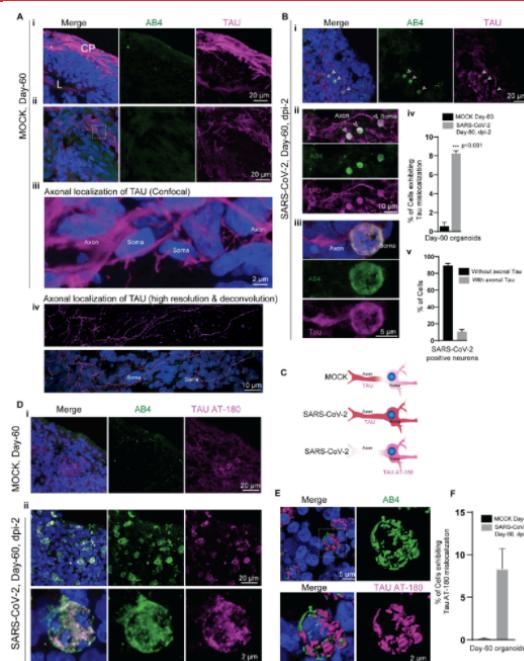


Figure 2. A. Tau immunoreactivity (magenta) specificities the cortical plate (CP) surrounding the lumen (L). B. Tau localization in SARS-CoV-2 positive neurons (AB4, green). Note the contrast and displayed mislocalization of Tau (magenta) into the somas of neurons (arrowheads). C. Schematic cartoon of differential Tau distribution in mock compared to SARS-CoV-2-positive neurons. D. In contrast to controls (i), Tau AT180 antibody (magenta) recognizes Threonine 231 of Tau protein distinctly localized at the somas of SARS-CoV-2 neurons (AB4, green). E. Co-localization of SARS-CoV-2 (AB4, green) and phosphorylated Tau protein (magenta) at somas of cortical neurons revealed by high-resolution imaging and de-convolution. F. Bar diagram that quantifies the fraction of Tau AT180-positive neurons that co-localize with SARS-CoV-2-positive neurons.

## TRANSMISSION & PREVENTION

### DEVELOPMENTS IN TRANSMISSION & PREVENTION

#### SHORT-TERM INHIBITION OF SARS-COV-2 BY HYDROGEN PEROXIDE IN PERSISTENT NASOPHARYNGEAL CARRIERS

Capetti AF, Borgonovo F, Morena V, Lupo A, Cossu MV, Passerini M, Dedivitiis G, Rizzardini G.. J Med Virol. 2020 Sep 3. doi: 10.1002/jmv.26485. Online ahead of print.

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

#### BLUF

A case series conducted by infectious disease experts at Luigi Sacco University Hospital in Milan, Italy found that among 7 patients persistently carrying SARS-CoV-2, treatment with an Atomix Wave kit to wash their nasopharynx with 3% H<sub>2</sub>O<sub>2</sub> solution for 14 days resulted in negative nasopharyngeal SARS-CoV-2 swabs for at least the first 48 hours\* and up to the full 14 days (2 patients). This study indicates that H<sub>2</sub>O<sub>2</sub> washes could be used to disrupt viral shedding, and further studies with more intensive nasopharyngeal washing are required to determine if better viral shedding suppression can be achieved to prevent transmission from long term SARS-CoV-2 carriers.

\*One patient tested weakly positive at 72 hours, and four tested weakly positive at day 7.

#### ABSTRACT

Asymptomatic and convalescent COVID-19 subjects may carry SARS-CoV-2 for months in their upper respiratory ways. Desiring to permanently clean the mucosal surfaces we investigated chemical agents fit to rapidly degrade the virus. Among these, hydrogen peroxide, initially tested by two of us for tolerability, showed both good performance and acceptable side effects (burning sensation for 15 - 20 seconds). We contacted circles of family physicians and the ATS Milano (Territorial Assistance and Prevention Service) and we tested this procedure on eight persistent carriers of SARS-CoV-2, performing swabs before the procedure and after it until reappearance of the virus or until 14 days (the incubation period), keeping the surfaces clean with hypertonic solution. Our patients had a median time from exposure or symptom onset of 111 days and three had relapsed after being declared 'cured' (two consecutive negative swabs after quarantine). One patient had a baseline negative swab and was excluded, two successfully ended the 14 days' course, four suppressed viral elimination for 72 hours and one for 48 hours, all rebounding to weak positive (cycle thresholds above 24). Although temporarily effective, such measure may have some place in the control of viral shedding, in order to protect the most fragile subjects. This article is protected by copyright. All rights reserved.

## PREVENTION IN THE COMMUNITY

#### THE IMPORTANCE OF MANDATORY COVID-19 DIAGNOSTIC TESTING PRIOR TO RELEASE FROM QUARANTINE

Jung J, Jang H, Kim HK, Kim J, Kim A, Ko KP.. J Korean Med Sci. 2020 Aug 31;35(34):e314. doi: 10.3346/jkms.2020.35.e314. Level of Evidence: 4 - Local non-random sample

#### BLUF

A retrospective study in Incheon, Korea from February 11 - July 5, 2020 of 19,296 people self-quarantined for a mandatory 14-days (due to close contact with confirmed COVID-19 or return from overseas travel) helped identify 56 (0.3%) cases of COVID-19, 18 of which were asymptomatic, through self-reported symptoms or mandatory pre-release RT-PCR testing (Figure 1, Table 1). These findings suggest that mandatory diagnostics prior to release from quarantine may assist in identifying asymptomatic COVID-19 cases to help control potential spread of the virus.

## ABSTRACT

A 14-day quarantine is implemented in many countries in response to the coronavirus disease pandemic. Korea implemented a mandatory quarantine for those who had close contact with infected patients and those returning from abroad. The present study explored the implications of mandatory coronavirus disease 2019 testing before releasing individuals from the 14-day quarantine in Incheon, Korea. From February 11 to July 5, 2020, 19,296 people were self-quarantined, and 56 (0.3%) of them were confirmed cases of COVID-19. Twenty (35.7%) were identified through the reporting of symptoms during quarantine, and 32 (57.1%) were identified using mandatory pre-release RT-PCR tests. Among the 32, 14 (25%) individuals reported mild symptoms and 18 (32.1%) were asymptomatic. It is suggested that mandatory diagnostic testing prior to release and the symptom-based surveillance after the 14-day quarantine may help control delayed or asymptomatic COVID-19 cases.

## FIGURES

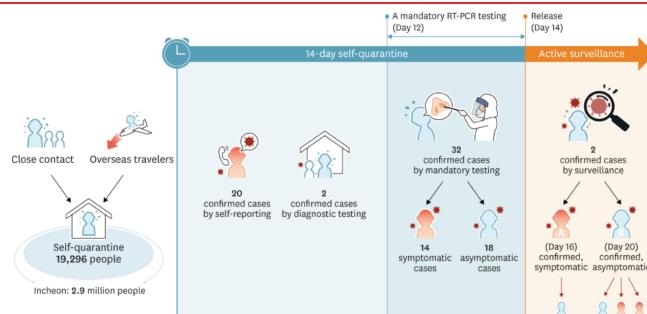


Figure 1. Schematic of the results showing the exposure, timing, and presence of symptoms among individuals identified as new cases by the investigation and surveillance system in Incheon, Korea, February 11, 2020 to July 5, 2020.

RT-PCR = reverse transcription polymerase chain reaction.

Characteristics	Confirmed during the quarantine through self-reporting (n = 20)	Confirmed by mandatory testing, symptomatic (n = 14)	Confirmed by mandatory testing, asymptomatic (n = 18)
Age, yr	43.5 (16–98)	43.7 (8–80)	45.9 (8–93)
Sex, male (%)	8 (40.0)	6 (42.9)	6 (33.3)
Symptoms			
Fever	11 (55.0)	5 (35.7)	
Cough	11 (55.0)	2 (14.3)	
Sputum	8 (40.0)	3 (21.4)	
Sore throat	9 (45.0)	4 (28.6)	
Headache	8 (40)	1 (7.1)	
Loss of taste or smell	4 (20)	5 (35.7)	

Table 1. Characteristics of 52 cases confirmed after self-quarantine from February 11 to July 4, 2020 in Incheon, Korea

## SARS-COV-2: THE INCREASING IMPORTANCE OF WATER FILTRATION AGAINST HIGHLY PATHOGENIC MICROBES

Siddiqui R, Khamis M, Ibrahim T, Khan NA.. ACS Chem Neurosci. 2020 Sep 2;11(17):2482-2484. doi: 10.1021/acschemneuro.0c00468. Epub 2020 Aug 13.

Level of Evidence: Other - Expert Opinion

## BLUF

An expert opinion by scientists and engineers from the American University of Sharjah (United Arab Emirates) compiled various case reports and interviews to highlight the potential of SARS-CoV-2 spread through wastewater, which can significantly impact developing countries. For example, SARS-CoV-2 has been detected in the wastewater near Amsterdam, and interviews with communities in India highlight the lack of awareness of potential SARS-CoV-2 spread through water (Figure 1). The authors advocate for nanoparticle water filtration devices as well as policy changes in regards to water sanitation and public education for safe water usage to reduce SARS-CoV-2 transmission.

## ABSTRACT

The presence of SARS-CoV-2 in human wastewater together with poor quality of public drinking water supplies in developing countries is of concern. Additionally, the frequent use of contaminated water for bathing, nasal irrigation, swimming, and ablution can be a risk factor in contracting infectious agents such as the brain-eating amoebae and possibly SARS-CoV-2. The use of appropriate tap water filters should be encouraged to remove pathogenic microbes, together with restrained nasal irrigation (not forcing water inside nostrils vigorously) during ritual ablution or bathing to avoid dangerous consequences for populations residing in developing countries.

## FIGURES

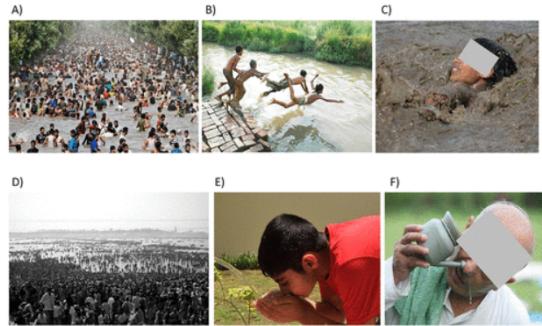


Figure 1. (A) Thousands of people can be seen swimming in the canal that passes through the city of Lahore, Pakistan, without nearby facilities for defecation and urination. (B, C) Children swimming in muddy water or swimming in unchlorinated pools can lead to exposure to infectious agents. (D) Millions of people gather at the Kumbh Mela yearly to take part in the holy bathing. (E) Ritual ablution for nasal cleansing using contaminated water. (F) The use of neti pots for nasal irrigation using contaminated water can lead to contracting infectious agents.

## MANAGEMENT

### ACUTE CARE

## DIAGNOSTIC RADIOLOGY

### CYTOTOXIC LESION OF THE CORPUS CALLOSUM AS PRESENTING NEURORADIOLOGICAL MANIFESTATION OF COVID-2019 INFECTION

Forestier G, de Beaurepaire I, Bornet G, Boulouis G.. J Neurol. 2020 Aug 18. doi: 10.1007/s00415-020-10166-1. Online ahead of print.

Level of Evidence: Other - Case Report

#### BLUF

Physicians within the fields of neurology and radiology describe a case report of a 55-year-old male presenting with a headache who was found to have neuroradiologic manifestations of COVID-19 infection. The patient had symptoms and MRI findings (Figure 1) consistent with a cytotoxic lesion of the corpus callosum (CLOCCs), an infection-related encephalopathy, and was found to be positive for SARS-CoV-2 by nasopharyngeal swab and chest CT. These findings suggest the possible need for additional brain imaging in patients suspected of having COVID-19 with neurologic complications.

#### FIGURES

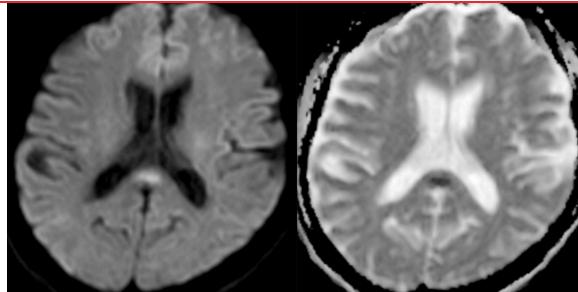


Figure 1. Axial brain MRI images demonstrate increased diffusion weighted signal in the splenium of the corpus callosum (left), confirmed as low signal on the ADC map (right)

## CRITICAL CARE

### ARE THE STEROIDS A BLANKET SOLUTION FOR COVID-19? A SYSTEMATIC REVIEW AND META-ANALYSIS

Sarkar S, Khanna P, Soni KD.. J Med Virol. 2020 Sep 3. doi: 10.1002/jmv.26483. Online ahead of print.

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

#### BLUF

Anesthetists and Critical & Intensive Care physicians from New Delhi, India conducted a systematic review and meta-analysis of two randomized control trials and ten cohort studies ( $n=15,754$  patients) (Figure 1), which found that steroid therapy for COVID-19 did not effectively reduce mortality, did not significantly change length of hospital stay, and was associated with delayed viral clearance (Figures 3, 4). These initial findings suggest that steroid therapy may not be effective in treating COVID-19, however this review is limited by significant heterogeneity and low-quality evidence and highlights the need for further study.

## ABSTRACT

**BACKGROUND:** Steroids may play a critical role in the current pandemic of coronavirus disease (COVID-19), given the dearth of specific therapeutic options. This review was conducted to evaluate the impact of glucocorticoid therapy in COVID-19 patients based on the publications reported to date. **METHODS:** A comprehensive screening was conducted using electronic databases up to 19th August 2020. The randomized controlled trials (RCTs) and cohort studies evaluating the effectiveness and safety of steroids in patients with COVID-19 are included for the meta-analyses. **RESULTS:** Our search retrieved twelve studies, including two RCTs and ten cohort studies, with a total of 15,754 patients. In patients with COVID-19, the use of systemic glucocorticoid neither reduce mortality [Odds ratio (OR = 1.94, 95% CI: 1.11 to 3.4, I<sup>2</sup> = 96%)], nor the duration of hospital stay [mean difference (MD = 1.18 d, 95% CI: -1.28 to 3.64, I<sup>2</sup> = 93%)] and period of viral shedding [mean difference (MD = 1.42 d, 95% CI: -0.52 to 3.37, I<sup>2</sup> = 0%)]. **CONCLUSIONS:** Systemic steroid therapy may not be effective for reducing mortality, duration of hospitalization, and period of viral shedding. Studies are mostly heterogeneous. Further randomized control trials (RCT) are required. This article is protected by copyright. All rights reserved.

## FIGURES

Figure 3: The efficacy of steroids on mortality in COVID-19 patients

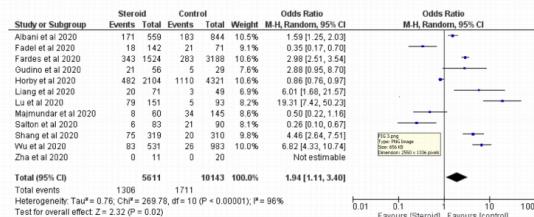


Figure 4: The effect of steroids on length of Hospital stay, & period of viral shedding in COVID-19 patients

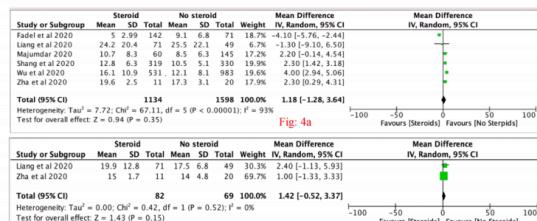


Figure 3: The efficacy of steroids on mortality in COVID-19 patients

Figure 4: (a) the effect of steroids on length of hospital stay in COVID-19 patients; (b) Impact of steroids on the period of viral shedding in COVID-19 patients

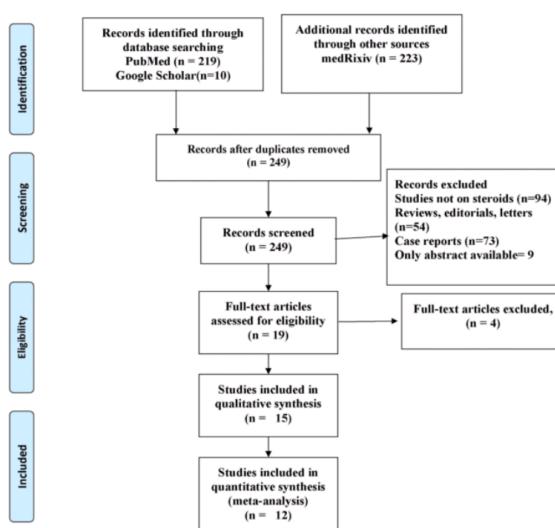


Figure 1: PRISMA 2009 Flow Diagram

# ADJUSTING PRACTICE DURING COVID-19

## FOR HEALTHCARE PROFESSIONALS

### RESUSCITATION AND COVID-19: RECALIBRATING PATIENT AND FAMILY EXPECTATIONS DURING A PANDEMIC

Sher T, Burger CD, DeMartino ES, de Moraes AG, Sharp RR.. Mayo Clin Proc. 2020 Sep;95(9):1848-1851. doi: 10.1016/j.mayocp.2020.06.035. Epub 2020 Jun 29.

Level of Evidence: Other - Guidelines and Recommendations

#### **BLUF**

A paper by physicians and bioethicists affiliated with Mayo Clinic in Rochester, Minnesota discussed ethical considerations of cardiopulmonary resuscitation (CPR) during the COVID-19 pandemic such as limited resources and substantial risk of exposure/infection, while also providing recommendations for enhanced personal protective equipment (PPE) use during CPR administration, use of automated chest compression devices, patient triage based on survival probability, and disaster-management strategies to assist decision making. Authors suggest these guidelines could be implemented to help preserve medical ethics while lessening challenges faced by healthcare providers and mitigating resource strain.

## R&D: DIAGNOSIS & TREATMENTS

### DEVELOPMENTS IN TREATMENTS

#### **GENERALIZED PUSTULAR FIGURATE ERYTHEMA. FIRST REPORT IN TWO COVID-19 PATIENTS ON HYDROXYCHLOROQUINE**

Abadías-Granado I, Palma-Ruiz AM, Cerro PA, Morales-Callaghan AM, Gómez-Mateo MC, Gilaberte Y, Schwartz RA.. J Eur Acad Dermatol Venereol. 2020 Sep 1. doi: 10.1111/jdv.16903. Online ahead of print.

Level of Evidence: 4 - Case-series

#### **BLUF**

Two case reports by dermatologists from the Miguel Servet University Hospital (Spain) and the New Jersey Medical School (USA) report the development of a generalized pustular figurate erythema (GPFE) 2-3 weeks following treatment in two patients with COVID-19 treated with hydroxychloroquine, a known risk factor for GPFE (Figures 1, 2). The authors recommend close monitoring for cutaneous manifestations such as GPFE in patients with COVID-19 being treated with hydroxychloroquine.

#### **SUMMARY**

Case Report 1:

64 year-old male patient with diffuse large B-cell lymphoma undergoing chemotherapy presenting with bilateral COVID-19-induced pneumonia.

Case Report 2:

60 year-old female patient with a rheumatoid arthritis on etanercept and prednisone (5mg/d) presenting with positive COVID-19.

COVID-19 treatment protocol for both patients:

hydroxychloroquine (400 mg twice a day first day followed by 200 mg twice a day for 10 days), lopinavir/ritonavir

(200mg/50mg twice a day), teicoplanin.

Azithromycin was also given to patient 2.

Side effect in both patients:

After 2-3 weeks of initiating treatment with hydroxychloroquine, both patients developed GPFE.

Treatment for both patients:

0.05% betamethasone dipropionate cream twice a day, methylprednisolone (40 mg/d), loratadine (10 mg/d), with recovery over four weeks.

#### **ABSTRACT**

Generalized pustular figurate erythema (GPFE) is a distinctive severe cutaneous drug reaction with widespread urticarial or edematous plaques scattered over the entire body that become topped with non-follicular pustules that evolve into erythematous and sometimes atypical targetoid plaques converging into annular and arcuate patterns prominent on the trunk and extremities (1). It has been linked with medications, especially hydroxychloroquine. We describe two COVID-19 patients on hydroxychloroquine who developed this eruption 2 and 3 weeks after the onset of hydroxychloroquine. This report is the first to our knowledge of COVID-19 patients on hydroxychloroquine developing GPFE.

## FIGURES

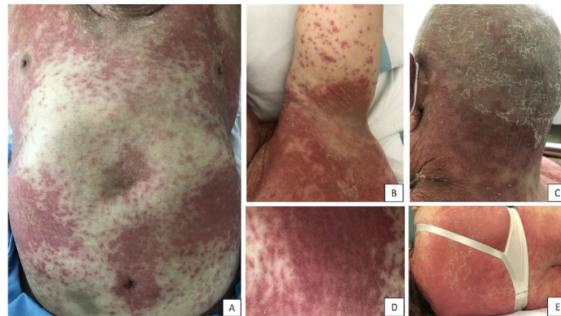


Figure 1. A-D Case 1. Purpuric erythematous rash with non-follicular pustules, on the trunk and limbs, with intense involvement of armpits and scalp. E) Case 2. Purpuric erythematous rash with non-follicular pustules and targetoid lesions on the back

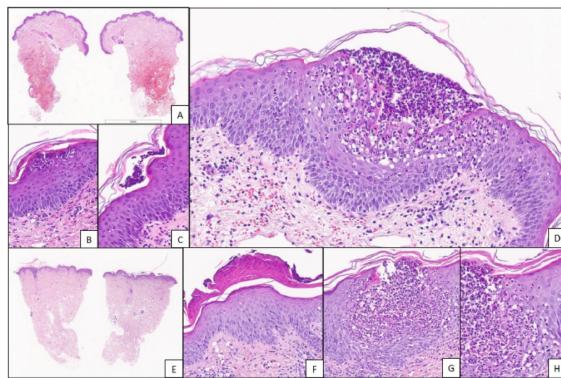


Figure 2. A-D Case 1. A) Panoramic view of the punch biopsy. B)-C) Pustules of neutrophils within the subcorneal and intracorneal layer of the epidermis (H&E 400x). D) Epidermis shows acanthosis with an intraepidermal neutrophilic pustule.

Exocytosis of neutrophils and mild spongiosis at the margins of the pustule are observed. Papillary dermis presents mild edema with erythrocytes extravasation, and mild perivascular lymphocytic infiltrated with occasional neutrophils (H&E 400x). E)-H) Case 2. E) Panoramic view of the punch biopsy. F) Foci of parakeratosis are presented (H&E 200x). G) Intraepidermal pustule (H&E 200x). H) Detail of the periphery of the pustule where exocytosis of neutrophils and spongiosis is showed (H&E 400x).

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