

# The Daily COVID-19 Literature Surveillance Summary

**November 24, 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	Non-randomized controlled cohort/follow-up study**	Case-series, case-control or historically controlled studies**	Mechanism-based reasoning
<b>Is this (early detection) test worthwhile? (Screening)</b>	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control or historically controlled studies**	Mechanism-based reasoning

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

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

## How to cite the Levels of Evidence Table

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

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# EXECUTIVE SUMMARY

## Epidemiology

- [Body Mass Index is correlated with Risk for Intubation or Death in SARS-CoV-2 Infection](#) according to a retrospective cohort study. The study, conducted at Columbia University Irving Medical Center, investigated the association between body mass index (BMI) and risk for intubation or death, inflammation, cardiac injury, or fibrinolysis from SARS-CoV-2 infection in 2,466 hospitalized COVID-19-positive adults. Compared to overweight patients, patients with class 3 obesity had the highest risk of intubation or death (hazard ratio, 1.6 [95% CI, 1.1 to 2.1]), though these effects were most clear in patients less than 65 years old. BMI was not associated with admission levels of biomarkers for inflammation (C-reactive protein and erythrocyte sedimentation rate), cardiac injury (troponin level), or fibrinolysis (D-dimer level). These results support previous studies showing increased risk of severe complications in overweight individuals, though this study also shows that other clinical correlates may demonstrate this increased risk upon admission.

## Management

- [Association of SARS-CoV-2 genomic load trends with clinical status in COVID-19](#) were found in a study of 42 COVID-19 patients with associated pneumonia admitted to NYU Langone Medical Center. Investigators analyzed each patients' genetic load of SARS-CoV-2 Cycle threshold (Ct) by rapid RT-PCR verses their Sequential Organ Failure Assessment (SOFA) score and found a statistically significant inverse correlation between the change in Ct value and change in clinical SOFA score. These findings suggest that a "decrease in viral load over time was associated with clinical improvement," highlighting the potential use of SARS-CoV-2 genomic load as a potential predictive value in disease outcome.

## Adjusting Practice During COVID-19

- [There may be increased susceptibility to SARS-CoV-2 infection in patients with reduced left ventricular ejection fraction.](#) Cardiovascular and regenerative medicine researchers at the Université de Strasbourg in France followed-up via telephone interviews with 889 acute coronary syndrome patients who received percutaneous coronary intervention. They found that the incidence of COVID-19-associated hospitalization or mortality was significantly greater in patients with reduced left ventricular ejection fraction (LVEF, n=91) versus patients with moderately reduced and preserved LVEF (n=798; 9% versus 1%, P 60; 0.001). Further, they observed that reduced LVEF was an independent predictor of COVID-19 hospitalization or mortality via multivariate logistic regression (OR: 6.91; 95% CI: 2.60-18.35, P 60; 0.001), suggesting that COVID-19 testing and treatment plans should be considered for patients with reduced cardiac function.

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## EPIDEMIOLOGY

### SYMPTOMS AND CLINICAL PRESENTATION

#### ADULTS

### BODY MASS INDEX AND RISK FOR INTUBATION OR DEATH IN SARS-COV-2 INFECTION : A RETROSPECTIVE COHORT STUDY

Anderson MR, Geleris J, Anderson DR, Zucker J, Nobel YR, Freedberg D, Small-Saunders J, Rajagopalan KN, Greendyke R, Chae SR, Natarajan K, Roh D, Edwin E, Gallagher D, Podolanczuk A, Barr RG, Ferrante AW, Baldwin MR.. Ann Intern Med. 2020 Nov 17;173(10):782-790. doi: 10.7326/M20-3214. Epub 2020 Jul 29.

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

#### BLUF

A retrospective cohort study, conducted at Columbia University Irving Medical Center, investigated the association between body mass index (BMI) and risk for intubation or death, inflammation, cardiac injury, or fibrinolysis from SARS-CoV-2 infection in 2,466 hospitalized COVID-19-positive adults. Compared to overweight patients, patients with class 3 obesity had the highest risk of intubation or death (hazard ratio, 1.6 [95% CI, 1.1 to 2.1]), though these effects were most clear in patients less than 65 years old (Table 2, Figure 3). BMI was not associated with admission levels of biomarkers for inflammation (C-reactive protein and erythrocyte sedimentation rate), cardiac injury (troponin level), or fibrinolysis (D-dimer level; Appendix Figure). These results support previous studies showing increased risk of severe complications in overweight individuals, though this study also shows that other clinical correlates may demonstrate this increased risk upon admission.

#### ABSTRACT

**BACKGROUND:** Obesity is a risk factor for pneumonia and acute respiratory distress syndrome. **OBJECTIVE:** To determine whether obesity is associated with intubation or death, inflammation, cardiac injury, or fibrinolysis in coronavirus disease 2019 (COVID-19). **DESIGN:** Retrospective cohort study. **SETTING:** A quaternary academic medical center and community hospital in New York City. **PARTICIPANTS:** 2466 adults hospitalized with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection over a 45-day period with at least 47 days of in-hospital observation. **MEASUREMENTS:** Body mass index (BMI), admission biomarkers of inflammation (C-reactive protein [CRP] level and erythrocyte sedimentation rate [ESR]), cardiac injury (troponin level), and fibrinolysis (D-dimer level). The primary end point was a composite of intubation or death in time-to-event analysis. **RESULTS:** Over a median hospital length of stay of 7 days (interquartile range, 3 to 14) days, 533 patients (22%) were intubated, 627 (25%) died, and 59 (2%) remained hospitalized. Compared with overweight patients, patients with obesity had higher risk for intubation or death, with the highest risk among those with class 3 obesity (hazard ratio, 1.6 [95% CI, 1.1 to 2.1]). This association was primarily observed among patients younger than 65 years and not in older patients ( $P$  for interaction by age = 0.042). Body mass index was not associated with admission levels of biomarkers of inflammation, cardiac injury, or fibrinolysis. **LIMITATIONS:** Body mass index was missing for 28% of patients. The primary analyses were conducted with multiple imputation for missing BMI. Upper bounding factor analysis suggested that the results are robust to possible selection bias. **CONCLUSION:** Obesity is associated with increased risk for intubation or death from COVID-19 in adults younger than 65 years, but not in adults aged 65 years or older. **PRIMARY FUNDING SOURCE:** National Institutes of Health.

#### FIGURES

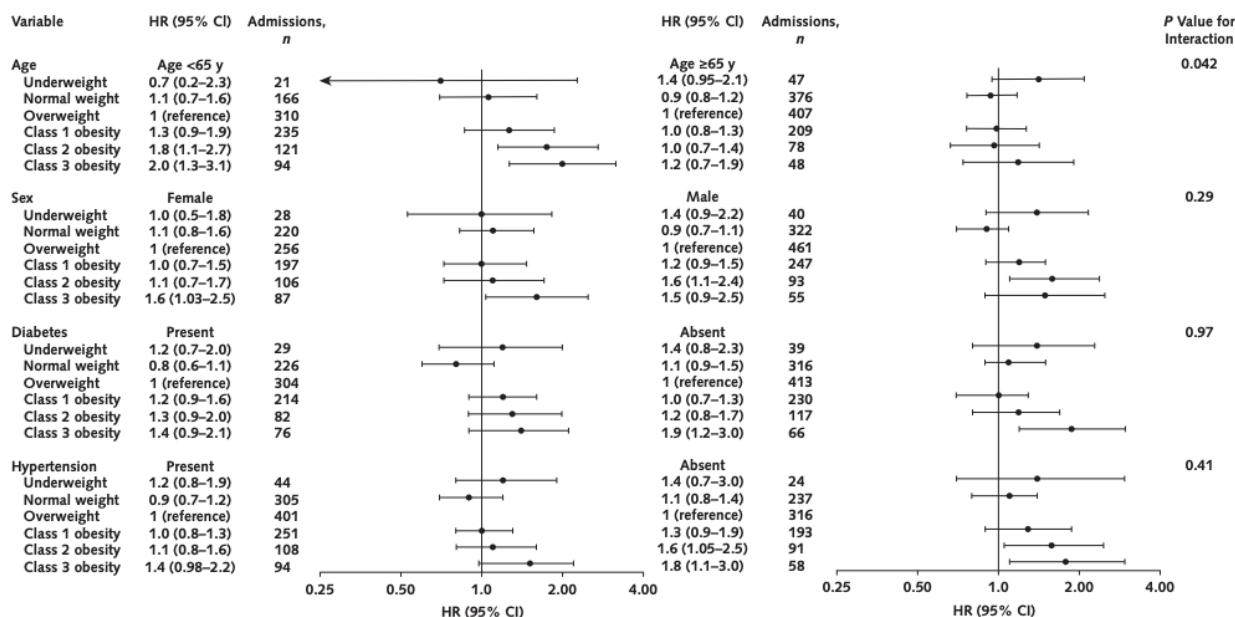
End Point	Underweight (n = 68)	Normal Weight (n = 542)	Overweight (n = 717)	Class 1 Obesity (n = 444)	Class 2 Obesity (n = 199)	Class 3 Obesity (n = 142)
In-hospital death at 28 days, n (%)	26 (38)	154 (28)	144 (20)	83 (19)	31 (16)	26 (18)
Deaths or intubations, n (%)	32 (47)	212 (39)	240 (33)	143 (32)	65 (33)	51 (36)
Combined death and intubation rate, n per 100 person-days	6.0 (4.2-8.4)	4.4 (3.8-5.0)	4.4 (3.9-5.0)	4.7 (3.9-5.5)	5.1 (3.9-6.4)	5.1 (3.8-6.3)
Hazard ratio (95% CI)						
Unadjusted	1.3 (0.9-1.9)	1.0 (0.9-1.2)	1 (reference)	1.0 (0.8-1.2)	1.1 (0.8-1.4)	1.1 (0.8-1.5)
Age-adjusted	1.2 (0.8-1.7)	1.0 (0.8-1.1)	1 (reference)	1.1 (0.9-1.3)	1.2 (0.9-1.6)	1.4 (1.1-2.0)
Partially adjusted†	1.2 (0.8-1.8)	1.0 (0.8-1.2)	1 (reference)	1.3 (0.97-1.7)	1.5 (1.1-2.2)	1.5 (1.1-2.1)
Fully adjusted‡	1.2 (0.9-1.8)	1.0 (0.8-1.2)	1 (reference)	1.1 (0.9-1.4)	1.3 (0.98-1.7)	1.6 (1.1-2.1)

\* Body mass index was categorized as underweight (<18.5 kg/m<sup>2</sup>), normal (18.5 to 24.9 kg/m<sup>2</sup>), overweight (25 to 29.9 kg/m<sup>2</sup>), class 1 obesity (30 to 34.9 kg/m<sup>2</sup>), class 2 obesity (35 to 39.9 kg/m<sup>2</sup>), or class 3 obesity (≥40 kg/m<sup>2</sup>). Subgroup sizes are based on patients with known body mass index. Effect estimates are generated from multiple imputation models.

† Adjusted for age, sex, and race.

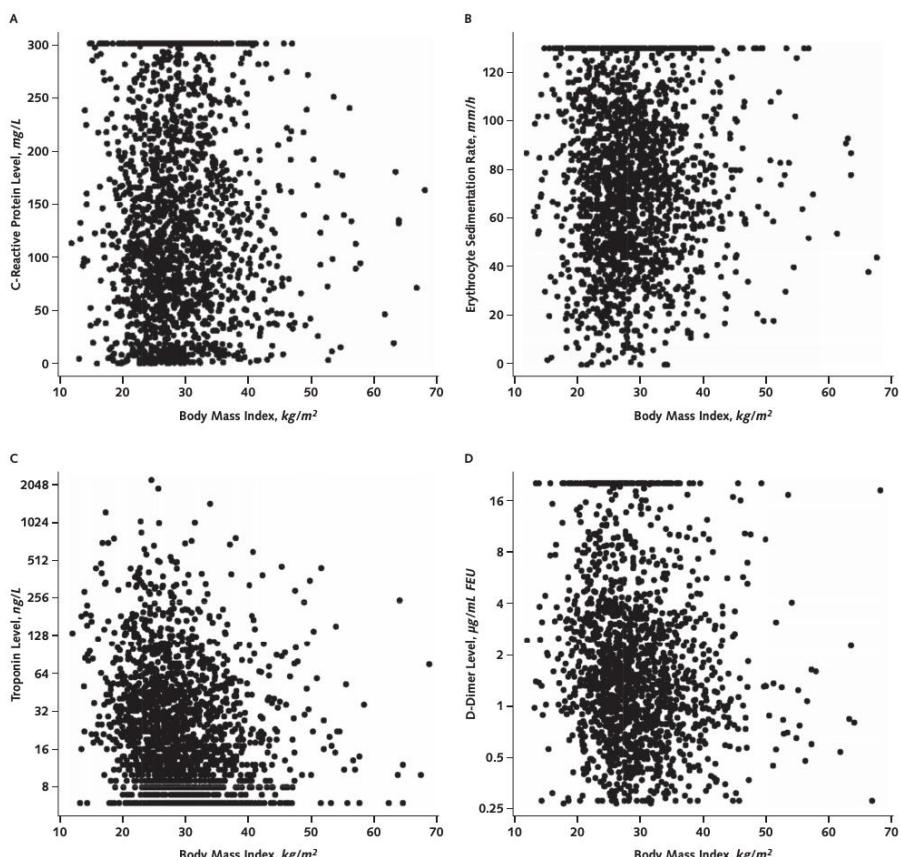
‡ Adjusted for age, sex, race/ethnicity, hypertension, asthma or chronic obstructive pulmonary disease, chronic kidney disease, pulmonary hypertension, smoking, cancer, and diabetes.

Table 2. Association Between Body Mass Index and Composite End Point of Death or Intubation



Body mass index was categorized as underweight (<18.5 kg/m<sup>2</sup>), normal (18.5 to 24.9 kg/m<sup>2</sup>), overweight (25 to 29.9 kg/m<sup>2</sup>), class 1 obesity (30 to 34.9 kg/m<sup>2</sup>), class 2 obesity (35 to 39.9 kg/m<sup>2</sup>), or class 3 obesity (≥40 kg/m<sup>2</sup>). Overweight is the reference category for the HRs. Subgroup sizes are based on patients with known body mass index. Effect estimates were generated from multiple imputation models. HR = hazard ratio.

Figure 3. Forest plots of multivariable-adjusted associations between body mass index and composite end point of death or intubation by prespecified stratification variables.



FEU = fibrinogen equivalent units. A. C-reactive protein level (1916 patients;  $r = -0.02$ ;  $P = 0.38$ ). To convert values to nmol/L, multiply by 9.524. B. Erythrocyte sedimentation rate (1815 patients;  $r = 0.03$ ;  $P = 0.25$ ). C. Troponin level (1915 patients;  $r = -0.15$ ;  $P < 0.001$ ). D. D-dimer level (1678 patients;  $r = -0.12$ ;  $P < 0.001$ ). To convert values to nmol/L, multiply by 5.476.

Appendix Figure. Scatter plots evaluating the association between body mass index and biomarkers of inflammation, cardiac injury, and fibrinolysis.

# UNDERSTANDING THE PATHOLOGY

## CYTOKINE STORM MAY NOT BE THE CHIEF CULPRIT FOR THE DETERIORATION OF COVID-19

Gao Y, Wang C, Kang K, Peng Y, Luo Y, Liu H, Yang W, Zhao M, Yu K.. Viral Immunol. 2020 Nov 17. doi: 10.1089/vim.2020.0243. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

### BLUF

Critical care physicians conducted a single-center retrospective case-control study from February 14 to March 26, 2020 on patients from First Affiliated Hospital of Harbin Medical University in Heilongjiang province to assess cytokine activity in COVID-19 deterioration. 167 patients with COVID-19 were divided into three groups (moderate, severe, and critical) and cytokine levels (such as IL-6, IL-10, TNF, and IFN- $\gamma$ ) were measured (Table 3). Findings showed elevated cytokine levels in the more critically ill patients, but the authors note possible confounding factors contributing to the this deterioration, such as organ function, inflammation, and coagulation. They propose that more studies need to look further into the pathophysiology of COVID-19 related deterioration.

### ABSTRACT

COVID-19 is spreading and ravaging all over the world, and the number of deaths is increasing day by day without downward trend. However, there is limited knowledge of pathogenesis on the deterioration of COVID-19 at present. In this study we aim to determine whether cytokine storm is really the chief culprit for the deterioration of COVID-19. The confirmed COVID-19 patients were divided into moderate group ( $n = 89$ ), severe group ( $n = 37$ ), and critical group ( $n = 41$ ). Demographic data were collected and recorded on admission to ICU. Clinical data were obtained when moderate, severe, or critical COVID-19 was diagnosed, and then compared between groups. The proportion of enrolled COVID-19 patients was slightly higher among males (52.5%) than females (47.5%), with an average age of 64.87 years. The number of patients without comorbidities exceed one third (36.1%), and patients with 1, 2, 3, 4 kinds of comorbidities accounted for 23.0%, 23.0%, 13.1%, and 4.9%, respectively. IL-6, IL-10, TNF, and IFN-gamma, including oxygenation index, sequential organ failure assessment score, white blood cell count, lymphocyte count, lymphocyte percentage, platelet, C-reaction protein, lactate dehydrogenase, creatine kinase isoenzyme, albumin, D-Dimer, and fibrinogen showed significant difference between groups. Some, but not all, cytokines and chemokines were involved in the deterioration of COVID-19, and thus cytokine storm maybe just the tip of the iceberg and should be used with caution to explain pathogenesis on the deterioration of COVID-19, which might be complex and related to inflammation, immunity, blood coagulation, and multiple organ functions. Future studies should focus on identification of specific signaling pathways and mechanisms after severe acute respiratory syndrome coronavirus 2 infections (IRB number: IRB-AF/SC-04/01.0).

### FIGURES

Table 3. Group Comparison and Pairwise Comparison of the Contents of Serum Cytokines and Chemokines					
	Moderate group	Severe group	Critical group	$\chi^2$	p
IL-2	1.20 ± 0.66	1.23 ± 0.81	1.44 ± 0.84	2.163	0.339
IL-4	1.22 ± 1.00	0.81 ± 0.76	1.20 ± 0.83	4.915	0.086
IL-6	22.64 ± 58.38	30.46 ± 70.64	1,680.90 ± 5,038.87 <sup>a</sup>	20.764	0.000
IL-10	6.54 ± 5.63	5.97 ± 3.04	42.40 ± 100.20 <sup>ab</sup>	28.332	0.000
TNF	0.99 ± 0.75	0.66 ± 0.61	1.57 ± 2.02 <sup>b</sup>	10.719	0.005
IFN- $\gamma$	1.15 ± 0.48	1.34 ± 0.77	1.74 ± 1.36 <sup>a</sup>	10.124	0.006

a,bRepresent significant difference compared with moderate group and severe group, respectively.

# PROFILE OF RT-PCR FOR SARS-COV-2: A PRELIMINARY STUDY FROM 56 COVID-19 PATIENTS

Xiao AT, Tong YX, Zhang S.. Clin Infect Dis. 2020 Nov 19;71(16):2249-2251. doi: 10.1093/cid/ciaa460.

Level of Evidence: 4 - Local non-random sample

## BLUF

Gastrointestinal surgeons from Tongji Medical College in China analyzed the viral dynamics of SARS-CoV-2 infection using 299 samples from 56 recovered COVID-19 patients hospitalized from January 21-February 12, 2020. They found the proportion of RT-PCR positive patients decreased weekly (89.3%, 66.1%, 32.1%, 5.4% and 0% at week 2, week 3, week 4, week 5 and week 6 respectively), with all negative by 6 weeks post-symptom onset (Figure 1). Because older patients and those with comorbidities were more likely to have prolonged shedding >24 days ( $p=0.011$ ), authors suggest following RT-PCR for a longer duration in these populations to ensure safe hospital discharges and mitigate SARS-CoV-2 transmission.

## ABSTRACT

A novel coronavirus (COVID-19) pandemic threatens the world. Here, we first studied the dynamics profile of SARS-CoV-2 from 56 recovered COVID-19 patients. We found virus shedding was up to 6 weeks after onset of symptoms. Prolonged observation period is necessary for older patients.

## FIGURES

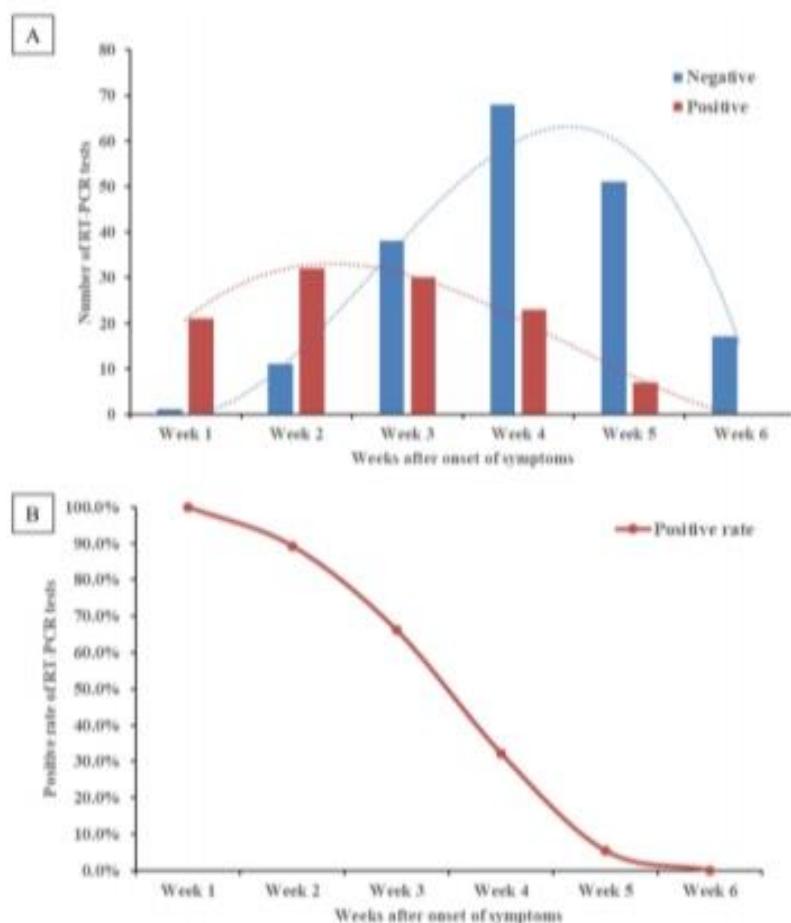


Figure 1: "Dynamic Profile of RT-PCR for SARS-CoV-2. (A) Dynamic Profile of SARS-CoV-2 Detected by RT-PCR from 56 COVID-19 Patients (N=299). Numbers of the positive (red bar) and negative (blue bar) results of SARS-CoV-2 RT-PCR were sum on weeks after the onset of symptoms. (B) Positive rate of SARS-CoV-2 Detected by RT-PCR from 56 COVID-19 Patients (N=299). Percentage of positive results of SARS-CoV-2 RT-PCR were calculated on weeks after the onset of symptoms".

# SEEDING BRAIN PROTEIN AGGREGATION BY SARS-COV-2 AS A POSSIBLE LONG-TERM COMPLICATION OF COVID-19 INFECTION

Tavassoly O, Safavi F, Tavassoly I.. ACS Chem Neurosci. 2020 Nov 18;11(22):3704-3706. doi:

10.1021/acscchemneuro.0c00676. Epub 2020 Nov 4.

Level of Evidence: Other - Mechanism-based reasoning

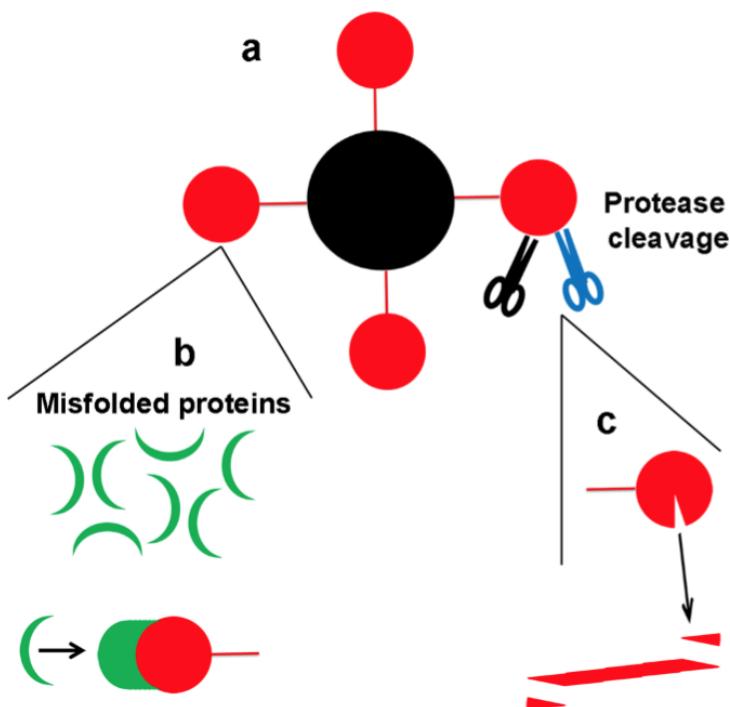
## BLUF

A team of neurobiologists review literature on post-infectious protein aggregation in the brain and discuss evidence supporting this possibility in SARS-CoV-2. They found documentation that SARS-CoV-2's spike S1 subunit possesses several heparin-binding sites that are known to cause aggregation of amyloid  $\beta$  in herpes simplex virus 1 infection, and that SARS-CoV-2's spike derived peptide has also been shown to have similar self-aggregating properties it (Figure 1). Authors conclude that further research could better delineate whether this phenomenon occurs in SARS-CoV-2 infection, and target therapeutic development accordingly.

## ABSTRACT

Postinfection complications of coronavirus disease 2019 (COVID-19) are still unknown, and one of the long-term concerns in infected people are brain pathologies. The question is that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection may be an environmental factor in accelerating the sporadic neurodegeneration in the infected population. In this regard, induction of protein aggregation in the brain by SARS-CoV-2 intact structure or a peptide derived from spike protein subunits needs to be considered in futures studies. In this paper, we discuss these possibilities using pieces of evidence from other viruses.

## FIGURES



**Figure 1.** Schematic representation showing the possible mechanisms that SARS-CoV-2 might involve in the brain's fibril formation. (A) Structure of SARS-CoV-2, including viral spikes. (B) Aggregation of misfolded proteins on the surface of the viral spike. (C) Cleavage of a viral spike protein by proteases leads to a viral peptide release that possesses high aggregation propensity. This peptide forms toxic fibrils in the brain.

# **CORONAVIRUS DISEASE 2019 (COVID-19): AN OVERVIEW OF THE IMMUNOPATHOLOGY, SEROLOGICAL DIAGNOSIS AND MANAGEMENT**

Anka AU, Tahir MI, Abubakar SD, Alsabbagh M, Zian Z, Hamedifar H, Sabzevari A, Azizi G.. Scand J Immunol. 2020 Nov 15:e12998. doi: 10.1111/sji.12998. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

## **BLUF**

Investigators mainly from Ahmadu Bello University (Nigeria) and Tokyo University of Science (Japan) performed a review of the pathophysiology and potential treatment targets for COVID-19. Their findings regarding the pathophysiology of SARS-CoV-2 include extensive inflammation via cytokine storm (including TNF-alpha, IL-6, IL-1b, iNOS; Figure 1), causing tissue damage such as acute respiratory distress syndrome (ARDS), leukopenia, and coagulopathy. Some of the most effective treatment approaches include viral neutralization via immunoglobulins, cell based therapy targeting mesenchymal stromal cells, and plasma therapy that increases the antibody response (Table 1). These findings can help guide future treatments for COVID-19.

## **ABSTRACT**

SARS-CoV-2 is a novel human coronavirus responsible for the Coronavirus disease 2019 (COVID-19) pandemic. Pneumonia and acute respiratory distress syndrome are the major complications of COVID-19. SARS-CoV-2 infection can activate innate and adaptive immune responses and result in massive inflammatory responses later in the disease. These uncontrolled inflammatory responses may lead to local and systemic tissue damage. In patients with severe COVID-19, eosinopenia and lymphopenia with a severe reduction in the frequency of CD4+ and CD8+ T cells, B cells, and natural killer (NK) cells is a common feature. COVID-19 severity hinges on the development of cytokine storm characterized by elevated serum levels of pro-inflammatory cytokines. Moreover, IgG, IgM, and IgA specific antibodies against SARS-CoV-2 can be detected in most patients, along with the viral RNA, forming the basis for assays that aid in patient diagnosis. Elucidating the immunopathological outcomes due to COVID-19 could provide potential targets for immunotherapy and are important for choosing the best clinical management by consultants. Currently, along with standard supportive care, therapeutic approaches to COVID-19 treatment involve the use of antiviral agents that interfere with the SARS-CoV-2 lifecycle to prevent further viral replication and utilizing immunomodulators to dampen the immune system in order to prevent cytokine storm and tissue damage. While current therapeutic options vary in efficacy, there are several molecules that were either shown to be effective against other viruses such as HIV or show promise in vitro that could be added to the growing arsenal of agents used to control COVID-19 severity and spread.

## FIGURES

S/N	Class of therapy	Example(s)	Mechanism of action	Reference(s)
1	Broad spectrum antivirals	$\beta$ -D-N4-hydroxycytidine (NHC),	Known activity against a number of human RNA viruses; reduces viral titer by introducing mutations in the viral RNA genome;	(88)
		Dihydroorotate dehydrogenase (DHODH)	Non-competitive inhibitor of the enzyme- Inosine-5'-monophosphate dehydrogenase (IMPDH), which is involved in the biosynthesis of host guanosine, and is capable of reducing the replication of SARS-CoV-2 <i>in vitro</i> ;	(89, 90)
		Merimepodib		
		N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC)	Show efficacy on less pathogenic human coronavirus HCoV-NL63, pseudotyped SARS-CoV-2, and MERS-CoV, in the airway of human epithelial cells	(91) (92)
2	Protease inhibitors	Peptidomimetic inhibitors (11a and 11b); Nelfinavir	Target the SARS-CoV-2 main protease ( $M^{pro}$ )	(93, 94)
3	RNA-dependent RNA polymerase (RdRp) inhibitors	Remdesivir	Adenosine triphosphate analog that prevents RdRp as a result of binding to RNA strands and inhibiting nucleotides addition, bringing about the termination of viral RNA transcription	(95)
4	Glucocorticoids	Ciclesonide, mometasone, and lopinavir	Reducing the function of certain aspects of the immune system such as inflammation and therefore, used in the treatment of diseases caused by an overactive immune system	(96)
5	JAK inhibitors (JAKinibs)	Baricitinib	Interrupts the passage as well as the intracellular assembly of SARS-CoV-2 into target cells through disruption of AAK1 signaling and also reduces inflammation in patients with ARDS; target both JAK1 and JAK2 which further affects signaling pathways downstream of the receptors, involved in the development of COVID-19;	(97)
		Ruxolitinib, memolitinib, and oclacitinib	its possibility of hindering a range of inflammatory cytokines including IFN- $\alpha$ , which plays a key role in reducing virus activity	(98)
6	Recombinant monoclonal antibody	Tocilizumab (TCZ)	Binds both soluble and membrane-bound IL-6 receptors (IL-6R) of immunoglobulin IgG1 subtype where such binding inhibits sIL-6R and mIL-6R-mediated signal transduction	(99, 100)
7	Chimeric monoclonal antibody	Siltuximab	Binding to IL-6 and blocking its effect	(101)

Table 1- Potential candidates drugs for the treatment of COVID-19

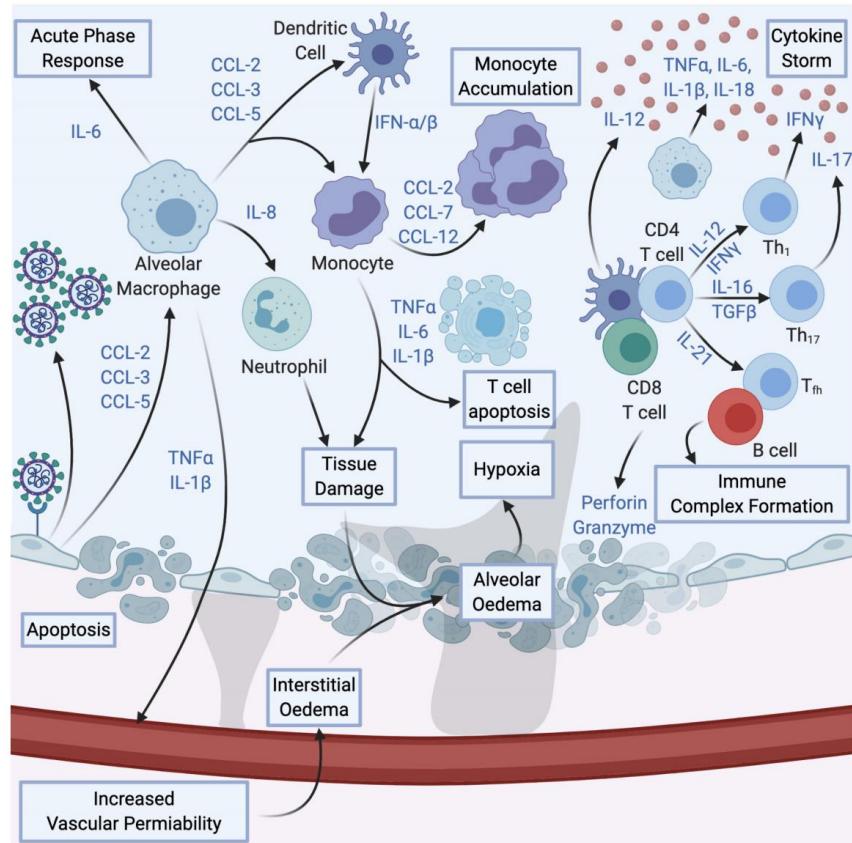


Figure 1. Cytokine storm in COVID-19

## IN VITRO

### MUCUS PRODUCTION STIMULATED BY IFN-AHR SIGNALING TRIGGERS HYPOXIA OF COVID-19

Liu Y, Lv J, Liu J, Li M, Xie J, Lv Q, Deng W, Zhou N, Zhou Y, Song J, Wang P, Qin C, Tong WM, Huang B.. Cell Res. 2020 Nov 6. doi: 10.1038/s41422-020-00435-z. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

#### BLUF

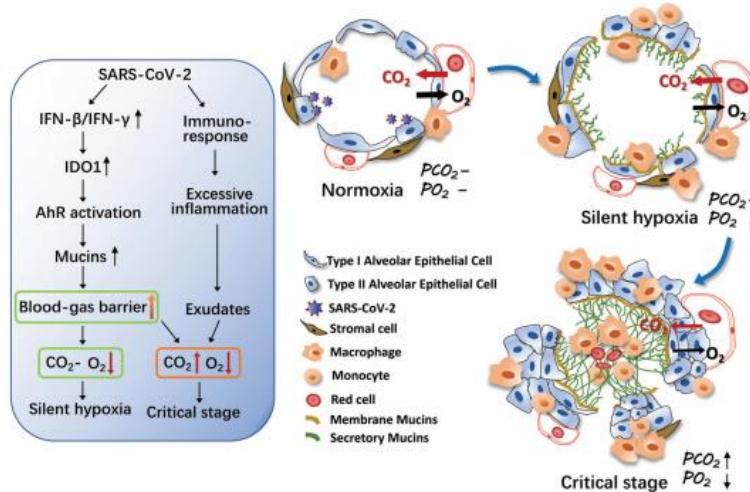
Immunologists at the Chinese Academy of Medical Sciences (CAMS) & Peking Union Medical College in Beijing, China assess possible mechanisms of hypoxia in COVID-19 via bronchoalveolar lavage (BAL) analysis from 8 SARS-CoV-2 positive patients and mucin samples from SARS-CoV-2 infected macaques (Figure 1). They found BALs from humans contained excessive carbohydrates suggestive of mucin-like substance and immunochemical staining in macaques showed upregulation of mucins 2, 5A and 5B. Further studies showed IFN- $\beta$  and IFN- $\gamma$  activation of the aryl hydrocarbon receptor (AhR) leads to increased mucin production via transcriptional upregulation (Figure 2), and authors suggest this excess mucin thickens the blood gas barrier in the lungs resulting in hypoxia (Figure 7).

#### ABSTRACT

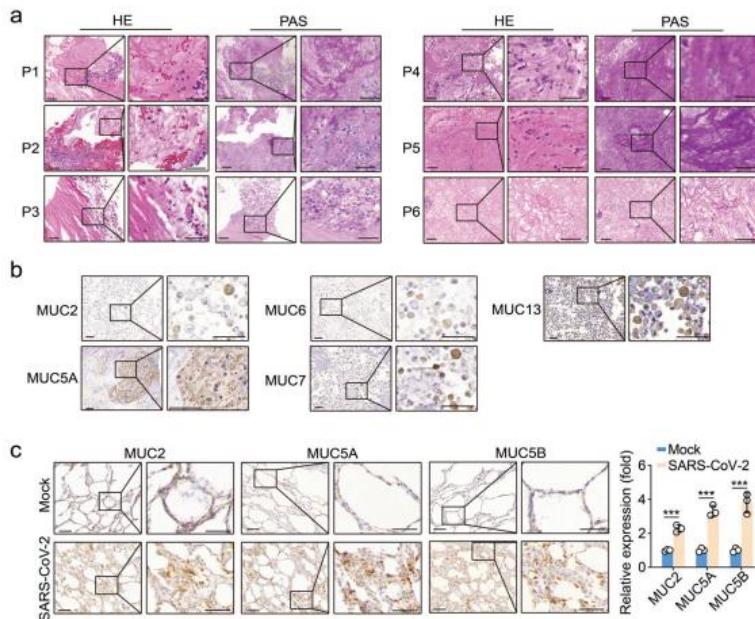
Silent hypoxia has emerged as a unique feature of coronavirus disease 2019 (COVID-19). In this study, we show that mucus are accumulated in the bronchoalveolar lavage fluid (BALF) of COVID-19 patients and are upregulated in the lungs of severe respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected mice and macaques. We find that induction of either interferon (IFN)-beta or IFN-gamma upon SARS-CoV-2 infection results in activation of aryl hydrocarbon receptor (AhR) signaling through an IDO-Kyn-dependent pathway, leading to transcriptional upregulation of the expression of mucins, both the secreted and membrane-bound, in alveolar epithelial cells. Consequently, accumulated alveolar mucus affects the blood-gas barrier, thus inducing hypoxia and diminishing lung capacity, which can be reversed by blocking AhR activity. These findings

potentially explain the silent hypoxia formation in COVID-19 patients, and suggest a possible intervention strategy by targeting the AhR pathway.

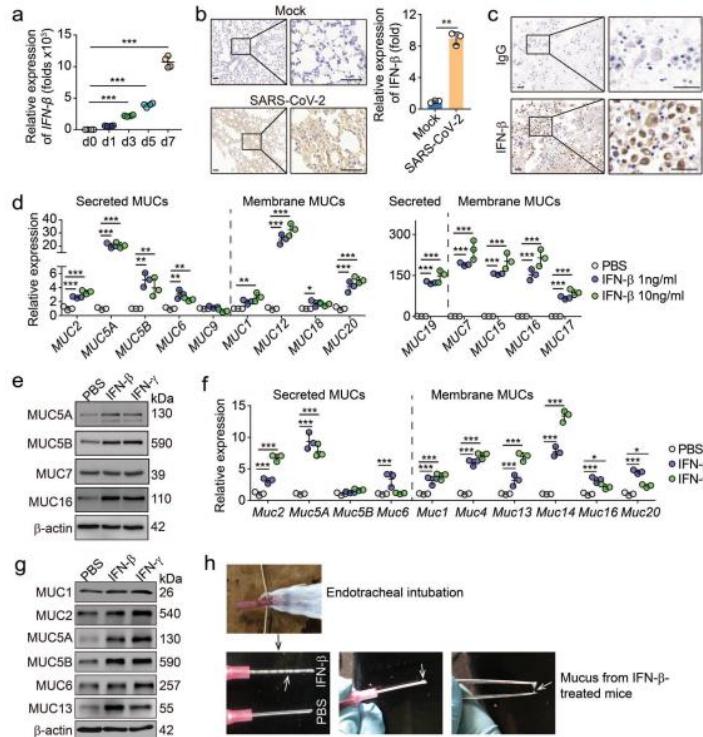
## FIGURES



**Fig. 7 A schematic for AhR-upregulated mucins in the hypoxia of COVID-19 patients.** A normal gas exchange between the alveoli and pulmonary capillary blood is achieved through a passive diffusion of  $O_2$  and  $CO_2$ . During SARS-CoV-2 infection, increased IFN- $\beta$  and IFN- $\gamma$  activate the AhR pathway, leading to the expression of mucins in alveolar epithelial cells. Mucins then stick to the blood-gas barrier and increase the thickness. Thickened barrier hinders  $O_2$  crossing but not  $CO_2$  at the beginning, leading to a clinical symptom of silent hypoxia. Companing the disease progression, more mucin production in combination with inflammation-induced exudate further increases barrier thickness, impeding the exchange of both  $O_2$  and  $CO_2$ , leading to a critical illness. “-” normal level.



**Fig. 1 Mucins are expressed in COVID-19 patients and nonhuman macaques.** **a** H&E and periodic acid-Schiff (PAS) staining of bronchoalveolar lavages (BALs) from COVID-19 patients. Scale bars, 50  $\mu$ m. **b** Immunohistochemical staining for mucins 2, 5A, 6, 7 and 13 in the BAL from COVID-19 patients. Scale bars, 50  $\mu$ m. **c** Immunohistochemical staining for mucins 2, 5A, and 5B from the lung sections of macaques infected with SARS-CoV-2 for 7 days ( $n = 3$  macaques/group). The data represent means  $\pm$  SD. Data (a, b) are representative images of 8 COVID-19 patients. Scale bars, 50  $\mu$ m. \*\*\* $P < 0.001$ , by two-tailed Student's  $t$  test (c).



**Fig. 2 Both IFN- $\beta$  and IFN- $\gamma$  upregulate the expression of mucins.** a HACE2-transgenic mice were infected with SARS-CoV-2 for the indicated time period. The expression of IFN- $\beta$  was measured by real-time PCR. b Immunohistochemical staining of IFN- $\beta$  from the lung sections of SARS-CoV-2-infected HACE2-transgenic mice for 5 days. Scale bars, 50  $\mu$ m. c Representative image of immunohistochemical staining of isotype control IgG or IFN- $\beta$  in BAL from three COVID-19 patients. Scale bars, 50  $\mu$ m. d BEAS-2B cells were treated with different doses of IFN- $\beta$  (1 or 10 ng/mL) for 24 h. The expression of secreted mucins (MUC2, 5A, 5B, 6, 9 and 19) and membrane-mucins (MUC1, 1, 7, 12, 15, 16, 17, 18 and 20) was determined by real-time PCR. e Western blot analysis of the expression of mucins 5A, 5B, 7 and 16 from BEAS-2B cells treated with PBS, IFN- $\beta$  (1 ng/mL) or IFN- $\gamma$  (10 ng/mL) for 48 h. f The same as (d), except that primary alveolar epithelial cells (PAECs) were treated with IFN- $\beta$  (1 ng/mL) or IFN- $\gamma$  (10 ng/mL). g Institute of Cancer Research (ICR) mice were treated with IFN- $\beta$  (1  $\mu$ g/mouse) or IFN- $\gamma$  (10  $\mu$ g/mouse) through the trachea once every day for 4 days. The expression of mucins 1, 2, 5A, 5B, 6 and 13 from the lung tissues was determined by western blot. h The same as (g), except the mucus was shown from the tracheal tubes. White arrow indicated the mucus. The data represent means  $\pm$  SD. Representative images are from three mice (b, e and g-h), four mice (a) or three independent experiments (d and f). \* $P$  < 0.05, \*\* $P$  < 0.01, \*\*\* $P$  < 0.001, by one-way ANOVA (a, d and f) or two-tailed Student's t-test (b).

### EFFECTIVENESS OF INFECTION-CONTAINMENT MEASURES ON SARS-COV-2 SEROPREVALENCE AND CIRCULATION FROM MAY TO JULY 2020, IN MILAN, ITALY

Cento V, Alteri C, Merli M, Di Ruscio F, Tartaglione L, Rossotti R, Travi G, Vecchi M, Raimondi A, Nava A, Colagrossi L, Fumagalli R, Ughi N, Epis OM, Fanti D, Beretta A, Galbiati F, Scaglione F, Vismara C, Puoti M, Campisi D, Perno CF.. PLoS One. 2020 Nov 20;15(11):e0242765. doi: 10.1371/journal.pone.0242765. eCollection 2020.

Level of Evidence: 4 - Case-series

#### BLUF

A cohort study conducted by physicians at ASST Grande Ospedale Metropolitano Niguarda in Milan, Italy from May 11, 2020 through July 5, 2020 found among 2753 patients who presented to the hospital, 5.1% tested positive for SARS-CoV-2 anti-N IgG, with a peak of 8.4% during week 2 and decreasing to 3.5% in the final week of the study (Table 1). The groups with the highest rates of anti-N IgG seropositivity were individuals aged 11-24 (p-value: 0.05), those from the provinces of Brescia, Bergamo or Cremona (p-value: 0.022), and those screened between May 18th and June 5th (p-value: 0.01) as depicted in Table 2. This study suggests that the Lombardy lockdown lasting from the beginning of March 2020 through the beginning of May 2020 was successful in reducing the rate of a SARS-CoV-2 anti-N seroprevalence, but that the risk of COVID-19 transmission is still very high and the population should continue to take precautions (Figure 1).

#### ABSTRACT

**OBJECTIVE:** Through a hospital-based SARS-CoV-2 molecular and serological screening, we evaluated the effectiveness of two months of lockdown and two of surveillance, in Milan, Lombardy, the first to be overwhelmed by COVID-19 pandemics during March-April 2020. **METHODS:** All subjects presenting at the major hospital of Milan from May-11 to July-5, 2020, underwent a serological screening by chemiluminescent assays. Those admitted were further tested by RT-PCR. **RESULTS:** The cumulative anti-N IgG seroprevalence in the 2753 subjects analyzed was of 5.1% (95%CI = 4.3%-6.0%), with a peak of 8.4% (6.1%-11.4%) 60-63 days since the peak of diagnoses (March-20). 31/106 (29.2%) anti-N reactive subjects had anti-S1/S2 titers >80 AU/mL. Being tested from May-18 to June-5, or residing in the provinces with higher SARS-CoV-2 circulation, were positively and independently associated with anti-N IgG reactivity (OR [95%CI]: 2.179[1.455-3.264] and 3.127[1.18-8.29], respectively). In the 18 RT-PCR positive, symptomatic subjects, anti-N seroprevalence was 33.3% (95% CI: 14.8%-56.3%). **CONCLUSION:** SARS-CoV-2 seroprevalence in Milan is low, and in a downward trend after only 60-63 days since the peak of diagnoses. Italian confinement measures were effective, but the risk of contagion remains concrete. In hospital-settings, the performance of molecular and serological screenings upon admission remains highly advisable.

#### FIGURES

Table 1. Overview of anti-N IgG seroprevalence and SARS-CoV-2 RT-PCR positivity by screening week.

	SARS-CoV-2 anti-N IgG screening result, N		Seroprevalence and 95% confidence interval <sup>a</sup>		SARS-CoV-2 RT-PCR result, N	RT-PCR positivity and 95% confidence interval <sup>a</sup>	
	Positive	Negative			Positive	Negative	
<b>Overall</b>	140	2613	5.1 (4.3–6.0)		45	2190	2.0 (1.5–2.7)
Week 1	20	526	3.7 (2.4–5.6)		4	235	1.7 (0.5–3.8)
Week 2	36	392	8.4 (6.1–11.4)		13	374	3.4 (1.9–5.5)
Week 3	22	309	6.6 (4.4–9.9)		5	304	1.6 (0.6–3.4)
Week 4	22	322	6.4 (4.3–9.5)		6	277	2.1 (0.8–4.2)
Week 5	8	295	2.6 (1.3–5.1)		1	293	0.3 (0.0–1.5)
Week 6	17	279	5.7 (3.6–9.0)		6	271	2.2 (0.9–4.3)
Week 7	6	245	2.4 (1.0–5.1)		3	228	1.3 (0.3–3.3)
Week 8	9	245	3.5 (1.9–6.6)		7	208	3.3 (1.4–6.2)

Anti-N = antibodies against viral nucleocapsid; N = number; RT-PCR = real-time polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

<sup>a</sup> Asymptotic (Wald) method.

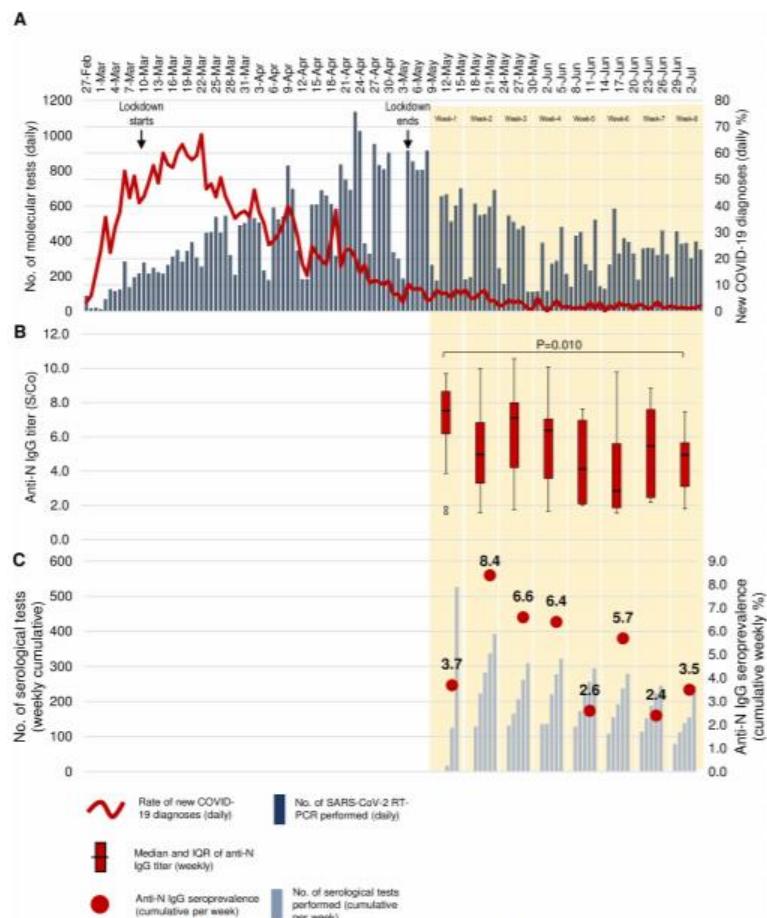
**Table 2. Potential predictors of anti-N IgG seropositivity.** Model adjusted for age, sex, province of residence, time of screening, and ward of admittance.

	SARS-CoV-2 anti-N IgG screening result		Odds ratio (95% CI)	P-value
	Positive	Negative		
<b>Age groups (years), n (%)</b>				
≤10 (N = 8)	0 (0%)	8 (100%)	-	
11–24 (N = 132)	11 (8.3%)	121 (91.7%)	1.989 (0.999–3.961)	0.050
25–49 (N = 786)	50 (6.4%)	736 (93.6%)	1.487 (0.978–2.260)	0.064
50–64 (N = 545)	24 (4.6%)	503 (95.4%)	1.044 (0.626–1.741)	0.868
65–84 (N = 984)	43 (4.4%)	941 (95.6%)	1 (ref)	
≥85 (N = 316)	12 (3.8%)	304 (96.2%)	0.864 (0.45–1.659)	0.660
<b>Sex, n (%)</b>				
Female (N = 1364)	77 (5.6%)	1287 (94.4%)	1.259 (0.895–1.772)	0.186
Male (N = 1389)	63 (4.5%)	1326 (95.5%)	1 (ref)	
<b>Province of residence, n (%)*</b>				
Brescia, Bergamo or Cremona (N = 36)	5 (13.9%)	31 (86.1%)	3.127 (1.18–8.29)	0.022
Milan (N = 2028)	97 (4.8%)	1931 (95.2%)	1 (ref)	
<b>Date of SARS-CoV-2 screening, n (%)</b>				
Before May 18 (N = 546)	20 (3.7%)	526 (96.3%)	1 (ref)	
Between May 18 and June 5, 2020 (N = 1103)	80 (7.3%)	1023 (92.7%)	2.138 (1.195–3.825)	0.01
After June 5, 2020 (N = 1104)	40 (3.6%)	1064 (96.4%)	0.954 (0.503–1.810)	0.885
<b>SARS-CoV-2 screening performed in the ER, n (%)</b>				
Yes (N = 2406)	122 (5.1%)	2284 (94.9%)	0.976 (0.587–1.623)	0.926
No (N = 347)	18 (5.2%)	329 (94.8%)	1 (ref)	

Data are n (%) unless otherwise stated. Odds ratio (95% CI) for anti-N IgG reactivity by univariate logistic regression analysis are shown for age groups, sex and ER screening; odds ratio (95% CI) for anti-N IgG reactivity by multivariate logistic regression analysis are shown for province of residence and date of SARS-CoV-2 screening. Age 65–84 years, male, residence in Milan, screening date Before May 18, and screening performed in hospital wards other than ER, are the reference groups, with which other groups are compared.

\*Only patients with known residence in Lombardy provinces (N = 2203) are included in this analysis.

Anti-N = antibodies against viral nucleocapsid; CI = Confidence interval; ER = Emergency Room; N = number; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.



**Fig 1.** Daily rate of laboratory-confirmed COVID-19 cases (A), weekly distribution of anti-N IgG titers (B), and weekly anti-N IgG seroprevalence (C). The daily rate of first-time positive real-time PCR results on nasopharyngeal swabs are reported for each day (red line), calculated on the total number of swabs.

## **SURGICAL MASK PARTITION REDUCES THE RISK OF NONCONTACT TRANSMISSION IN A GOLDEN SYRIAN HAMSTER MODEL FOR CORONAVIRUS DISEASE 2019 (COVID-19)**

Chan JF, Yuan S, Zhang AJ, Poon VK, Chan CC, Lee AC, Fan Z, Li C, Liang R, Cao J, Tang K, Luo C, Cheng VC, Cai JP, Chu H, Chan KH, To KK, Sridhar S, Yuen KY.. Clin Infect Dis. 2020 Nov 19;71(16):2139-2149. doi: 10.1093/cid/ciaa644.

Level of Evidence: Other - Mechanism-based reasoning

### **BLUF**

Clinical microbiologists from the University of Hong Kong tested the efficacy of a polyvinyl chloride air porous partition like those found in surgical masks for prevention of SARS-CoV-2 transmission between golden Syrian hamsters. They found transmission between caged naive hamsters and SARS-CoV-2-challenged index hamsters with the external portion of the partition facing towards the naive hamsters was significantly less than with no barrier (16.7% vs. 66.7%, p=0.019)(Figures 2, 3A; Table 3). Because there was no statistically significant transmission reduction when the external portion faced the index hamsters (33.3% vs. 66.7%, p=0.128)(Figure 3B), authors suggest that surgical masks can be utilized to effectively reduce the risk of transmission of SARS-CoV-2, particularly when worn by the infected individual.

### **ABSTRACT**

**BACKGROUND:** Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is believed to be mostly transmitted by medium-to-large sized respiratory droplets although airborne transmission is theoretically possible in healthcare settings involving aerosol-generating procedures. Exposure to respiratory droplets can theoretically be reduced by surgical mask usage. However, there is a lack of experimental evidence supporting surgical mask usage for prevention of COVID-19. **METHODS:** We used a well-established golden Syrian hamster SARS-CoV-2 model. We placed SARS-CoV-2-challenged index hamsters and naive hamsters into closed system units each comprising two different cages separated by a polyvinyl chloride air porous partition with unidirectional airflow within the isolator. The effect of a surgical mask partition placed in between the cages was investigated. Besides clinical scoring, hamster specimens were tested for viral load, histopathology, and viral nucleocapsid antigen expression. **RESULTS:** Non-contact transmission was found in 66.7% (10/15) of exposed naive hamsters. Surgical mask partition for challenged index or naive hamsters significantly reduced transmission to 25% (6/24, P=0.018). Surgical mask partition for challenged index hamsters significantly reduced transmission to only 16.7% (2/12, P=0.019) of exposed naive hamsters. Unlike the severe COVID-19 manifestations of challenged hamsters, infected naive hamsters had lower clinical scores, milder histopathological changes, and lower viral nucleocapsid antigen expression in respiratory tract tissues. **CONCLUSIONS:** SARS-CoV-2 could be transmitted by respiratory droplets or airborne droplet nuclei in the hamster model. Such transmission could be reduced by surgical mask usage, especially when masks were worn by infected individuals.

## FIGURES

Figure 3A

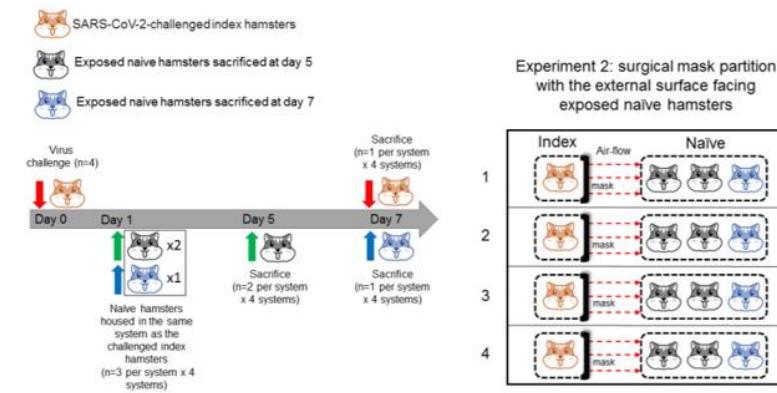
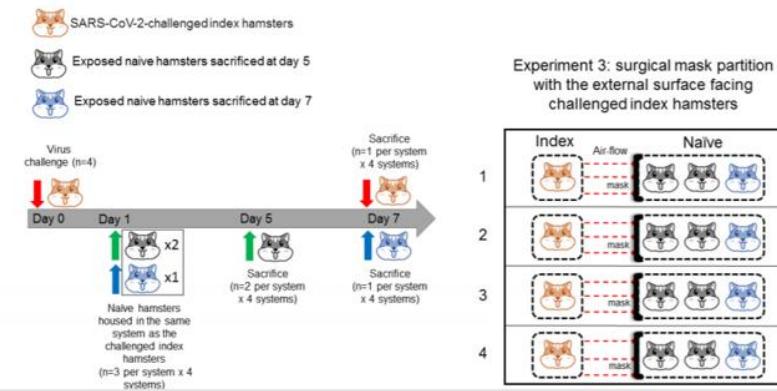


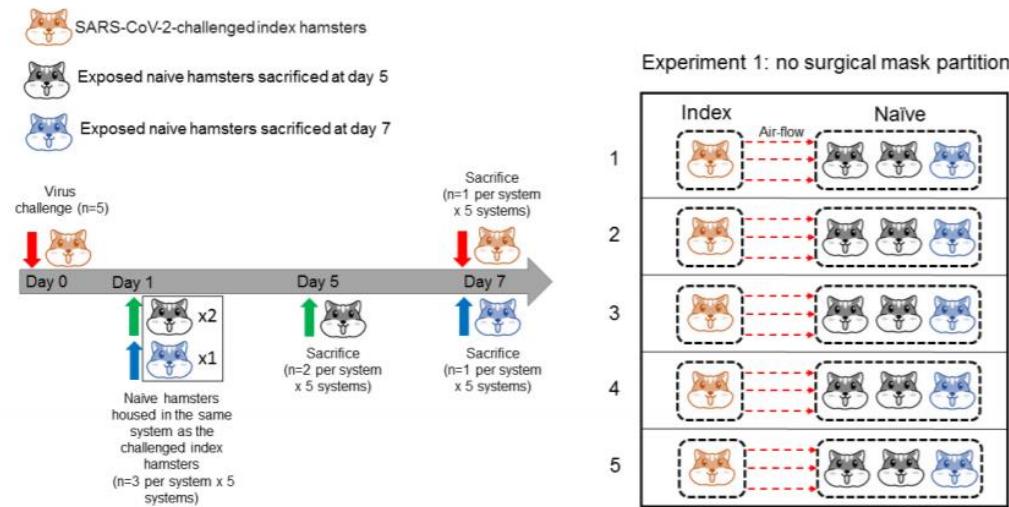
Figure 3B



'Figure 3. Non-contact transmission of SARS-CoV-2 from virus-challenged index hamsters to exposed naïve hamsters with surgical mask partition between the cages.'

Surgical mask partition with the external surface facing (A) exposed naïve hamsters (experiment 2) to mimic the situation of the mask being worn by the challenged index hamster for preventing the emission of SARS-CoV-2 infected droplets, or (B) facing the challenged index hamsters to mimic the situation of the mask being worn by the exposed naïve hamsters to prevent the reception of SARS-CoV-2-infected droplets from the challenged index hamsters. The timing of virus challenge and sacrifice of animals was the same as experiment 1. A total of 4 systems (n=16) were included in experiment 2 and another 4 systems (n=16) were included in experiment 3

**Figure 2**



'Figure 2. Non-contact transmission of SARS-CoV-2 from virus-challenged index hamsters to exposed naïve hamsters without surgical mask partition between the cages (experiment 1).'

SARS-CoV-2 was intranasally inoculated to the index hamsters ( $n=5$ ) at day 0. Twenty-four hours later, three naïve hamsters were transferred to the adjacent cage and exposed to the cage housing the virus-challenged index hamster. Two exposed naïve hamsters in each system were sacrificed at day 5 post-inoculation (4 days after exposure). The challenged index animal and the remaining exposed naïve animal in each system were then sacrificed at 7 dpi. A total of 5 systems ( $n=20$ ) were included in experiment 1.

**Table 3. Non-contact transmission rate from challenged hamsters to exposed naïve hamsters with or without surgical mask partition<sup>a</sup>**

Group	5 dpi	P-value <sup>a</sup>	7 dpi	P-value <sup>a</sup>	Total	P-value <sup>a</sup>
Naïve (no mask)	6/10 (60.0%)		4/5 (80.0%)		10/15 (66.7%)	
Naïve (any mask)	4/16 (25.0%)	0.109	2/8 (25.0%)	0.103	6/24 (25.0%)	0.018
Naïve (masked index)	1/8 (12.5%)	0.066	1/4 (25.0%)	0.206	2/12 (16.7%)	0.019
Naïve (masked naïve)	3/8 (37.5%)	0.637	1/4 (25.0%)	0.206	4/12 (33.3%)	0.128

<sup>a</sup>P-values represent comparison between the naïve (no mask) group with the other groups (Fisher's exact test).

## PERSONAL PROTECTIVE EQUIPMENT DURING COVID-19 PANDEMIC: A NARRATIVE REVIEW ON TECHNICAL ASPECTS

Saran S, Gurjar M, Baronia AK, Lohiya A, Azim A, Poddar B, Rao NS.. Expert Rev Med Devices. 2020 Nov 18. doi: 10.1080/17434440.2020.1852079. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

### BLUF

Intensivists from the Sanjay Gandhi Post Graduate Institute of Medical Sciences and Superspeciality Cancer Institute in Uttar Pradesh, India reviewed 48 articles on the technical aspects of and standards for personal protective equipment (PPE) published before June 30, 2020. They found most research indicates level 4 medical protection per Association for the Advancement of Medical Instrumentation standards (Table 3) is required for adequate prevention of SARS-CoV-2 infection, though breathability, comfort, good visibility, and minimal problems with prolonged usage impact compliance with PPE usage

(Table 1). Authors suggest these factors should be considered when manufacturing PPE, particularly emphasizing the importance of testing PPE materials to ensure they constitute class 1 medical devices (Table 2).

## ABSTRACT

**INTRODUCTION:** The current pandemic of novel Corona Virus Disease 2019 (COVID-19) has created a significant shortage of personal protective equipment (PPE) in many countries of the world, stressing medical services during this crisis. Along with addressing problems of demand and supply mismatch, there also need to ensure procurement of high quality PPEs that provide both safety and comfort to users. The purpose of this article is to review existing standards and recommendations on the technical aspects of PPE. Areas covered: For this review, MEDLINE, Google Scholar, and Research Gate were searched. Studies reporting technical aspects of component of PPE including mask and respirator, gown and coverall, gloves, goggles, face shields or visors, and boots, are included in this review. Expert commentary: The design and materials of PPE needs further research, which might have minimal carriage of infective biological load like use of antimicrobial repellent finishes along with adequate tensile strength and breathability through the fabric. Respirators should have least resistance while providing maximum protection; goggles should not have fogging. Also, there is need of formulating universal technical specifications for medically used PPE, and ensuring easy availability of testing facility.

## FIGURES

Table 1: Various certifications required for Personal Protective Equipment (PPE)

No	Purpose	Applicable Standards	Description			
<b>Respiratory Protection Devices</b>						
1.	Testing for bacterial filtration efficiency (BFE)	ASTM F2101	This test measures the percentage of bacteria larger than 3 microns filtered out by the mask, using a biological aerosol of <i>Staphylococcus aureus</i> . It evaluates medical face mask materials as an item of protective clothing but does not evaluate materials for regulatory approval as respirators.	3. Ability of fabric to resist water penetration exposed through spray contact	AATCC 42	The test measures the resistance of fabrics to the penetration of water by impact.
4.	Hydrostatic pressure method for determining the resistance of fabrics to penetration by water.	ISO 811	The method is applicable to all types of fabrics which are intended to be water resistant, whether or not they have been given a water-resistant or water-repellent finish.			
5.	Standard test method for resistance of materials used in protective clothing to penetration by synthetic blood	ISO 16604:2004 or ASTM F1670 or IEC 60529:2013	The penetration resistance of protective clothing is based on visual detection of synthetic blood penetration at a specific applied mechanical pressure.			
6.	Tested for penetration resistance to synthetic blood	ISO 16603:2005	Grouped into specific classes in response to applied pressure according to ISO 16603 indicating that higher class fabrics withstand higher pressure. Various classes from 1 to 5 are available. Class 3 and above are usually recommended for PPE used for medical protection tolerating up to 3.5 kPa (357 cm H <sub>2</sub> O).			
7.	Standard test method for resistance of materials used in protective clothing to penetration by bacteria (wet penetration)	ISO 22610	The test determines the resistance of a material to the penetration of bacteria, carried by a liquid, where subjected to mechanical rubbing.			
8.	Standard test method for resistance of materials used in protective clothing to penetration by blood-borne pathogens, using Phi-X174 Bacteriophage preparation as a test system	ASTM F1671	Users of the test method should review designs for worker/clothing exposure and assess the appropriateness of this test method for their specific applications.			
9.	Standard guide for accelerated aging of sterile barrier systems for medical devices	ASTM F1980	Define the desired shelf life of the package. Define package material properties, seal strength and integrity tests, sample sizes, and acceptance criteria.			
10.	Performance, durability and test methods for protective clothing against infective agents	EN 14126:2003	Types 1, 2 and 3 protective garments are referred to as full body "FB" type and Type 3, 4 and 6 protective garment standards include partial body "PB" garments covering only a part of the body.			
11.	Standard Test Methods for water vapor transmission rate	ASTM E96	The standard's testing methods are the - Desiccant Method: Test specimen is sealed to a test dish containing a			
<b>Gown or Coveralls</b>						
1.	Standard test method for tearing or tensile strength of non-woven fabrics by the Trapezoid procedure	ASTM D5733	Test method assesses the maximum tearing force required to continue or propagate a tear that started previously in the specimen.			
2.	Standard test method for breaking strength and elongation of Textile Fabrics (Grab Test)	ASTM D5034	Applicable to the determination of the effective strength of the fabric; the strength of the yarns in a specific width together with the fabric assistance from the adjacent yarns.			
<b>(WVTR) of Materials</b>						
12.	Test method for air permeability of textile fabrics	ASTM D737-96	desiccant, and the assembly is placed in a controlled atmosphere. Periodic weighing's are used to assess rate of water vapor transmission through the specimen. The desiccant is dried.			
<b>Goggles and Face Shields</b>						
1.	Goggles and face shields should comply with the quoted quality standards	EU standard directive 86/886/EEC, EN 166, ANSI/ISEA Z87.1-2010 or its equivalent	- Water Method: Dish containing desiccant and water-proof fabrics rated in medical fields. Air permeability is defined by the volume of air in cubic centimetres passing through the specimen at 100 cm <sup>2</sup> of fabric at a pressure difference of 10 hPa head of water.			
<b>Gloves</b>						
1.	Specification for gloves for medical applications	ASTM D6319-19, ASTM D6320-19, rubber examination gloves, ASTM D5250-19, polyvinyl chloride gloves, EN 374 certification	Optical quality, i.e. rough wrap around the design, scratch resistance and anti-misting/ fogging minimization are included.			
			Tests to assess the degree of sterility, freedom from holes, physical requirements before and after ageing, amount of powder on the glove, tensile strength and ultimate elongation.			
			Should results penetration to air and water, passing both air leak and water leak tests, offering minimum level 2 protection.			
			Tested ISO 374-5-2016 standard	Protection against penetration and permeation from micro-organisms		
<b>Shoes</b>						
1.	Should comply with the quoted quality standards	EN ISO 20345	bore pathogens Test method using Phi-X 174 bacteriophage.			
<b>Packing</b>						
1.	Packaging for terminally sterilized medical devices	ISO 11607	This safety footwear standard requires all safety shoes to have front foot protection against a 200 Joule impact. This is the amount of energy the toe region can absorb before breaking.			
			It ensures minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the sterile contents at the point of use.			

**Abbreviations:** ASTM: American Society of Testing and Materials; ISO: International Organization for Standardization; EN: European Standard; IEC: International Electrotechnical Commission; AATCC: American Association of Textile Chemists and Colorists; ISEA: International Society of Exposure Analysis; CPSC: Consumer Product Safety Commission; CFR: Code of Federal Regulations and UL: Underwriters Laboratory.

**Table 3: Comparison of various respirators with filtration efficiency ≥ 94-95%**

Name of the Respirator	N 95	FFP 2	KN95	P2	Korea 1 <sup>st</sup> class	DS/DL2
Country	USA	UK	China	Australia / New Zealand	South Korea	Japan
Certification	NIOSH-42C FR84	EN 149-2001	GB2626-206	AN/NZS 1716:2012	KMOEL-2017-64	JMHLW 214,2018
Test agent	NaCl	NaCl and paraffin oil	NaCl	NaCl	NaCl and paraffin oil	NaCl
Tested Flow rate (L/min)	85	95	85	95	95	85
Resistance during inspiration (Maximum Pressure drop) at tested flow rate	≤ 343 Pa	≤ 240 Pa	≤ 350 Pa	≤ 240 Pa	≤ 240 Pa	At 40 L/min: ≤ 70 Pa with valve ≤ 50 Pa without valve
<sup>a</sup> Resistance during expiration (Maximum Pressure drop)	≤ 245 Pa at 85L/min	≤ 300 Pa at 160L/min	≤ 250 Pa at 85L/min	≤ 120 Pa at 85L/min	≤ 300 Pa at 160L/min	≤ 70 Pa with valve ≤ 50 Pa without valve at 40L/min
Total inward leakage (TIL) [tested on human subjects performing exercise]	N/A	≤ 8% (arithmetic mean)	≤ 8% (arithmetic mean)	≤ 8% (individual and arithmetic mean)	≤ 8% (arithmetic mean)	N/A
Force applied (approximately)	245 Pa	N/A	1180 Pa	250 Pa	N/A	1470 Pa
CO <sub>2</sub> clearance requirement	N/A	≤ 1%	≤ 1%	≤ 1%	≤ 1%	≤ 1%

**Table 2: Respirators classification as per European and American Standards**

Classification	Basic weight (GSM)	Resistance (Pa)	Filtration efficiency (%)	Usage
<b>EU Standard</b>				
FFP 1	40	70	>93	3 ply face mask
	80	50	>93	
FFP 2	45	125	>99	Standard respirator used in mines
	60	110	>99	
	100	90	>99	Offers low airway resistance
FFP 3	90	150	>99.5	Chemical labs where high filtration is required
<b>US Standard</b>				
N 90	30	<60	>93	A soft product with lower airway resistance
	60	<40	>95	
N 95	30	<90	>98	Standard respirator used in mines
	50	<60	>98	
	80	<50	>98	Offers low airway resistance, high dust capacity
N 99	80	<95	>99.5	Cup shaped mask
N 100	120	<145	>99.995	Very high filtration efficiency

**Abbreviations used:** EU: European Union; US: United States; FFP: Filtering face piece; GSM: grams per square meter; Pa: Pascals; N: not resistant to oil.

## ASSOCIATION OF SARS-COV-2 GENOMIC LOAD TRENDS WITH CLINICAL STATUS IN COVID-19: A RETROSPECTIVE ANALYSIS FROM AN ACADEMIC HOSPITAL CENTER IN NEW YORK CITY

Zacharioudakis IM, Zervou FN, Prasad PJ, Shao Y, Basu A, Inglima K, Weisenberg SA, Aguero-Rosenfeld ME.. PLoS One. 2020 Nov 17;15(11):e0242399. doi: 10.1371/journal.pone.0242399. eCollection 2020.

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

### BLUF

Investigators from NYU Grossman School of Medicine conducted a retrospective cohort study of 42 COVID-19 patients with associated pneumonia admitted to NYU Langone Medical Center from March 31st to April 10th, 2020. They analyzed each patients' genetic load of SARS-CoV-2 Cycle threshold (Ct) (Figure 2) by rapid RT-PCR verses their Sequential Organ Failure Assessment (SOFA) score and found a statistically significant inverse correlation between the change in Ct value and change in clinical SOFA (Figure 4) score. These findings suggest that a "decrease in viral load over time was associated with clinical improvement," highlighting the potential use of SARS-CoV-2 genomic load as a potential predictive value in disease outcome.

### ABSTRACT

The Infectious Diseases Society of America has identified the use of SARS-CoV-2 genomic load for prognostication purposes as a key research question. We designed a retrospective cohort study that included adult patients with COVID-19 pneumonia who had at least 2 positive nasopharyngeal tests at least 24 hours apart to study the correlation between the change in the genomic load of SARS-CoV-2, as reflected by the Cycle threshold (Ct) value of the RT-PCR, with change in clinical status. The Sequential Organ Failure Assessment (SOFA) score was used as a surrogate for patients' clinical status. Among 457 patients with COVID-19 pneumonia between 3/31/2020-4/10/2020, we identified 42 patients who met the inclusion criteria. The median initial SOFA score was 2 (IQR 2-3). 20 out of 42 patients had a lower SOFA score on their subsequent tests. We identified a statistically significant inverse correlation between the change in SOFA score and change in the Ct value with a decrease in SOFA score by 0.05 (SE 0.02; p<0.05) for an increase in Ct values by 1. This correlation was independent of the duration of symptoms. Our findings suggest that an increasing Ct value in sequential tests may be of prognostic value for patients diagnosed with COVID-19 pneumonia.

### FIGURES

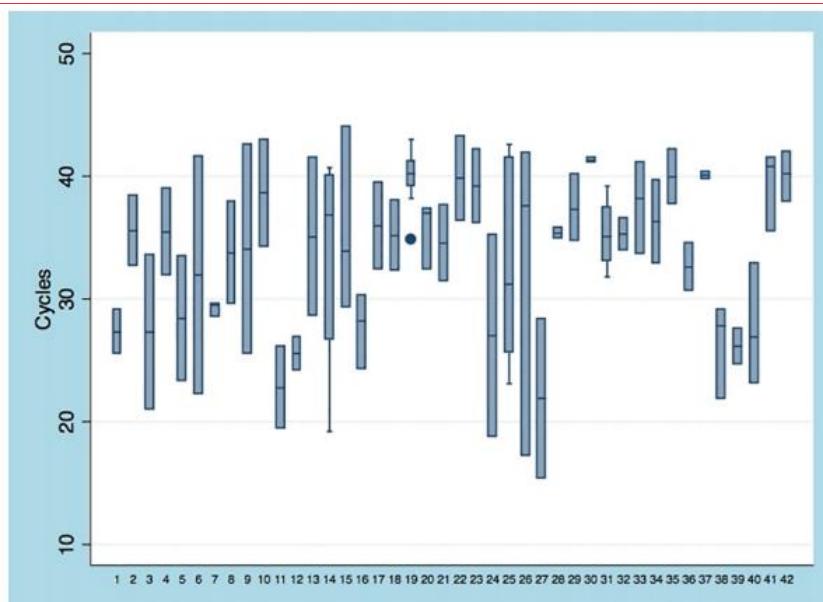


Figure 2. A graph of the Cycle threshold (Ct) values of the Cepheid Xpert1 Xpress SARS-CoV-2 assay measured on repeat screening of the 42 included patients.

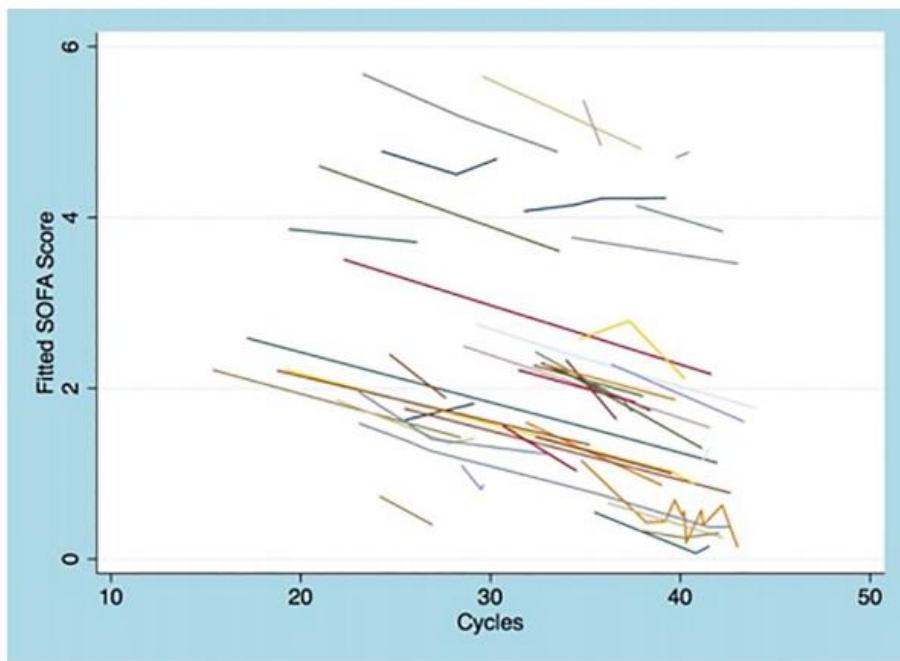


Figure 4. Graph of the fitted SOFA scores based on the cycle threshold values per patient.

# ADJUSTING PRACTICE DURING COVID-19

## FOR HEALTHCARE PROFESSIONALS

### COVID-19: MAKING THE RIGHT DIAGNOSIS

Schiff G, Mirica M.. Diagnosis (Berl). 2020 Nov 18;7(4):377-380. doi: 10.1515/dx-2020-0063.

Level of Evidence: Other - Expert Opinion

#### BLUF

A team from the Primary Care Research in Diagnostic Errors (PRIDE) project at Brigham and Women's Hospital in Boston comment on factors influencing the accuracy of COVID-19 diagnostics. They discuss sensitivity and specificity of new diagnostic tests, differential diagnoses, disruption of the physical exam due to telemedicine, secondary complications, development of reliable follow-up protocols, and the post-pandemic implementation of deferred diagnostic procedures. Authors suggest that several of the guiding principles for conservative diagnosis developed by their project (see Summary) are relevant to COVID-19 and emphasize the need for support from patients, public and healthcare personnel, and institutions in making timely, accurate diagnoses.

#### SUMMARY

The authors have highlighted principles 1, 2, 5, and 6 of the PRIDE project for making the conservative diagnosis of the COVID-19 pandemic.

- Principle #1: Patients with anxiety and somatic problems need to be attended during COVID-19 to avoid further stress and anxiety due to false-positive results from diagnostic testings.
- Principle #2: It is vital to have efficient and proper communication with the patients about this disease to prevent anxiety among the patients.
- Principle #5: Implementing "watchful waiting" and treating the patients without a definitive diagnosis at home while tracking the symptoms using a pulse oximeter plays a vital role in this pandemic.
- Principle #6: Analysing the "relationship between diagnosis and treatment".

#### ABSTRACT

The commentary below was written by Dr. Gordon Schiff and Maria Mirica for the PRIDE (Primary Care Research in Diagnostic Errors) project, an initiative of the Betsy Lehman Center for Patient Safety and Brigham and Women's Hospital Center for Patient Safety Research and Practice with support from the Gordon and Betty Moore Foundation. It highlights some of the key issues related to diagnostic accuracy issues for COVID-19 and beyond.

## MEDICAL SUBSPECIALTIES

### CARDIOLOGY

#### INCREASED SUSCEPTIBILITY TO SARS-COV-2 INFECTION IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTION

Matsushita K, Marchandot B, Carmona A, Curtiaud A, El Idrissi A, Trimaille A, Kibler M, Cardi T, Heger J, Hess S, Reydel A, Jesel L, Ohlmann P, Morel O.. ESC Heart Fail. 2020 Nov 18. doi: 10.1002/ehf2.13083. Online ahead of print.

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

#### BLUF

A cohort study, conducted by cardiovascular and regenerative medicine researchers at the Université de Strasbourg (France), followed-up via telephone interviews with acute coronary syndrome patients who received percutaneous coronary intervention between February 2014 and October 2018 (n=889). They found that the incidence of COVID-19-associated hospitalization or mortality was significantly greater in patients with reduced left ventricular ejection fraction (LVEF, n=91) versus patients with moderately reduced and preserved LVEF (n=798; 9% versus 1%, P 60; 0.001; Figure 2). Further, they observed that reduced LVEF was an independent predictor of COVID-19 hospitalization or mortality via multivariate logistic

regression (OR: 6.91; 95% CI: 2.60-18.35, P 60; 0.001; Table 3), suggesting that COVID-19 testing and treatment plans should be considered for patients with reduced cardiac function.

## ABSTRACT

**AIMS:** Cardiovascular disease has been recognized as a major determinant of coronavirus disease 2019 (COVID-19) vulnerability and severity. Angiotensin-converting enzyme (ACE) 2 is a functional receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is up-regulated in patients with heart failure. We sought to examine the potential association between reduced left ventricular ejection fraction (LVEF) and the susceptibility to SARS-CoV-2 infection.

**METHODS AND RESULTS:** Of the 1162 patients with acute coronary syndrome (ACS) who underwent percutaneous coronary intervention between February 2014 and October 2018, we enrolled 889 patients with available clinical follow-up data. Follow-up was conducted by telephone interviews 1 month after the start of the French lockdown which began on 17 March 2020. Patients were divided into two groups according to LVEF 60;40% (reduced LVEF) ( $n = 91$ ) or  $\geq 40\%$  (moderately reduced + preserved LVEF) ( $n = 798$ ). The incidence of COVID-19-related hospitalization or death was significantly higher in the reduced LVEF group as compared with the moderately reduced + preserved LVEF group (9% vs. 1%,  $P = 60$ ; 0.001). No association was found between discontinuation of ACE-inhibitor or angiotensin-receptor blockers and COVID-19 test positivity. By multivariate logistic regression analysis, reduced LVEF was an independent predictor of COVID-19 hospitalization or death (odds ratio: 6.91, 95% confidence interval: 2.60 to 18.35,  $P = 60$ ; 0.001). **CONCLUSIONS:** In a large cohort of patients with previous ACS, reduced LVEF was associated with increased susceptibility to COVID-19. Aggressive COVID-19 testing and therapeutic strategies may be considered for patient with impaired heart function.

## FIGURES

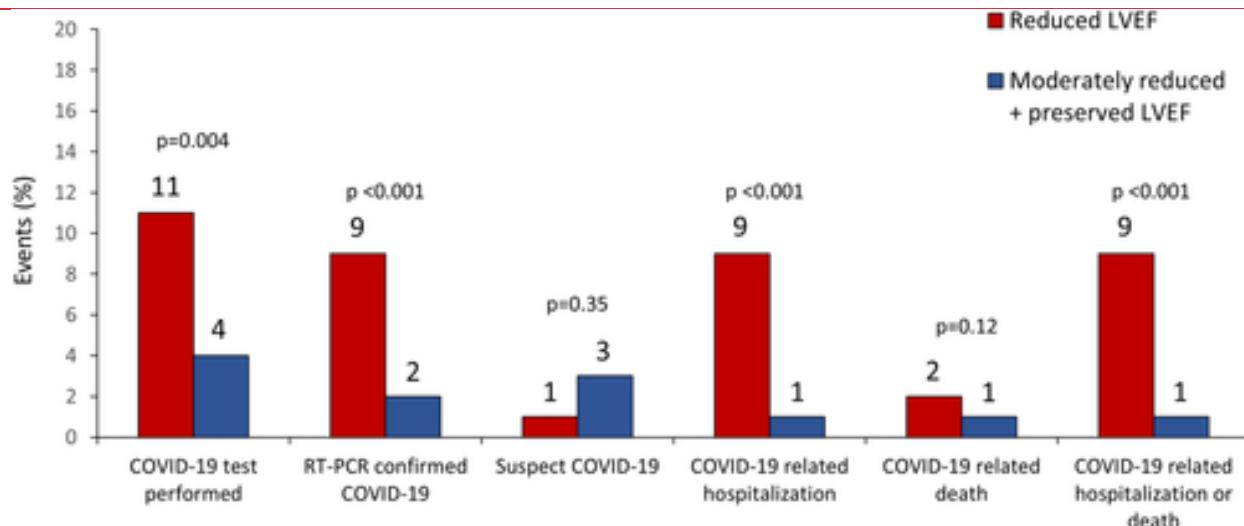


Figure 2. Prevalence of COVID-19-related events in reduced and moderately reduced + preserved LVEF groups. COVID-19, coronavirus disease 2019; LVEF, left ventricular ejection fraction; RT-PCR, reverse-transcriptase–polymerase-chain-reaction.

Characteristic	Total ( $N = 889$ )	Reduced LVEF ( $N = 91$ )	Moderately reduced + preserved LVEF ( $N = 798$ )	P value
Primary end point				
COVID-19-related hospitalization or death	18 (2)	8 (9)	10 (1)	60;0.001
Death				
COVID-19-related death	6 (1)	2 (2)	4 (1)	0.12
All cause death since 1 January 2020	22 (2)	4 (4)	18 (2)	0.27
Cardiovascular death since 1 January 2020	3 (0.3)	0 (0)	3 (0.4)	1.00
Hospitalization				
COVID-19-related hospitalization	18 (2)	8 (9)	10 (1)	60;0.001
Hospitalization in ICU	5 (1)	1 (1)	4 (1)	0.42
All cause hospitalization since 1 January 2020	35 (4)	9 (10)	26 (3)	0.006
Heart failure hospitalization since 1 January 2020	7 (1)	2 (2)	5 (1)	0.16

COVID-19, coronavirus disease 2019; ICU, intensive care unit; LVEF, left ventricular ejection fraction.

Values are  $n$  (%).

Table 3. Clinical Outcomes

## R&D: DIAGNOSIS & TREATMENTS

### DEVELOPMENTS IN DIAGNOSTICS

#### EARLY DETECTION OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 ANTIBODIES AS A SEROLOGIC MARKER OF INFECTION IN PATIENTS WITH CORONAVIRUS DISEASE 2019

Rongqing Z, Li M, Song H, Chen J, Ren W, Feng Y, Gao GF, Song J, Peng Y, Su B, Guo X, Wang Y, Chen J, Li J, Sun H, Bai Z, Cao W, Zhu J, Zhang Q, Sun Y, Sun S, Mao X, Su J, Chen X, He A, Gao W, Jin R, Jiang Y, Sun L.. Clin Infect Dis. 2020 Nov 19;71(16):2066-2072. doi: 10.1093/cid/ciaa523.

Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

#### BLUF

Biotechnology developers from AnyGo Technology Company in Beijing, China analyzed test characteristics of their ELISA kit, which recognizes SARS-CoV-2-specific antibodies using the SARS-CoV-2 S1 protein as a capturing antigen. Results showed high specificity (97.5%) when tested against 412 normal human samples and high sensitivity (97.1%) when tested against 69 samples from hospitalized and/or recovered COVID-19 patients. Authors claim that their ELISA assay can effectively identify SARS-CoV-2-specific antibodies and may be useful for identifying asymptomatic spreaders.

#### ABSTRACT

**BACKGROUND:** Thousands of medical staff had been infected with SARS-CoV-2 virus with hundreds of deaths reported. Such loss could be prevented if there is a serologic assay for SARS-CoV-2-specific antibodies for serological surveillance of its infection at the early stage of disease. **METHODS:** Using CHO cell expressed full length SARS-CoV-2 S1 protein as capturing antigen, a COVID-19/SARS-CoV-2 S1 serology ELISA kit was developed and validated with negative samples collected prior to the outbreaks or during the outbreak, and positive samples from patients confirmed with COVID-19. **RESULTS:** The specificity of the ELISA kit was 97.5%, as examined against total 412 normal human samples. The sensitivity was 97.1% by testing against 69 samples from hospitalized and/or recovered COVID-19 patients. The overall accuracy rate reached 97.3%. The assay was able to detect SARS-CoV-2 antibody on day one after the onset of COVID-19 disease. The average antibody levels increased during the hospitalization and after been discharged for two weeks. SARS-CoV-2 antibodies were detected in 28 out of 276 asymptomatic medical staff and one out of five nucleic acid test-negative "Close contacts" of COVID-19 patient.

**CONCLUSION:** With the assays developed here, we can screen medical staff, in-coming patients, passengers and people who are in close contact with the confirmed patients to identify the "innocent viral spreaders", protect the medical staff and stop the further spreading of the virus.

### DEVELOPMENTS IN TREATMENTS

#### HISTAMINE RECEPTORS AND COVID-19

Ennis M, Tiligada K.. Inflamm Res. 2020 Nov 18. doi: 10.1007/s00011-020-01422-1. Online ahead of print.

Level of Evidence: 1 - Review / Literature Review

#### BLUF

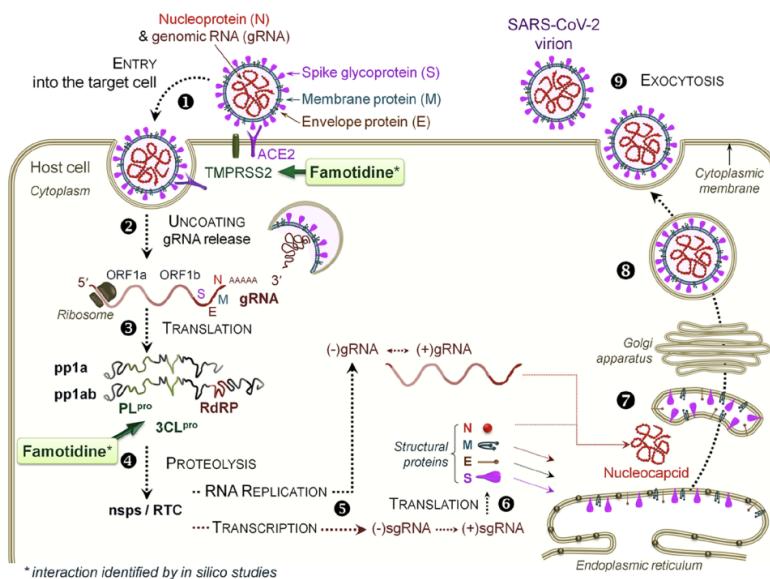
A literature review conducted on September 19, 2020 found that histamine antagonists, such as famotidine, may be a beneficial adjuvant COVID-19 therapy by directly interacting with major enzymes involved in the viral fusion and replication of SARS-CoV-2 (Figure 1). The authors caution that delirium is a potential adverse side affect of famotidine, suggesting that prospective randomized clinical trials are needed to investigate the efficacy and safety of repurposing histamine antagonists for the treatment of SARS-CoV-2 infection.

#### ABSTRACT

**OBJECTIVE:** Reports that the over-the-counter histamine H2 receptor antagonist famotidine could help treat the novel coronavirus disease (COVID-19) appeared from April 2020. We, therefore, examined reports on interactions between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and histamine receptor antagonists. **METHODS:** A systematic literature search was performed by 19 September 2020, and updated on 28 October 2020, in PubMed, Scopus, Cochrane

Library and Google Scholar using (COVID-19 OR coronavirus OR SARS-CoV-2) AND (histamine antagonist OR famotidine OR cimetidine). ClinicalTrials.gov was searched for COVID-19 and (famotidine or histamine). RESULTS: Famotidine may be a useful addition in COVID-19 treatment, but the results from prospective randomized trials are as yet awaited. Bioinformatics/drug repurposing studies indicated that, among several medicines, H1 and H2 receptor antagonists may interact with key viral enzymes. However, *in vitro* studies have to date failed to show a direct inhibition of famotidine on SARS-CoV-2 replication. CONCLUSIONS: Clinical research into the potential benefits of H2 receptor antagonists in managing COVID-19 inflammation began from a simple observation and now is being tested in multi-centre clinical trials. The positive effects of famotidine may be due to H2 receptor-mediated immunomodulatory actions on mast cell histamine-cytokine cross-talk, rather than a direct action on SARS-CoV-2.

## FIGURES



**Fig. 1** Schematic presentation of the life cycle of SARS-CoV-2 in the host cell and proposed sites of famotidine action. The attachment and entry of the virus into the host cell (**①**) require the interaction of angiotensin-converting enzyme 2 (ACE2) with the viral S glycoprotein, which is processed by the cellular transmembrane protease serine 2 (TMPRSS2). Following viral fusion with the target cell cytoplasmic membrane, the positive-sense single-stranded genomic RNA [(+)-gRNA] of the virus is released into the host cytoplasm (**②**) and the open reading frames (ORF) 1a and 1b are translated into the polyproteins pp1a and pp1ab (**③**). These are cleaved by the viral papain-like (PL<sup>pro</sup>) and 3C-like (3CL<sup>pro</sup>) proteases to generate 16 non-structural proteins (nsps), including RNA-dependent RNA polymerase (RdRP), a core constituent of the replication-transcription com-

plex (RTC) (**④**). During replication (**⑤**), the negative-sense genomic RNA [(-)-gRNA] serves as template for the (+)-gRNA, whereas the nested subgenomic RNAs [(+)-sgRNA] produced by fragmented transcription through negative-strand intermediates [(-)-sgRNA] (**⑥**) are translated into the SARS-CoV-2 structural (**⑦**) and accessory proteins. The nucleocapsids assembled from gRNA encapsidated by N protein and the structural proteins S, E and M inserted in the endoplasmic reticulum move along the secretory pathway (**⑧**) and form mature virions that are transported to the cell surface in vesicles (**⑨**) and released from the infected cell by exocytosis (**⑩**) [**7, 10, 11**]. Bold arrows indicate the sites of action of the histamine H<sub>2</sub> receptor antagonist famotidine as proposed by computational studies [**5, 36, 40**], yet not experimentally confirmed [**43, 51**]

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