The Daily COVID-19 Literature Surveillance Summary

March 02, 2021

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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)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

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

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

How to cite the Levels of Evidence Table

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

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

EXECUTIVE SUMMARY

Understanding the Pathology

- T cell lymphopenia may be more prevalent in symptomatic SARS-CoV-2 infections. A multidisciplinary group of infectious disease and immunology experts from the London School of Hygiene and Tropical Medicine conducted a systematic review of 61 articles on the T-cell immune response against SARS-CoV-2 in humans. They found T-cell peripheral lymphopenia (CD4+, CD8+) occurred more in symptomatic adults compared to children and asymptomatic adults, with a correlation between T cell lymphopenia and disease severity, duration of positivity, and mortality. Authors suggest T-cell responses to SARS-CoV-2 are complex and under-studied, and urge researchers to conduct further studies in asymptomatic patients and vaccine recipients.

Transmission & Prevention

- Outdoor settings continues to show decreased transmission. A systematic review of articles conducted at the University of California Berkeley by the Joint Medical Program that included 12 highly heterogeneous studies concerning outdoor transmission of viruses (5 studies with SARS-CoV-2; 7 studies with influenza or adenovirus) found that there is far lower transmission outdoors compared to indoors. However, without further study, risks may mitigate the benefits of resuming outdoor experiences without sufficient caution.

- COVID-19 emergency alert text messages may be effective in promoting the practice of preventive behaviors. Members of the Department of Public Health Sciences, in cooperation with local and central governments of South Korea, conducted a web-based survey of 990 participants about the association between alarm text messages and preventive behaviors during March 2020. They found 49.2% always read the alarm messages, and those who always read the messages were more likely to wear facial masks (β=.074, P=.01), avoid crowded place (β=.078, P=.01), and cancel social gatherings (β=.103, P<.001). Authors suggest that broadcasting public health information via text message is an effective strategy for disseminating important health information during the pandemic.

- Airborne dispersion of droplets during coughing correlates with distance. Investigators from the A*STAR Institute of High Performance Computing and Singapore General Hospital analyzed the transmission of viral particles by modeling the disbursement of droplets in the setting of a spontaneous indoor cough. They found the probability of droplet transmission decreased with increasing distance (0.5 vs 1 meter) from cougher to listener, use of facial covering, and increased relative humidity of 60%. This study highlights the importance of adherence to social distancing and mask wearing to aid in the decrease of SARS-CoV-2 transmission during the pandemic.

Management

- Systematic review and patient-level meta-analysis shows SARS-CoV-2 viral dynamics are more amenable to treatments with antiviral therapies. Experts in infectious disease and immunology from University College London, among others, conducted a systematic review of 45 papers (645 patients) and used extracted data to generate models of viral load trajectories under different treatment protocols. They found faster viral clearance in patients treated with remdesivir (adjusted hazard ratio [AHR]: 9.19, p<0.001), interferon (AHR: 2.2, p=0.015), and interferon plus ribavirin (AHR: 6.04, p = 0.006) while older, male, and more severely ill patients had slower viral clearance. The authors suggest that early use of antivirals may play a significant role in altering viral trajectories and recommend clinical trials to corroborate their findings.

- In-hospital use of statins is associated with a reduced risk of mortality in COVID-19. Endocrinologists from Universitas Padjadjaran in Indonesia conducted a systematic review and meta-analysis of 13 articles investigating the effect of statins on mortality in 52,122 COVID-19 patients published before November 2020. They found in-hospital use of statins decreased mortality (RR 0.54, 95% CI 0.50–0.58, p<0.00001; I2: 0%, p = 0.87); pre-hospital chronic statin therapy had no effect (RR 1.18, 95% CI 0.79–1.77, p = 0.415; I2: 68.6%, p = 0.013). Authors suggest in-hospital use of statins may reduce of mortality risk among patients with COVID-19 though recognize limitations of the retrospective and non-randomized methodology included in this analysis.

Adjusting Practice During COVID-19

- How do you manage regional bone banks during a declaration of a state of emergency concerning COVID-19? Researchers from the Kitasato University School of Medicine Department of Orthopedic Surgery and the Kitasato University Bone Bank found that changes were needed in the management of the bone bank in order to prevent the transmission of COVID-19. They suggest screening donors and recipients for COVID-19 with PCR and implementation of biological inactivation

methods, including heat treatment of bone grafts.

R&D: Diagnosis & Treatments

- Does famotidine reduce the risk of progression to severe disease, death, and intubation for COVID-19 patients? Internists and epidemiologists from several American and Chinese institutions conducted a systematic review and meta-analysis of five articles assessing the use of famotidine in COVID-19 patients. They found famotidine use produced no statistically significant effect in decreasing progression to severe disease, intubation, or death (RR: 0.82 [95% CI = 0.52–1.30], P = 0.40). Patients who received famotidine had lower reported median ferritin (P = 0.030), CRP (P = 0.002), and procalcitonin (P = 0.004) levels. Authors suggest though famotidine does not appear to decrease poor outcomes in COVID-19 patients, there still may be some potential benefit to its use given their observation of lower serum markers thought to be associated with COVID-19 prognosis.

- Diagnostic performance of COVID-19 serological assays during early infection may not be as helpful as later on. This systematic review and meta-analysis by researchers from the National University of Singapore analyzes the diagnostic performances of COVID-19 IgM and IgG serological assays during early infection in 55 studies with virologically confirmed SARS-CoV-2. Results showed the overall sensitivity and specificity to be 0.727 and 0.918 for IgM testing and 0.788 and 0.948 for IgG. They also found test accuracy significantly rose for both assays using enzyme-linked immunosorbent assay (ELISA) after Day 14. The authors conclude that because seroconversion of IgM and IgG were found to be low during the first week of infection (37.5% and 35.4%, respectively) and rose around Day 21 (81.3% and 93.3%, respectively), these assays are most practical later after symptom onset, and this understanding should be considered when choosing diagnostic testing for COVID-19.

- Early anti-SARS-CoV-2 immunoglobulin G response may be associated with disease severity in patients with COVID-19. A prospective study conducted at the Toho University School of Medicine in Tokyo, Japan found that 7 of 21 patients who tested positive by PCR produced an early SARS-CoV-2 IgG response. This response was associated with higher severity of disease, elevated CRP and D-dimer levels upon admission and higher respiratory rate and lower lymphocyte percentage on Day 7 of hospitalization compared to late SARS-CoV-2 IgG responders. It was also determined that early-IgG response was associated with lower viral load, which is contrary to previous studies that have associated increasing COVID-19 infection severity with higher viral load. These results suggest potential for early production of IgG to be used as a clinical indicator for disease severity, however further studies are needed to analyze and differentiate early vs. late IgG responses in regards to clinical presentation.

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OCCURRENCE AND DISTRIBUTION OF DISINFECTION BYPRODUCTS IN DOMESTIC WASTEWATER EFFLUENT, TAP WATER, AND SURFACE WATER DURING THE SARS-COV-2 PANDEMIC IN CHINA

Li Z, Song G, Bi Y, Gao W, He A, Lu Y, Wang Y, Jiang G.. Environ Sci Technol. 2021 Feb 1. doi: 10.1021/acs.est.0c06856. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Investigators from various institutions in China analyzed the accumulation of both traditional and newer disinfection byproducts (DBPs) in waste water, drinking water, and surface water during the COVID-19 pandemic in different geographic areas of Beijing and Wuhan, examining a total of 34 compounds. They found measurable amounts of DBPs in all three water categories (Figure 1a), with the highest levels in wastewater; all levels were still below the maximum guideline values of chemical compounds. This study can provide insight for public guidance for water system regulation and inspection given the increased use of disinfectants during the COVID-19 pandemic.

ABSTRACT

Intensified efforts to curb transmission of the Severe Acute Respiratory Syndrome Coronavirus-2 might lead to an elevated concentration of disinfectants in domestic wastewater and drinking water in China, possibly resulting in the generation of numerous toxic disinfection byproducts (DBPs). In this study, the occurrence and distribution of five categories of DBPs, including six trihalomethanes (THMs), nine haloacetic acids (HAAs), two haloketones, nine nitrosamines, and nine aromatic halogenated DBPs, in domestic wastewater effluent, tap water, and surface water were investigated. The results showed that the total concentration level of measured DBPs in wastewater effluents (78.3 mug/L) was higher than that in tap water (56.0 mug/L, $p = 0.05$), followed by surface water (8.0 mug/L, $p < 0.01$). Moreover, HAAs and THMs were the two most dominant categories of DBPs in wastewater effluents, tap water, and surface water, accounting for >90%, respectively. Out of the regulated DBPs, none of the wastewater effluents and tap water samples exceeded the corresponding maximum guideline values of chloroform (300 mug/L), THM4 (80 mug/L), NDMA (100 ng/L), and only 2 of 35 tap water samples (67.6 and 63.3 mug/L) exceeded the HAA5 (60 mug/L) safe limit. HAAs in wastewater effluents showed higher values of risk quotient for green algae. This study illustrates that the elevated use of disinfectants within the guidance ranges during water disinfection did not result in a significant increase in the concentration of DBPs.

FIGURES

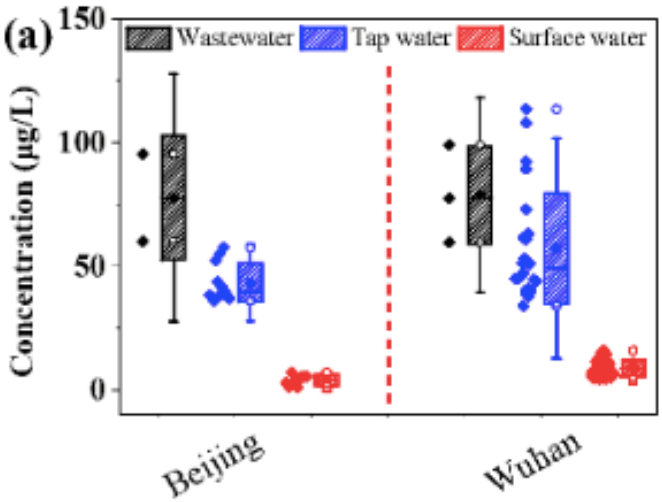


Figure 1a. Boxplot of total concentrations of the 35 measured DBPs in domestic wastewater, tap water, and surface water samples in Beijing and Wuhan.

ASYMPTOMATIC SARS-COV-2 INFECTIONS AMONG PERSONS ENTERING CHINA FROM APRIL 16 TO OCTOBER 12, 2020

Ren R, Zhang Y, Li Q, McGoogan JM, Feng Z, Gao GF, Wu Z.. JAMA. 2021 Feb 2;325(5):489-492. doi: 10.1001/jama.2020.23942.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

Researchers from the Chinese Center for Disease Control and Prevention conducted a retrospective cohort study of 3,103 international travelers entering China with a positive SARS-CoV-2 PCR test between April 16 - October 12, 2020 to examine distinguishing characteristics between asymptomatic and symptomatic patients with SARS-CoV-2 infection. There was a significant association between presence of symptoms and age, and a significant increase in the proportion of asymptomatic infections in their cohort indicating a possible global trend in the rise of asymptomatic infections (Table 1).

FIGURES

Table. Characteristics of International Entrants to China From April 16, 2020, to October 12, 2020

Characteristics	No. (%)				P value
	All entrants to China[a]	All participants[a,b]	Confirmed COVID-19 cases[c,d]	Asymptomatic SARS-CoV-2 infection[c,e]	
Overall	19 398 384 (100)	3103 (100)	1491 (48.1)	1612 (51.9)	
Sex					
Male		2343 (75.5)	1109 (47.3)	1234 (52.7)	.61[f]
Female		760 (24.5)	382 (50.3)	378 (49.7)	
Age group, y					
<20		167 (5.4)	79 (47.3)	88 (52.7)	
20-29		931 (30.0)	426 (45.8)	505 (54.2)	
30-39		854 (27.5)	389 (45.6)	465 (54.4)	<.001[g]
40-49		721 (23.2)	347 (48.1)	374 (51.9)	
≥50		430 (13.9)	250 (58.1)	180 (41.9)	
Country traveling from					
Philippines		500 (16.1)	209 (41.8)	291 (58.2)	
Russian Federation		453 (14.6)	193 (42.6)	260 (57.4)	
Singapore		242 (7.8)	75 (31.0)	167 (69.0)	
US		160 (5.2)	103 (64.4)	57 (35.6)	
86 other countries		1748 (56.3)	911 (52.1)	837 (47.9)	
Entry SARS-CoV-2 screening result					
Negative	19 395 281 (>99.9)	0	0	0	
Positive	3103 (<0.1)	3103 (100)	1491 (48.1)	1612 (51.9)	
Timing of symptoms					
Present at first test (ie, symptomatic cases)		1354 (43.6)	1354 (100)	0	
Present at second test (ie, presymptomatic cases)		137 (4.4)	137 (100)	0	
Never present (ie, asymptomatic infections)		1612 (51.9)	0	1612 (100)	
Study period					
April 16-30	538 905 (2.8)	162 (5.2)	117 (72.2)	45 (27.8)	
May 1-15	669 229 (3.5)	40 (1.3)	28 (70.0)	12 (30.0)	
May 16-30	737 938 (3.8)	61 (2.0)	43 (70.5)	18 (29.5)	
May 31-June 14	757 881 (3.9)	161 (5.2)	98 (60.9)	63 (39.1)	
June 15-29	999 726 (5.2)	123 (4.0)	80 (65.0)	43 (35.0)	
June 30-July 14	1 252 065 (6.5)	142 (4.6)	69 (48.6)	73 (51.4)	
July 15-29	1 759 192 (9.1)	143 (4.6)	72 (50.4)	71 (49.7)	<.001[g]
July 30-August 13	2 272 675 (11.7)	337 (10.9)	192 (57.0)	145 (43.0)	
August 14-28	2 842 526 (14.7)	485 (15.6)	222 (45.8)	263 (54.2)	
August 29-September 12	2 479 043 (12.8)	443 (14.3)	165 (37.3)	278 (62.8)	
September 13-27	2 589 730 (13.4)	479 (15.4)	191 (39.9)	288 (60.1)	
September 28-October 12	2 499 474 (12.9)	527 (17.0)	214 (40.6)	313 (59.4)	

Table 1. Characteristics of International Entrants to China from April 16, 2020 to October 12, 2020.

ADULTS

COVID-19 AND HUMAN PAPILLOMAVIRUS: PARADOXICAL IMMUNITY

Demirbaş A, Eker H, Elmas ÖF, Ulutaş Demirbaş G, Atasoy M, Türsen Ü, Lotti T.. J Cosmet Dermatol. 2021 Feb 24. doi: 10.1111/jocd.14022. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Dermatologists from several academic institutions in Turkey report the case of a 26-year-old female with a 10-year history of treatment-resistant verruca vulgaris of the hands who presented with SARS-CoV-2 infection requiring hospitalization in November 2020. She was treated with enoxaparin and favipiravir, and both her COVID-19 and verruca vulgaris completely resolved (Figure 1). There was no recurrence in two months of follow up. Because favipiravir should not impact DNA viruses like HPV, authors suggest this patients' regression is related to the COVID-19 immune response or delayed hypersensitivity reaction to SARS-Cov-2 infection.

FIGURES

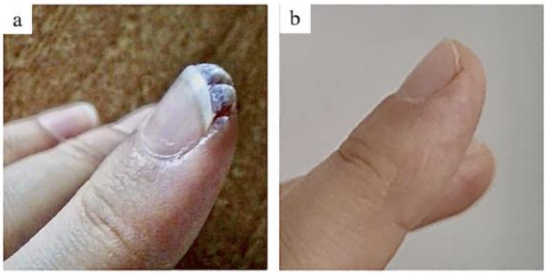


Figure 1. a. Periungual verruca vulgaris before COVID-19 , b. Lesions that spontaneously regress after COVID-19.

T CELL RESPONSE TO SARS-COV-2 INFECTION IN HUMANS: A SYSTEMATIC REVIEW

Shrotri M, van Schalkwyk MCI, Post N, Eddy D, Huntley C, Leeman D, Rigby S, Williams SV, Bermingham WH, Kellam P, Maher J, Shields AM, Amirthalingam G, Peacock SJ, Ismail SA.. PLoS One. 2021 Jan 25;16(1):e0245532. doi: 10.1371/journal.pone.0245532. eCollection 2021.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A multidisciplinary group of infectious disease and immunology experts from the London School of Hygiene and Tropical Medicine conducted a systematic review of 61 articles published prior to June 30, 2020 on the T-cell immune response against SARS-CoV-2 in humans (Figure 1). They found T-cell peripheral lymphopenia (CD4+, CD8+) occurred more in symptomatic adults compared to children and asymptomatic adults (Table 2), with a correlation between T cell lymphopenia and disease severity, duration of positivity, and mortality (see summary). Authors suggest T-cell responses to SARS-CoV-2 are complex and under-studied, and urge researchers to conduct further studies in asymptomatic patients and vaccine recipients.

SUMMARY

Authors from the UK conducted a systematic review of 61 articles via MEDLINE, Embase, COVID-19 Primer published before the end of June 2020 on T cell immune response against SARS-CoV-2 in humans(Figure 1). They found:
1. Symptomatic adults cases have T cell lymphopenia correlated with poorer outcomes:
- Symptomatic adult patients had peripheral T cell lymphopenia (CD4+, CD8+) whereas T cell counts were preserved in asymptomatic and pediatric patients.
- T cell lymphopenia positively correlated with disease severity, non-survival, and duration of RNA positivity.
- T cell count recovered with RNA negativity (Table 2).

2. "People with severe or critical disease generally develop more robust, virus-specific T cell responses."
- Severe/critically ill patients present with highly activated T cell response that increased with disease severity.
- Critically ill patients developed strong inflammatory cytokine T cell responses against Spike(S), Membrane(M), and Nuceocapsid(NP) proteins. Elevated IL-6, IL-10, TNF-alpha were seen in severe patients.
- IL-6 showed a positive correlation with disease severity and lymphopenia. Multivariate regression reveals IL-6>20 pg/ml correlated with higher in-hospital mortality(OR 9.78, P<0.001).
- Patients who recovered from the severe disease had significantly higher breadth(p=0.010) and magnitude(p=0.002) of T cell response than mild patients.
- Magnitude of T cell response correlated with anti-S and anti-NP antibodies while a weak statistically significant relationship was observed between CD8+T cells and anti-RBD antibodies(r = 0.386 p = 0.0321)

3. The study suggests memory and helper T cell responses against multiple viral epitopes may ensure enduring T cell immunity.
- The cross-reactive T cell responses have been observed between human coronaviruses and studies demonstrated cross-reactive T cells in unexposed and uninfected adults. One study shows pre-existing T cells in 81% of unexposed individuals.
- The duration of T cell immunity is unknown, although it is expected to be 6-8 months post-infection according to recent reports

ABSTRACT

BACKGROUND: Understanding the T cell response to SARS-CoV-2 is critical to vaccine development, epidemiological surveillance and disease control strategies. This systematic review critically evaluates and synthesises the relevant peer-reviewed and pre-print literature published from 01/01/2020-26/06/2020. METHODS: For this systematic review, keyword-structured literature searches were carried out in MEDLINE, Embase and COVID-19 Primer. Papers were independently screened by two researchers, with arbitration of disagreements by a third researcher. Data were independently extracted into a pre-designed Excel template and studies critically appraised using a modified version of the MetaQAT tool, with resolution of disagreements by consensus. Findings were narratively synthesised. RESULTS: 61 articles were included. 55 (90%) studies used observational designs, 50 (82%) involved hospitalised patients with higher acuity illness, and the majority had important limitations. Symptomatic adult COVID-19 cases consistently show peripheral T cell lymphopenia, which positively correlates with increased disease severity, duration of RNA positivity, and non-survival; while asymptomatic and paediatric cases display

preserved counts. People with severe or critical disease generally develop more robust, virus-specific T cell responses. T cell memory and effector function has been demonstrated against multiple viral epitopes, and, cross-reactive T cell responses have been demonstrated in unexposed and uninfected adults, but the significance for protection and susceptibility, respectively, remains unclear. CONCLUSION: A complex pattern of T cell response to SARS-CoV-2 infection has been demonstrated, but inferences regarding population level immunity are hampered by significant methodological limitations and heterogeneity between studies, as well as a striking lack of research in asymptomatic or pauci-symptomatic individuals. In contrast to antibody responses, population-level surveillance of the T cell response is unlikely to be feasible in the near term. Focused evaluation in specific sub-groups, including vaccine recipients, should be prioritised.

FIGURES

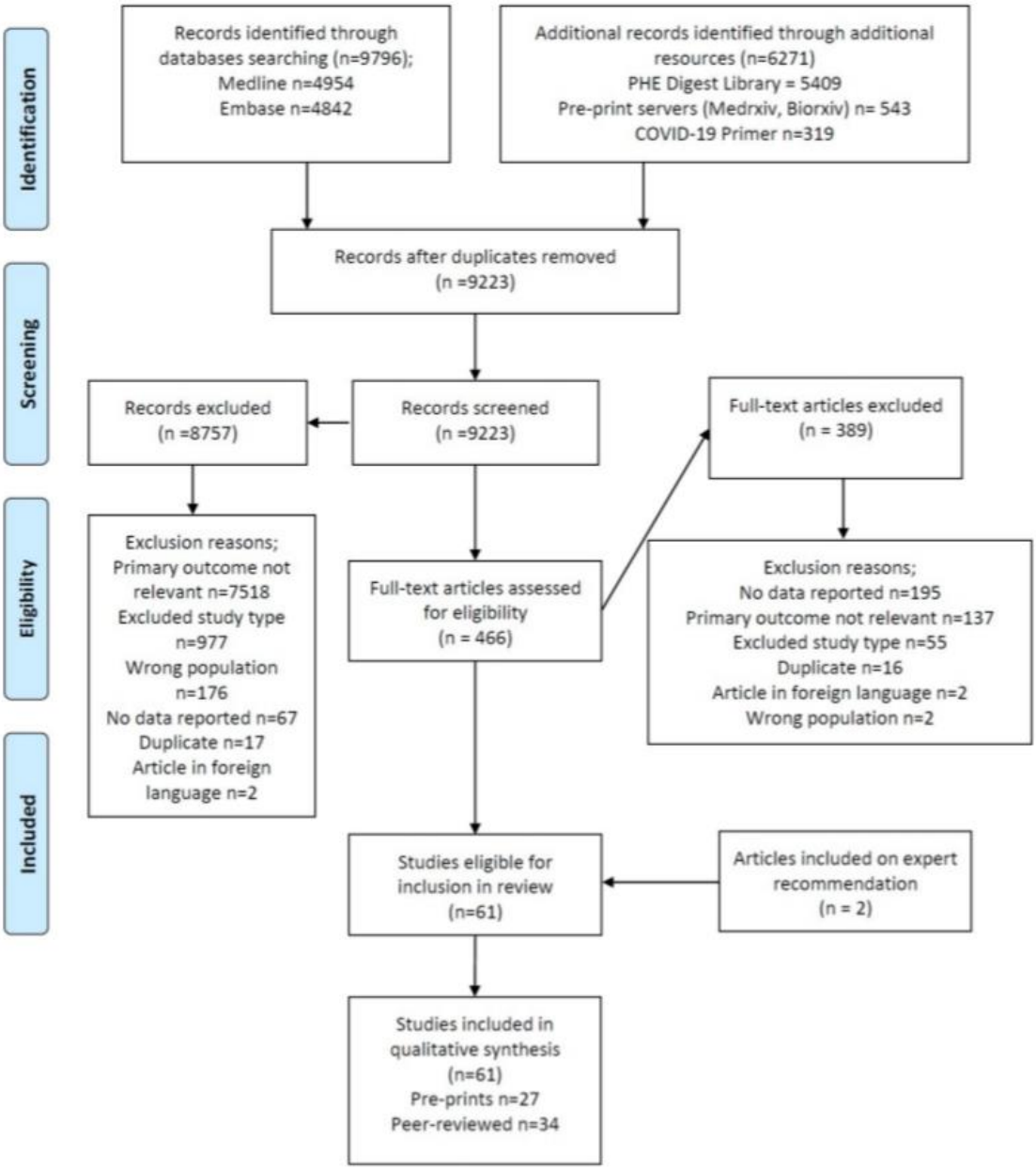


Figure 1: "PRISMA flowchart documenting the search and screening process for this review".

Category	Correlate	Dimension or sub-population	Findings
Clinical	Disease severity*	Asymptomatic or pauci-symptomatic	1. • One study evaluated T cell responses in asymptomatic patients (n = 20) and found little change in the circulating T cell frequencies within this group [51].
		Moderate disease	• Reduced numbers of both $CD4^+$ and $CD8^+$ T cells in moderate and severe cases, alongside increased numbers of activated $CD4^+$ and $CD8^+$ T cells expressing PD-1 or Tim-3; as well as potential reductions in cytotoxic potential and polyfunctionality were reported in one narrative review [3].
		Severe or critical disease	*Cell counts*
			• A medium quality meta-analysis found that patients with severe disease had statistically significant, two-fold decreases in both $CD4^+$ and $CD8^+$ T cells, as well as in $CD3^+$ T cells (1.7-fold) and overall lymphocyte number (1.44-fold), alongside statistically significant increases in neutrophils (1.33-fold) and overall leukocytes (1.2-fold) [67].
			• A large study (N = 599) reported reduced total, $CD4^+$, and $CD8^+$ T cells being associated with more severe disease, comparing n = 43 ICU-admitted patients with non-ICU-admitted patients, and comparing critical/severe non-ICU patients with mild/moderate non-ICU patients (as per Chinese national definitions") [37].
			• Other large studies [11, 18, 32, 36] showed comparable findings, and 3 studies also reported reduced $CD3^+$ cells in more severe disease [18, 32, 36]; however, one only found significant cell count differences for critical vs severe disease, and not for severe vs moderate disease [18].
			Cell ratios
			• Six studies reported marked increases in CD4/CD8 ratio (due to increases in CD4+ but reductions in CD8+ cells) in severe and critical patients compared to those with moderate disease [22, 25, 36, 62, 65]. The last of these also showed $CD8^+$ T cell counts were much slower to normalise than CD4+ in patients with severe disease [25].
			• Two studies however, reported significant reductions in $CD4^+$, but not in $CD8^+$, T cells in severe disease (n = 452), or 'aggravated' disease, defined as clinically progressive at 7 days (n = 17) [26, 34].
			• A small study from Iran reported increased CD8 expression in ICU patients relative to healthy controls, quantified by flow cytometry as mean fluorescence intensity (MFI), with no significant differences seen in CD4/CD8 ratio, or CD4+ T cell MFI [40].

Table 2: "Evidence on clinical and demographic correlates of T cell response to SARS-CoV-2 infection from studies included in this review (*disease severity was defined in various ways in included studies; for some according to intensive care unit admission; a number used the Chinese National Health Commission definition".

	Clinical endpoint	Survival vs non-survival	• Two studies with large cohorts followed up COVID-19 patients until death or discharge, both conducting multivariate analysis. Luo *et al.* (n = 1018), reported significantly lower $CD3^+$, $CD4^+$ and especially $CD8^+$ counts in non-survivors than survivors, and found that $CD8^+$ T cell counts <165 cells/μL (OR 5.93) were independently associated with mortality after adjustment for age, sex and comorbidities [21]. Liu *et al.* (n = 340) reported that lower helper T cells (OR 0.22) and higher CD4/CD8 ratio (OR 4.8) were highly significant predictors of mortality [63].
			• Whilst also reporting lower $CD8^+$ counts in non-survivors throughout the disease course, Wang *et al.* (n = 157) also found that non-survivors had lower $CD4^+$ counts only evident in middle and late stages of disease, and that non-survivors had a lower CD4/CD8 ratio [29].
			• Based on 28 deaths amongst 187 patients, Xu *et al.* demonstrated that total T cell counts <500/μl, CD3+ counts <200/μl, $CD4^+$ or $CD8^+$ counts <100/μ as well as B cell counts <50/μL, were significantly associated with risk of in-hospital death, however this is only on univariate analysis [32].
			• In a cohort of n = 548, Chen *et al.* reported significantly elevated neutrophil-to-lymphocyte ratio (NLR), platelets-to-lymphocytes ratio (PLR), reduced peripheral $CD3^+$, $CD4^+$ and particularly $CD8^+$ counts in non-survivors [36]. He *et al.* (n = 204) reported that T cell levels continued to fall until death in non-survivors, whilst in survivors with severe disease, levels increased after 15 days and normalised after 25 days of treatment [11].
		RNA persistence	• Four small but high or medium quality clinical cohort studies from China showed that slower resolution of PCR-positivity is associated with reductions in peripheral T cells.
			• Jiang *et al.* (n = 23) found that the baseline abnormalities in $CD3^+$, $CD4^+$ and $CD8^+$ T cells underwent robust recovery in patients who became RNA negative 2 weeks after diagnosis, whilst they did not do so in those who remained persistently positive [12].
			• Liu *et al.* compared 37 cases who remained positive at day 20, with 37 patients at their point of diagnosis, as well as 54 healthy controls, and showed that both the persistently positive and control groups had higher $CD3^+$ and $CD4^+$ levels, suggesting that these subsets do normalise despite viral persistence [45].
			• In a similar study, though with a persistence threshold of 15 days, Dong *et al.* (n = 18) also found global reductions across $CD3^+$, $CD4^+$ and $CD8^+$ subsets for persistent positives, which increased between admission and discharge; as well as significant negative correlation between overall T cell count and duration of positive nucleic acid test [38].
			• Liu *et al.* (n = 39) also reported higher global T and B cells in patients becoming RT-PCR negative within 14 days [20].
	Co-morbid disease status		• Three studies considered the effect of comorbid status, all originating from China and spanning patients with non-severe, severe and critical clinical presentations [11, 20, 39]. Two had significant methodological limitations [20, 39].
			• One study (n = 204) found significantly lower total lymphocyte and lymphocyte subset counts in patients with comorbidities compared with those without (though "comorbidities" not defined) [11].
			• The second (n = 39) found statistically significant differences in $CD8^+$ counts between patients with comorbid disease and those without (p = 0.046), but no difference in $CD4^+$ counts—although here again the range of comorbidities considered was not defined [20].
			• The final study compared outcomes in a paediatric cohort with or without "allergic disease" (not clearly defined) and showed no effect on clinical course, total lymphocyte or lymphocyte subset counts [39].
Demographic	Age	Older adults	• A high-quality clinical cohort study and a medium-quality case-control study, both from China, reported lower T cell total and subset counts, including $CD3^+$, $CD4^+$, $CD8^+$ subsets, for older patients aged 60 or over [11, 37].
		Children	• Four medium-quality studies—1 case control and 3 case series—considered cellular responses in children in samples from China, all showing comparable $CD3^+$, $CD4^+$ and $CD8^+$ counts to healthy paediatric controls, or where the comparison group was adults, higher T cell counts across subsets [19, 33, 35]. However, potential confounders such as disease severity or comorbidities were not controlled for in these studies.
	Sex		• One medium-quality case series (n = 27) from China examined differences in cytokine secretion by sex of cases, showing reductions in $CD4^+$ and $CD8^+$ count for all patients irrespective of gender but more generalised cytokine responses were observed among male participants than females, for IL-6, TNF-α and procalcitonin–although the statistical significance of these differences was not tested [24].

Table 2: "Evidence on clinical and demographic correlates of T cell response to SARS-CoV-2 infection from studies included in this review (* disease severity was defined in various ways in included studies; for some according to intensive care unit admission; a number used the Chinese National Health Commission definition".

COINFECTION WITH INFLUENZA A VIRUS ENHANCES SARS-COV-2 INFECTIVITY

Bai L, Zhao Y, Dong J, Liang S, Guo M, Liu X, Wang X, Huang Z, Sun X, Zhang Z, Dong L, Liu Q, Zheng Y, Niu D, Xiang M, Song K, Ye J, Zheng W, Tang Z, Tang M, Zhou Y, Shen C, Dai M, Zhou L, Chen Y, Yan H, Lan K, Xu K.. Cell Res. 2021 Feb 18. doi: 10.1038/s41422-021-00473-1. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Virologists and immunologists from Wuhan University in China analyzed potential effects of influenza A (IAV) and SARS-CoV-2 co-infection using cultured cells (A549) and K18-hACE2 transgenic mice. In cell culture, they isolated more copies of SARS-CoV-2 E and N genes (A549 cells), observed higher SARS-CoV-2 infectivity (Calu-3, NHBE cells), and found higher ACE2 mRNA levels (A549, Calu-3, NHBE) in cells pre-infected with IAV compared to those only infected with SARS-CoV-2. Co-infected mice had significantly higher SARS-CoV-2 viral load and increased lung pathogenicity in lung homogenates compared mice infected only with SARS-CoV-2 (Figures 1, 2, 3). Authors suggest influenza infection may faciliate or worsen SARS-CoV-2 infection and encourage administration of influenza vaccines to decrease COVID-19 severity in persons with high risk for co-infection.

ABSTRACT

The upcoming flu season in the Northern Hemisphere merging with the current COVID-19 pandemic raises a potentially severe threat to public health. Through experimental coinfection with influenza A virus (IAV) and either pseudotyped or live SARS-CoV-2 virus, we found that IAV preinfection significantly promoted the infectivity of SARS-CoV-2 in a broad range of cell types. Remarkably, in vivo, increased SARS-CoV-2 viral load and more severe lung damage were observed in mice coinfected with IAV. Moreover, such enhancement of SARS-CoV-2 infectivity was not observed with several other respiratory viruses, likely due to a unique feature of IAV to elevate ACE2 expression. This study illustrates that IAV has a unique ability to aggravate SARS-CoV-2 infection, and thus, prevention of IAV infection is of great significance during the COVID-19 pandemic.

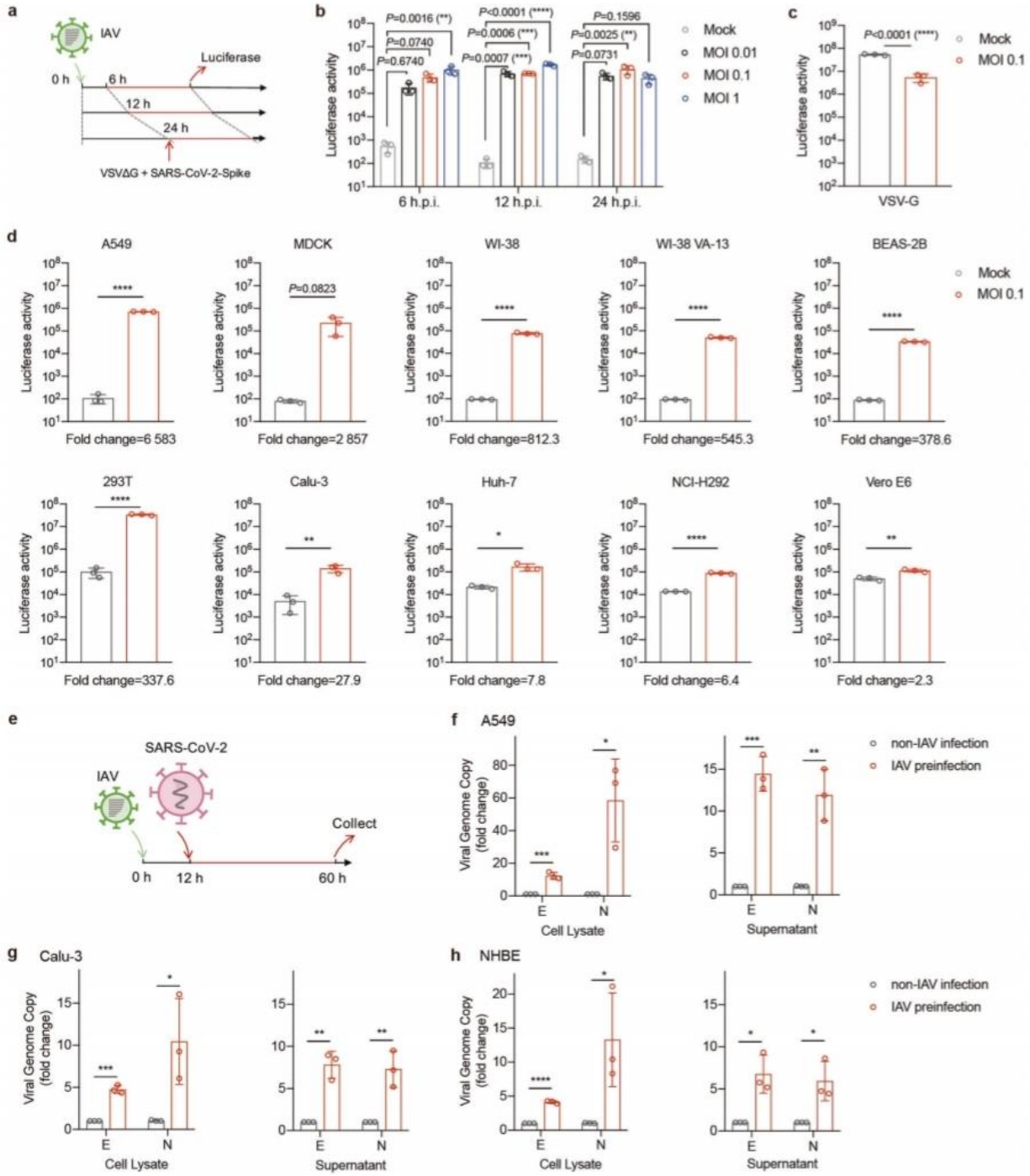


Figure 1: "IAV promotes SARS-CoV-2 virus infectivity.
a Diagram of the experimental procedure. b A549 cells were infected with A/WSN/33(WSN) at the indicated MOIs. At 6, 12, and 24 h post-IAV infection, cells were infected with pseudo-SARS-CoV-2 for another 24 h. Luciferase activity was measured to reflect virus entry efficiency. P values are from unpaired one-way ANOVA. c A549 cells were infected with WSN at an MOI of 0.1. At 12 h post-IAV infection, cells were infected with VSV-G-Luc for another 24 h. Luciferase activity was measured to reflect virus entry efficiency. d The indicated cells were infected with WSN at an MOI of 0.1. At 12 h post-IAV infection, cells were infected with pseudo-SARS-CoV-2 for another 24 h. Luciferase activity was measured to reflect virus entry efficiency. e Experimental procedure of IAV and live SARS-CoV-2 coinfection. A549 (f), Calu-3 (g), and NHBE (h) cells were preinfected with WSN at an MOI of 0.1 for 12 h. Cells were then infected with live SARS-CoV-2 at an MOI of 0.01 for another 48 h. Total RNA in cell lysates and the supernatants was collected to detect the E and N genes via TaqMan-qRT-PCR. The data are expressed as fold changes in viral RNA levels in IAV preinfected cells relative to the non-IAV infection control. Values represent means ± SD of three independent experiments. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001".

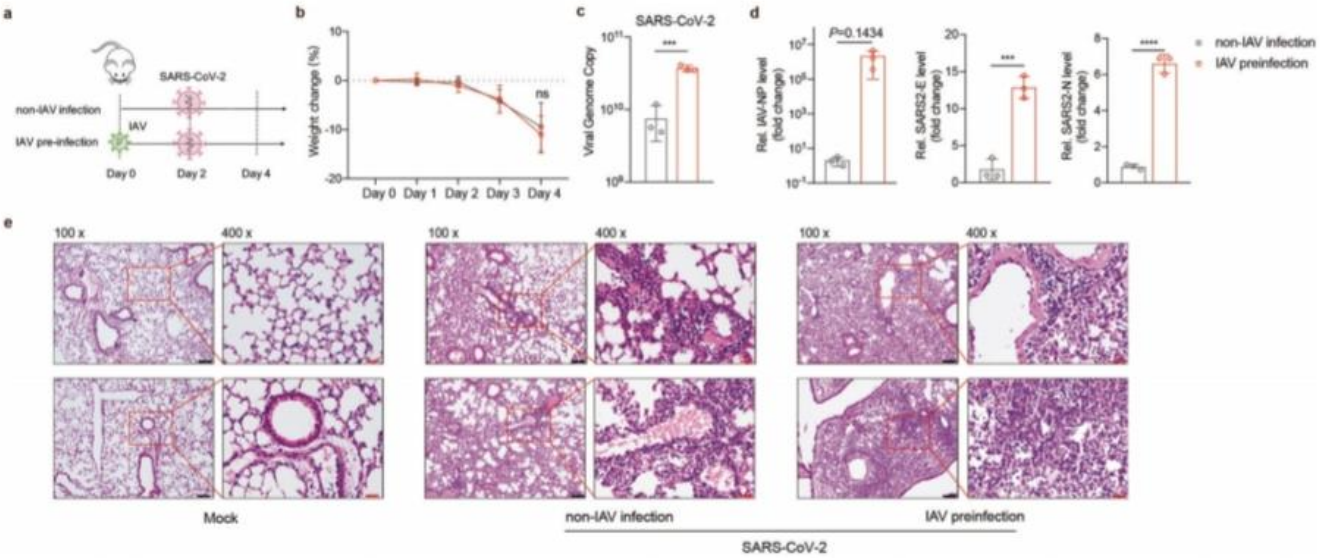


Figure 2: "IAV and SARS-CoV-2 coinfection induced more severe pathology in infected mice.
a Diagram of the experimental procedure. K18-hACE2 transgenic mice were first intranasally infected with 2000 PFU of WSN or PBS on day 0. Two days post-IAV infection, mice were intranasally infected with 3 × 105 live SARS-CoV-2 or PBS. On day 4, half of the lung tissues collected from all the mice were homogenized to detect RNA or protein levels. b The body weights and survival were monitored until day 4 (non-IAV treatment group, n = 4; IAV preinfection group, n = 4). The dotted lines indicate the initial weight. The body weights are presented as the mean percentage of weight change ± SD. c The viral genome copy numbers of SARS-CoV-2 N were quantified. Values represent means ± SD of three individual mice. d The relative mRNA levels of IAV NP (d, left), SARS-CoV-2 E (d, middle) and the N gene (d, right) were measured from lung homogenates in the indicated groups and normalized to GAPDH for the individual mouse. The data are expressed as fold changes relative to the non-IAV infection control. Values represent means ± SD of three individual mice. e Histopathologic and immunohistochemical studies were performed with lung slide samples in the indicated groups c–d. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001".

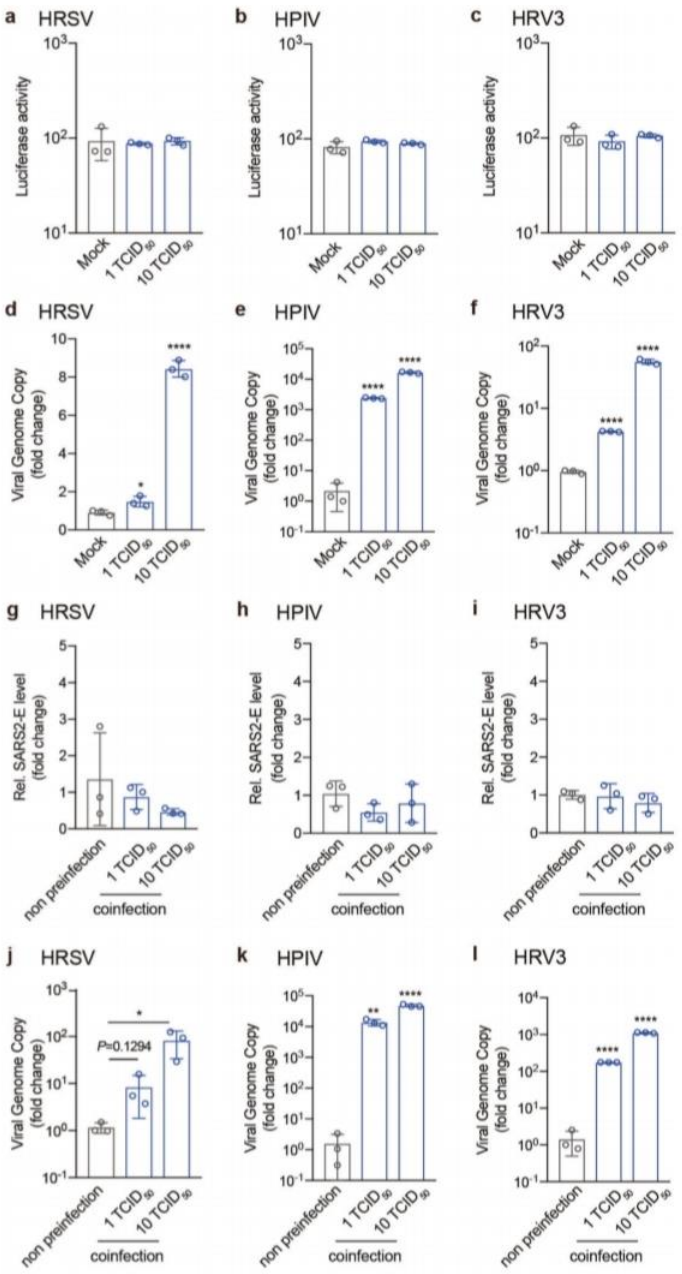


Figure 3: "SARS-CoV-2 infection in response to HRSV, HPIV, or HRV3.
a–c A549 cells were preinfected with HRSV, HPIV, or HRV3 at the indicated doses for 12 h. Cells were then infected with pseudo-SARS-CoV-2 for another 24 h followed by measurement of luciferase activity. d–f The propagation of HRSV (d), HPIV (e), or HRV3 (f) in A549 cells was measured by qRT-PCR 12 h.p.i. targeting the individual viral genes respectively. g–i A549 cells were preinfected with HRSV (g), HPIV (h), or HRV3 (i) at the indicated doses for 12 h. Cells were then infected with live SARS-CoV-2 for another 48 h followed by measurement of SARS-CoV-2 E gene copies via Taqman-qRT-PCR. j–l The propagation of HRSV (j), HPIV (k), or HRV3 (l) in A549 cells was measured at 60 h.p.i. by qRT-PCR targeting the individual viral genes respectively. The data are expressed as fold changes relative to the non-preinfection group. Values represent means ± SD of three independent experiments. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001".

AUTOANTIBODIES MAY DRIVE COVID-19 BLOOD CLOTS

Hampton T.. JAMA. 2021 Feb 2;325(5):425. doi: 10.1001/jama.2020.25699.
Level of Evidence: 5 - Opinion

BLUF

In this review, a genetic researcher and science journalist details a recent study published in Science Translational Medicine that analyzed 172 hospitalized COVID-19 patients, finding antiphospholipid (aPL) antibodies in 30-52% of them, suggesting similar pathogenic mechanisms of coagulopathy complications in SARS-CoV-2 infections and antiphospholipid syndrome (APS). They also found COVID-19 patients with higher aPL antibody levels had more severe respiratory disease, lower kidney function, and immune system hyperactivity, suggesting that aPL antibodies may contribute to the hypercoagulability observed in many COVID-19 patients.

MONOCYTES AND MACROPHAGES, TARGETS OF SARS-COV-2: THE CLUE FOR COVID-19 IMMUNOPARALYSIS

Boumaza A, Gay L, Mezouar S, Bestion E, Diallo AB, Michel M, Desnues B, Raoult D, La Scola B, Halfon P, Vitte J, Olive D, Mege JL.. J Infect Dis. 2021 Jan 25:jiab044. doi: 10.1093/infdis/jiab044. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

An experiment conducted by researchers at Aix-Marseille University, Marseille, France found that, upon extensive investigation of monocytes from COVID-19 patients, acute infection of monocytes and macrophages impaired the host immune response, as measured by impaired production of interferons and increased production of Interleukin-6 (Figure 1), suggesting these effects may be targeted to impair viral pathogenesis.

SUMMARY

Peripheral blood mononuclear cells were isolated from the serum of patients diagnosed with COVID-19. Upon purification of samples, cells were infected with strains of COVID-19. Cell supernatants were used to measure levels of significant markers of immune response, including tumor necrosis factor-a, interferon, and transforming growth factor-B1. Results demonstrated unequal infection of monocytes and macrophages, in addition to significant increases in immune inflammatory markers. The expression of CD163, a marker of immunoregulation, in all cell subsets indicated a suppression in activation of monocytes, and a shift in immune behavior. An important limitation of the study was that the clinical expression of the disease in all patients were of moderate expression.

ABSTRACT

BACKGROUND: Covid-19 clinical expression is pleiomorphic, severity is related to age and comorbidities such as diabetes and hypertension, and pathophysiology involves aberrant immune activation and lymphopenia. We wondered if the myeloid compartment was affected during Covid-19 and if monocytes and macrophages could be infected by SARS-CoV-2. METHODS: Monocytes and monocyte-derived macrophages from Covid-19 patients and controls were infected with SARS-CoV-2, and extensively investigated with immunofluorescence, viral RNA extraction and quantification, total RNA extraction followed by reverse transcription and q-PCR using specific primers, supernatant cytokines (IL-10, TNF-alpha, IL-1beta, IFN-beta, TGF-beta1 and IL-6), flow cytometry. The effect of M1- versus M2-type or no polarization prior to infection was assessed. RESULTS: SARS-CoV-2 efficiently infected monocytes and MDMs but their infection is abortive. Infection was associated with immunoregulatory cytokines secretion and the induction of a macrophagic specific transcriptional program characterized by the upregulation of M2-type molecules. In vitro polarization did not account for permissivity to SARS-CoV-2, since M1- and M2-type MDMs were similarly infected. In Covid-19 patients, monocytes exhibited lower counts affecting all subsets, decreased expression of HLA-DR, and increased expression of CD163, irrespective of severity. CONCLUSION: SARS-CoV-2 drives monocytes and macrophages to induce host immunoparalysis for the benefit of Covid-19 progression.

FIGURES

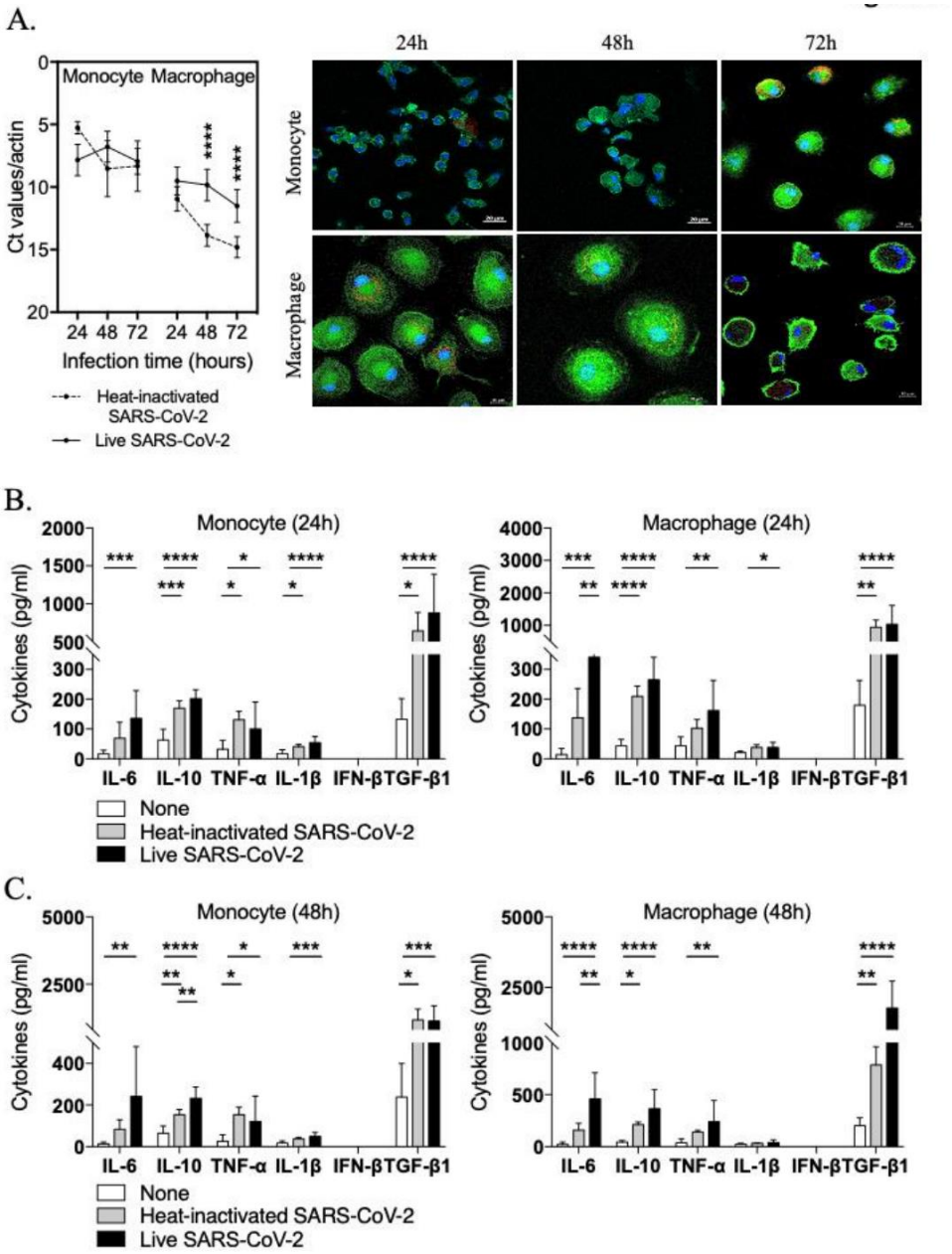


Figure 1. SARS-CoV-2 infects monocytes and macrophages and stimulates cytokine release. (A) MDM macrophages were incubated with live- or heat-inactivated-SARS-CoV-2 IHU-MI3 strain (0.1 MOI) for 24, 48 or 72 hours (n = 11). (B) SARS-CoV-2 was quantified by RT-PCR, expressed as Ct values normalized with the actin housekeeping gene and observed by immunofluorescence: virus in red, nucleus in blue and F-actin in green (n = 11). Images were acquired using a confocal microscope (63x). ****P < 0.0001 using two-way ANOVA and Turkey’s test for post-hoc comparisons. (B, C) Pro-(IFN-, IL-6, TNF-, IL-1) and anti-inflammatory (TGF-, IL-10) cytokines release was evaluated in supernatants from live- or heat-inactivated-SARS-CoV-2-stimulated monocytes and macrophages at (B) 24 and (C) 48 hours (n = 11). Results are expressed as mean ± standard error of the mean. *P < 0.05, **P < 0.01, ***P < 0.001 and ****P < 0.0001 using Mann-Whitney U test.

SARS-COV-2 IMMUNITY AND REINFECTION

Dan J, Mehta S.. Clin Infect Dis. 2021 Jan 2:ciaa1936. doi: 10.1093/cid/ciaa1936. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

Infectious disease physicians from the University of California San Diego comment on a recently published case report regarding symptomatic SARS-CoV-2 reinfection 185 days post-symptomatic primary infection in an immunocompetent healthcare worker. They discuss the importance of understanding the patients' immune response to their primary infection (antibody titers, neutralizing assays, CD4+/CD8+ T-cell assays) and note that, in this case, reinfection occurred by a unique variant. Authors speculate on the role of mucosal anti-SARS-CoV-2 IgA and the role all these responses may play in vaccine development.

OUTDOOR TRANSMISSION OF SARS-COV-2 AND OTHER RESPIRATORY VIRUSES: A SYSTEMATIC REVIEW

Bulfone TC, Malekinejad M, Rutherford GW, Razani N.. J Infect Dis. 2021 Feb 24;223(4):550-561. doi: 10.1093/infdis/jiaa742.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A systematic review of articles published through August 12, 2020 conducted at the University of California Berkeley by the Joint Medical Program that included 12 highly heterogeneous studies concerning outdoor transmission of viruses (5 studies with SARS-CoV-2; 7 studies with influenza or adenovirus) found that there is far lower transmission outdoors compared to indoors (Table 1). However, without further study, risks may mitigate the benefits of resuming outdoor experiences without sufficient caution.

SUMMARY

- The goal of the study was to examine if the idea that transmission rates were lower outdoors was plausible using multiple studies.

- 12 studies met the criteria, with a high heterogeneity in study quality and the definitions of what constitutes an outdoor setting.

- It is important to note that there are only a few factors which can be identified which increase the risk of outdoor transmission: exposure time, lack of personal protective equipment, and time gathering indoors during an outdoor experience.

- In addition, confounding variables identified include age, activities performed, social class, and ethnicity.

ABSTRACT

BACKGROUND: While risk of outdoor transmission of respiratory viral infections is hypothesized to be low, there is limited data of SARS-CoV-2 transmission in outdoor compared to indoor settings. METHODS: We conducted a systematic review of peer-reviewed papers indexed in PubMed, EMBASE and Web of Science and pre-prints in Europe PMC through August 12 th, 2020 that described cases of human transmission of SARS-CoV-2. Reports of other respiratory virus transmission were included for reference. RESULTS: Five identified studies found that a low proportion of reported global SARS-CoV-2 infections have occurred outdoors (<10%) and the odds of indoor transmission was very high compared to outdoors (18.7 times; 95% CI 6.0, 57.9). Five studies described influenza transmission outdoors and two described adenovirus transmission outdoors. There was high heterogeneity in study quality and individual definitions of outdoor settings which limited our ability to draw conclusions about outdoor transmission risks. In general, factors such as duration and frequency of personal contact, lack of personal protective equipment and occasional indoor gathering during a largely outdoor experience were associated with outdoor reports of infection. CONCLUSION: Existing evidence supports the wide-held belief that the the risk of SARS-CoV-2 transmission is lower outdoors but there are significant gaps in our understanding of specific pathways.

FIGURES

Table 1. Comparison of Respiratory Virus Transmission Outdoors Compared to Indoors Ordered by Virus Studied

Outcome	Virus Studied	Estimate of Effect		Relative Estimate of Effect	Number of Participants in the Study
		Outdoor	Indoor		
Number of cases [14]	SARS-CoV-2	2/7324 cases	7322/7324 cases	<1% of transmissions happened outdoors	7324 cases, totaling 318 outbreaks
Number of cases [15]	SARS-CoV-2	4/103 cases	99/103 cases	5% of work-related cases occurred outdoors	103 possible work-related cases among a total of 690 local transmissions
Odds of transmission [16]	SARS-CoV-2	Raw data not available	Raw data not available	Odds of transmission in closed environments 18.7 (95% CI, 6.0–57.9) times greater than in open air	110 cases: 27 primary cases and 83 secondary cases
Number of super-spreading events and odds of transmission[a] [16]	SARS-CoV-2	1/7 super-spreading events	6/7 super-spreading events	Odds ratio of super-spreading in closed environments: 32.6 (95% CI, 3.7–289.5)	110 cases: 27 primary cases and 83 secondary cases
Number of cases [17]	SARS-CoV-2	95/10 926 cases	10 831/10 926 cases	<1% of transmissions happened outdoors	10 926 cases, totaling 201 events of transmission
Number of cases [18]	H1N1 2009 influenza	0/3 cases	24/29 cases	Of 32 total people in a holiday camp, 29 traveled together in a train wagon	32 people at a holiday camp
Mortality [19]	H1N1 1918 influenza	28/820 deaths sleeping in hammocks outside, 34.1 persons/1000	39/267 deaths sleeping in cabins inside, 146.1 persons/1000	Risk ratio 4.28 (95% CI, 2.69–6.81)	Total 1217 people on the ship

Abbreviations: CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Super-spreading defined as events where the number of secondary cases generated by a single primary case is greater than the 95th percentile of the distribution (ie, transmission to 3 or more persons).

Comparison of Respiratory Virus Transmission Outdoors Compared to Indoors Ordered by Virus Studied

THE BNT162B2 (BIONTECH/PFIZER) VACCINE HAD 95% EFFICACY AGAINST COVID-19 ≥7 DAYS AFTER THE 2ND DOSE

Chagla Z.. Ann Intern Med. 2021 Feb 2. doi: 10.7326/ACPJ202102160-015. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

An internist from McMaster University in Canada created a summary sheet presenting and evaluating the recently published clinical trial data from Polack, et al regarding the effectiveness of the BioNtech/Pfizer COVID-19 vaccine. They conclude the vaccine has 95% efficacy 7 days after the second dose with minimal adverse events.

SUMMARY

The author summarizes this randomized placebo controlled trial evaluating the efficacy of the BNT16b2 BioNTech/Pfizer vaccine (defined as presence of COVID-19 symptoms) greater than or equal to 7 days after the second dose. Of 34,922 study participants who were greater than 16 years old and were without previous infection, only 8 out of the vaccine group developed symptoms for COVID-19 vs. 162 out of the placebo group. These results calculate out to a 95% efficacy rate which provides strong evidence to the efficacy of the vaccine.

PREVENTION IN THE COMMUNITY

EFFECTS OF COVID-19 EMERGENCY ALERT TEXT MESSAGES ON PRACTICING PREVENTIVE BEHAVIORS: CROSS-SECTIONAL WEB-BASED SURVEY IN SOUTH KOREA

You M, Lee M.. J Med Internet Res. 2021 Feb 25;23(2):e24165. doi: 10.2196/24165.
Level of Evidence: 3 - Local non-random sample

BLUF

Members of the Department of Public Health Sciences, in cooperation with local and central governments of South Korea, conducted a web-based survey of 990 participants about the association between alarm text messages and preventive

behaviors during March 2020. They found 49.2% always read the alarm messages, and those who always read the messages were more likely to wear facial masks (β=.074, P=.01), avoid crowded place (β=.078, P=.01), and cancel social gatherings (β=.103, P<.001)(Table 6). Authors suggest that broadcasting public health information via text message is an effective strategy for disseminating important health information during the pandemic.

ABSTRACT

BACKGROUND: Sending emergency messages via mobile phone text message can be a promising communication tool to rapidly disseminate information and promote preventive behavior among the public during epidemic outbreaks. The battle to overcome COVID-19 is not yet over; thus, it is essential that the public practice preventive measures to prevent the spread of COVID-19. OBJECTIVE: The present study investigates the effectiveness of reading and obtaining information from emergency alert text messages on the individual's practice of preventive behaviors during the early stages of the COVID-19 outbreak in South Korea. METHODS: A cross-sectional online survey took place over three days (March 25-27, 2020) and included 990 subjects. A multivariable logistic regression revealed which sociodemographic factors might influence reading behavior in the emergency alert text messages. A hierarchical linear regression model estimated the associations between reading emergency alert text messages for each precautionary behavior practiced against COVID-19. Additionally, the indirect effects of reading the text messages on each precautionary behavior via psychological factors (i.e., perceived risk and response efficacy) were calculated. All data were weighted according to the Korea census data in 2019. RESULTS: Overall, 49.2% (n = 487) of respondents reported that they "always read the message and visit the linked site to get more information." Factors such as being female (OR 1.68, 95%CI 1.28-2.21), being older (30-39 years age group OR 2.02, 95%CI 1.25-3.28; 40-49 years age group OR 2.84, 95%CI 1.80-4.47; 50-59 years age group OR 3.19, 95%CI 2.01-5.06; 60 years and over age group OR 3.12, 95%CI 2.00-4.86 versus 18-29 years age group) were identified as being related to higher frequency of reading the text messages. Respondents who always read the text messages practiced wearing facial masks (beta = .074, P = .012) more frequently than those who do not. In terms of social distancing, respondents who reported they always read the text messages practiced "avoiding crowded places" (beta =.078, P =.014) and "canceling or postponing social gatherings" (beta =.103, P < .001) than those who do not. Reading text messages directly and indirectly affected practicing precautionary behaviors, as the mediation effect of response efficacy between reading text messages and practicing was significant. CONCLUSIONS: Our findings support that emergency alert text messages sent to individuals' mobile phones are timely and effective strategies for encouraging preventive behavior in public. Sending emergency alert text messages to provide the public with accurate and reliable information could be positively considered by the health authorities, which might reduce the negative impact of the infodemics. CLINICALTRIAL:

FIGURES

Table 6. Direct and indirect effects of reading emergency alert text messages on practicing preventive behaviors based on perceptions (eg, perceived susceptibility, severity, and response efficacy). Unstandardized point estimates represent the indirect effect of the independent variable on the dependent variable through the mediator.

Dependent variable	Preventive behaviors		Social distancing behaviors	
	Wearing facial masks	Hand hygiene	Keeping away from crowded places	Canceling or postponing social events
	Estimate (95% CI[a])	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Total effect	0.1257 (0.0475 to 0.2039)	0.0795 (0.0031 to 0.1558)	0.1772 (0.0682 to 0.2861)	0.2190 (0.1020 to 0.3361)
Direct effect	0.0887 (0.0178 to 0.1595)	0.0602 (−0.0088 to 0.1292)	0.1276 (0.0228 to 0.2323)	0.1804 (0.0684 to 0.2924)
Indirect effect (via perceived susceptibility)	−0.0001 (−0.0039 to 0.0035)	−0.0006 (−0.0047 to 0.0027)	−0.0004 (−0.0061 to 0.0043)	−0.0014 (−0.0084 to 0.0037)
Indirect effect (via perceived severity	0.0005 (−0.0029 to 0.0047)	0.0009 (−0.0036 to 0.0063)	0.0006 (−0.0039 to 0.0063)	0.0012 (−0.0046 to 0.0095)
Indirect effect (via response efficacy)	0.0366 (0.0041 to 0.0705)	0.019 (0.0134 to 0.0508)	0.0494 (0.0161 to 0.0847)	0.0389 (0.0043 to 0.0769)

[a]Bias-corrected CI (these 95% CIs do not cross zero; thus, mediation is assumed).

AIRBORNE DISPERSION OF DROPLETS DURING COUGHING: A PHYSICAL MODEL OF VIRAL TRANSMISSION

Li H, Leong FY, Xu G, Kang CW, Lim KH, Tan BH, Loo CM.. Sci Rep. 2021 Feb 25;11(1):4617. doi: 10.1038/s41598-021-84245-2.
Level of Evidence: 5 - Modeling

BLUF

Investigators from the A*STAR Institute of High Performance Computing and Singapore General Hospital analyzed the transmission of viral particles by modeling the disbursement of droplets in the setting of a spontaneous indoor cough. They found the probability of droplet transmission decreased with increasing distance (0.5 vs 1 meter) from cougher to listener, use of facial covering, and increased relative humidity of 60% (Figure 6). This study highlights the importance of adherence to social distancing and mask wearing to aid in the decrease of SARS-CoV-2 transmission during the pandemic.

FIGURES

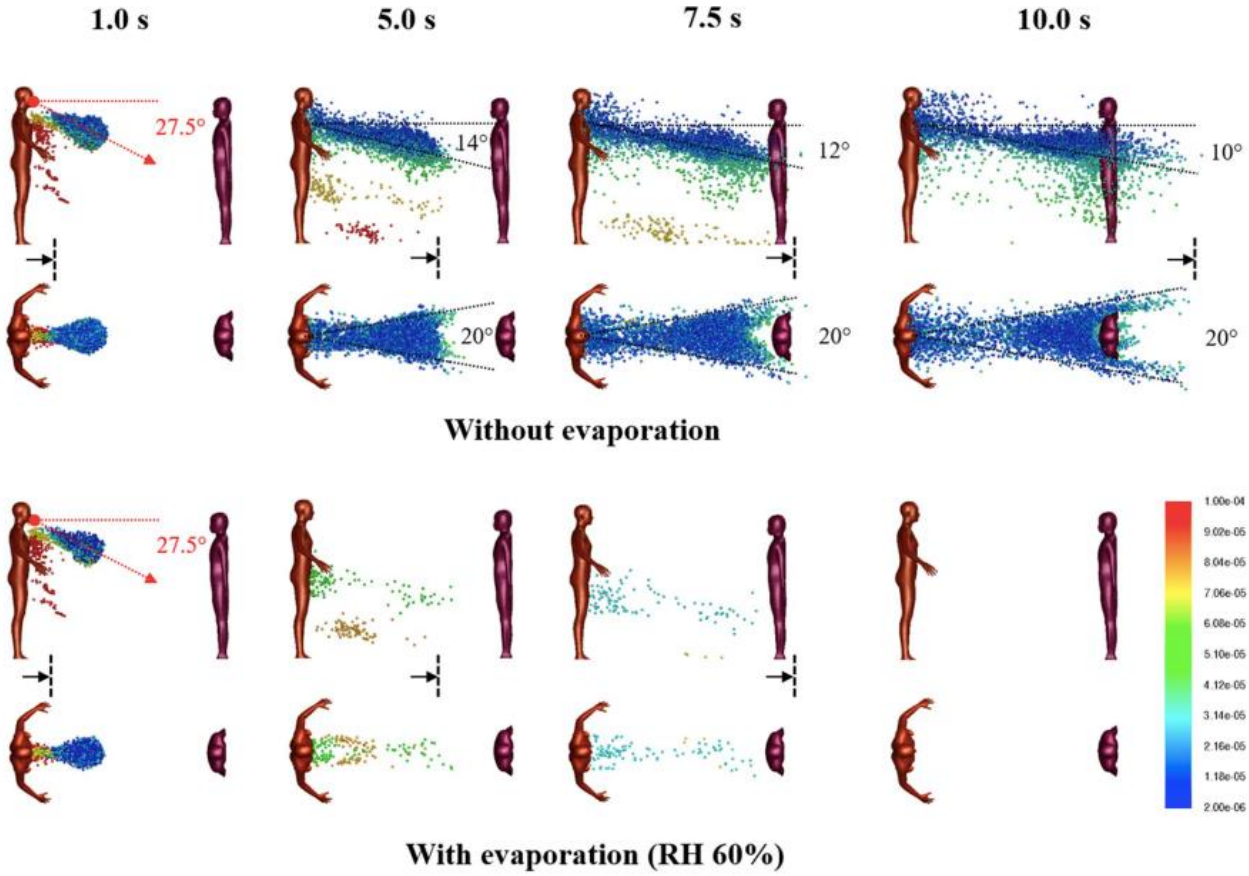


Figure 6. Droplet dispersion (side and top-down views) from a single cough inclined downwards at 27.5° for non-evaporative (top) and evaporative (bottom) cases at relative humidity of 60%. Listener is 2 m away facing Cougher. Color bar indicates droplet sizes (2–100 µm). Vertical lines are spaced 1 m apart and arrows are drif markers based on a background wind speed of 0.3 m/s. Ambient air temperature is 25 °C and breath temperature is 36 °C. Plume angles 14–10° from the chest level and lateral dispersion fts a 20° forward wedge.

IMPACT OF THE TIMING AND ADHERENCE TO FACE MASK USE ON THE COURSE OF THE COVID-19 EPIDEMIC IN FRANCE

Hoertel N, Blachier M, Sánchez-Rico M, Limosin F, Leleu H.. J Travel Med. 2021 Jan 28:taab016. doi: 10.1093/jtm/taab016. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

A microsimulation model analysis conducted at the Corentin Celton Hospital from July to September 2020 by the AP-HP Centre found that an 80% adherence rate of the French population to use face masks would decrease the incidence, mortality, and hospital-bed occupancy related to COVID-19 (Figure 1), providing more evidence that this protective measure is essential to national health.

SUMMARY

- While the French government required masks in indoor venues and workplaces, there was overall low adherence to face mask use

-The microsimulation model of the epidemic includes demographics, medical comorbidities, with simulations of social contact networks and the disease model known of COVID-19.

- Extrapolations of the model suggest the disparity between low-adherence and 80% adherence would widen further from September 23rd and onwards.

FIGURES

Figure 1. Model predicted cumulative incidence of SARS-COV-2 infection (A), COVID-19-related hospital admissions (B), ICU admissions (C) and deaths (D) in France from July 1st, 2020 to February 1st 2021.

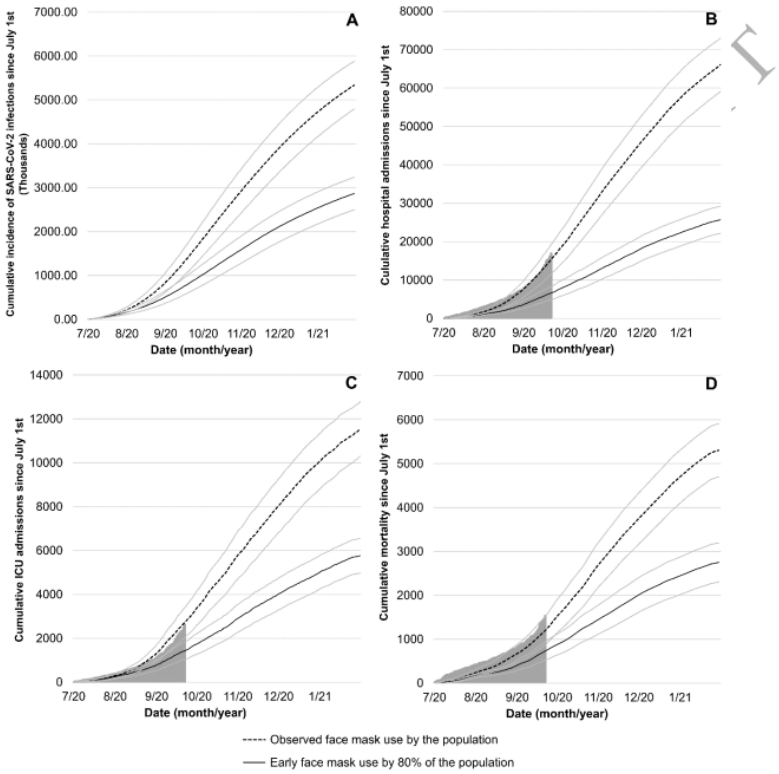


Figure 1. Model predicted cumulative incidence of SARS-COV-2 infection (A), COVID-19-related hospital admissions (B), ICU admissions (C) and deaths (D) in France from 1 July 2020 to 1 February 2021. The grey area represents the actual observed data for France. The solid grey lines represent the uncertainty range (95% prediction range) stemming from the uncertainty in the parameter values. (A) no data are available for new infections, only for diagnosed cases

NORMAL BREATHING RELEASES SARS-COV-2 INTO THE AIR

Di Carlo P, Falasca K, Ucciferri C, Sinjari B, Aruffo E, Antonucci I, Di Serafino A, Pompilio A, Damiani V, Mandatori D, De Fabritiis S, Dufrusine B, Capone E, Chiacchiaretta P, Brune WH, Di Bonaventura G, Vecchiet J.. J Med Microbiol. 2021 Feb 25. doi: 10.1099/jmm.0.001328. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

Experts in atmospheric science and infectious disease from the University "G. d'Annunzio" of Chieti-Pescara in Italy, among others, analyzed oropharyngeal, nasopharyngeal and saliva swabs from 5 patients and compared them to air samples from their negative pressure rooms. They found air samples from the rooms of patients testing positive for SARS-CoV-2 (n=3) had detectable virus as close as 1cm away from the patient's mouth. SARS-CoV-2 was not detected in air samples in those patients with negative SARS-CoV-2 swabs (Table 1). Authors suggest SARS-CoV-2 enters the air with normal breathing and reinforce the necessity for isolation precautions for positive patients.

FIGURES

	RT-PCR swab analysis on the day of the air sample		Air sample RT-PCR analysis		
	Target	Cycle threshold value	Distance away from the patient's mouth	Target	Cycle threshold value
Patient 1 **Symptoms:** Cough, fever, shortness of breath					
Oropharyngeal: **Positive**	ORF1ab	26.331	1 cm: **Positive**	ORF1ab	32.764
	N	26.740		N	33.404
	S	26.189		S	33.239
Nasopharyngeal: **Positive**	ORF1ab	27.886	100 cm: **Negative**	ORF1ab	36.535
	N	27.035		N	U*
	S	28.563		S	39.877
Salivary: **Positive**	ORF1ab	29.749			
	N	29.883			
	S	26.846			
Patient 2 **Symptoms:** Cough, fever, shortness of breath					
Oropharyngeal: **Positive**	ORF1ab	13.787	1 cm: **Positive**	ORF1ab	25.573
	N	15.710		N	25.584
	S	13.589		S	25.411
Nasopharyngeal: **Positive**	ORF1ab	15.221	100 cm: **Negative**	ORF1ab	U*
	N	16.871		N	U*
	S	14.324		S	U*
Salivary: **Positive**	ORF1ab	23.474	1 cm†: **Negative**	ORF1ab	U*
	N	28.971		N	U*
	S	28.372		S	U*
Patient 3 **Symptoms:** Cough, fever, shortness of breath					
Oropharyngeal: **Negative**	ORF1ab	U*	1 cm: **Negative**	ORF1ab	U*
	N	U*		N	U*
	S	U*		S	U*
Nasopharyngeal: **Negative**	ORF1ab	U*	100 cm: **Negative**	ORF1ab	U*
	N	U*		N	U*
	S	U*		S	U*

Table 1. Assessment of SARS-CoV-2 RNA presence in swabs (oropharyngeal, nasopharyngeal, salivary) and ambient air samples. All samples were assayed for SARS-CoV-2 RNA using RT-PCR, through the detection of ORF1ab, N gene and S gene. Cycle threshold value is referred to the number of cycles necessary for the fluorescent signal to cross the threshold, considering threshold=5.000, baseline=5, and cut-off=37 cycles. The viral load was considered higher as long as the cycle threshold value was lower. Samples were considered ‘Positive’ when at least two genes have a cycle threshold value <37, whereas ‘Negative’ when the cycle threshold value is Undetermined or >37. All air samples collected in the patients’ room, starting on the day of the observation, were negative.

Table 1. Continued

	RT-PCR swab analysis on the day of the air sample		Air sample RT-PCR analysis		
Salivary: **Negative**	ORF1ab	U*			
	N	U*			
	S	U*			
Patient 4 **Symptoms:** Cough					
Oropharyngeal: **Negative**	ORF1ab	U*	1 cm: **Negative** 10 cm: **Negative**	ORF1ab	U*
	N	U*		N	U*
	S	U*		S	U*
Nasopharyngeal: **Negative**	ORF1ab	U*	100 cm: **Negative**	ORF1ab	U*
	N	U*		N	U*
	S	U*		S	U*
Salivary: **Negative**	ORF1ab	U*	1 cm†: **Negative**	ORF1ab	U*
	N	U*		N	U*
	S	U*		S	U*
Patient 5 **Symptoms:** Astenia					
Oropharyngeal: **Positive**	ORF1ab	U*	1 cm: **Negative**	ORF1ab	U*
	N	U*		N	U*
	S	U*		S	U*
Nasopharyngeal: **Positive**	ORF1ab	U*	100 cm: **Negative**	ORF1ab	U*
	N	U*		N	U*
	S	U*		S	U*
Salivary: **Negative**	ORF1ab	U*	1 cm†: **Negative**	ORF1ab	U*
	N	U*		N	U*
	S	U*		S	U*

*U, Undetermined.
†Air sample collected while the patient was wearing a surgical mask.

SYSTEMATIC REVIEW AND PATIENT-LEVEL META-ANALYSIS OF SARS-COV-2 VIRAL DYNAMICS TO MODEL RESPONSE TO ANTIVIRAL THERAPIES

Gastine S, Pang J, Boshier FAT, Carter SJ, Lonsdale DO, Cortina-Borja M, Hung IFN, Breuer J, Kloprogge F, Standing JF.. Clin Pharmacol Ther. 2021 Feb 28. doi: 10.1002/cpt.2223. Online ahead of print.
Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

Experts in infectious disease and immunology from University College London, among others, conducted a systematic review of 45 papers (645 patients) published between January 1 and May 31, 2020 (Figure 1) and used extracted data to generate models of viral load trajectories under different treatment protocols (see summary). They found faster viral clearance in patients treated with remdesivir (adjusted hazard ratio [AHR]: 9.19, p<0.001), interferon (AHR: 2.2, p=0.015), and interferon plus ribavirin (AHR: 6.04, p = 0.006)(Figure 3) while older, male, and more severely ill patients had slower viral clearance (Table 2). The authors suggest that early use of antivirals may play a significant role in altering viral trajectories and recommend clinical trials to corroborate their findings.

SUMMARY

Publications (case reports, case series and clinical trial data) between 1/1/2020 and 31/5/2020 following PRISMA guidelines were identified for this study.

Paper inclusion criteria - papers containing individual patient-level data of viral load with time (either since symptom onset or time since start of monitoring for asymptomatic subjects) and sampling site; if papers only had summaries, authors were contacted to get individual data

The following modeling methods were used:
- Multivariable Cox proportional hazards regression model (Cox-PH) - time to viral clearance; fitted to respiratory and stool samples
- Simplified four parameter nonlinear mixed-effects (NLME) model - viral load trajectories in all sampling sites
- Covariate modelling of respiratory viral dynamics - performed in order to quantify time dependent drug effects

FIGURES

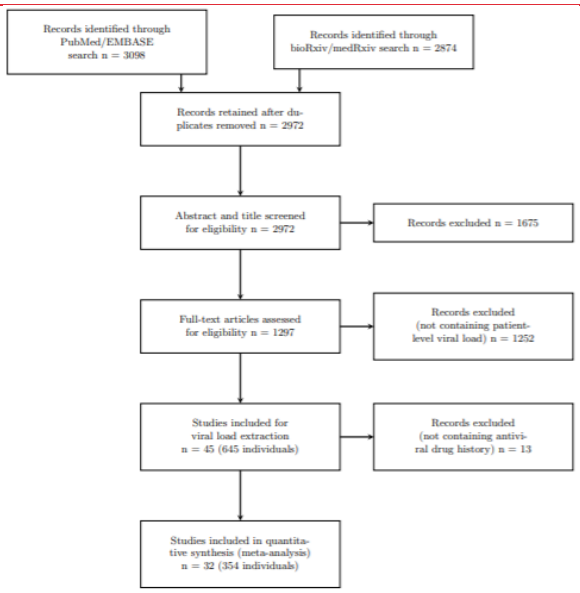


Figure 1: PRISMA diagram detailing the systematic search results

Table 2 Overview extracted variables across different analyses, median [range] (%missing data records). n, number of individuals included.

descriptive (%missing)	All Data	Cox-PH - Full data set	NLME/ reduced Cox-PH
	n=645	*n*=354	*n*=317
Age [years]	46 [0.1 – 100]	48 [0.1-100]	46 [0.1-100]
	(31.3%)	(0%)	(0%)
Sex [male/female]	217/189	215/139	182/135
	(37%)	(0%)	(0%)
ICU admission [yes/no]*	36/371	8/271	8/257
	(36.9%)	(21.2%)	(16.4%)
Invasive ventilation [yes/no]*	14/348	9/262	5/247
	(43.9%)	(23.4%)	(20.5%)
Death [yes/no]	1/455	1/330	1/293
	(29.3%)	(6.5%)	(7.3%)
Disease severity*			
	(12.7%)	(0%)	(0%)
Asymptomatic	24	19	16
Mild	376	258	239
Moderate	79	52	44
Severe	84	25	18

*There is discord between the reported ICU and mechanical ventilation and disease severity score due to incomplete reporting in some papers. Disease severity was taken from individual reports of disease status in cases where ICU admission and invasive ventilation were not specifically mentioned, and only Disease severity was used in the analyses.

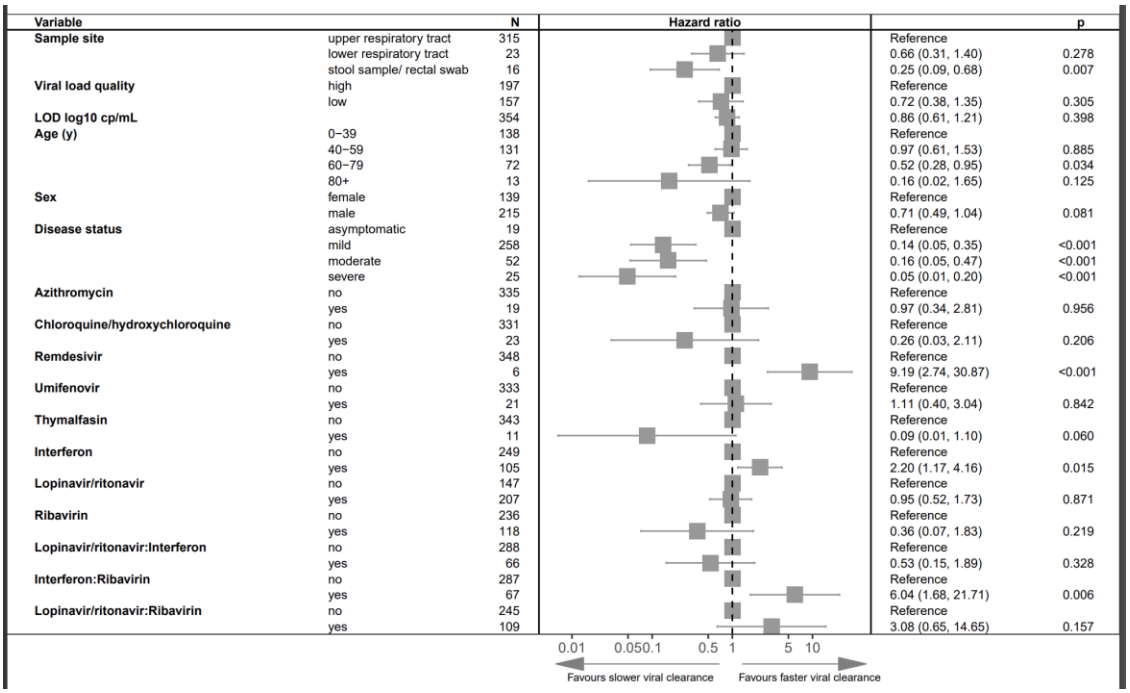


Figure 3: Multivariable Cox proportional hazard results on all drug quality 1 and drug quality 2 data from respiratory and stool/rectal sampling sites. Adjusted hazard ratios exceeding 1 indicate virus being more likely to become undetectable.

ACUTE CARE

IN-HOSPITAL USE OF STATINS IS ASSOCIATED WITH A REDUCED RISK OF MORTALITY IN CORONAVIRUS-2019 (COVID-19): SYSTEMATIC REVIEW AND META-ANALYSIS

Permana H, Huang I, Purwiga A, Kusumawardhani NY, Sihite TA, Martanto E, Wisaksana R, Soetedjo NNM.. Pharmacol Rep. 2021 Feb 20. doi: 10.1007/s43440-021-00233-3. Online ahead of print.
Level of Evidence: 2 - Systematic review of randomized trials or n-of-1 trials

BLUF

Endocrinologists from Universitas Padjadjaran in Indonesia conducted a systematic review and meta-analysis of 13 articles investigating the effect of statins on mortality in 52,122 COVID-19 patients published before November 2020 (Figure 1). They found in-hospital use of statins decreased mortality (RR 0.54, 95% CI 0.50–0.58, p<0.00001; I2: 0%, p = 0.87) (Figure 2); pre-hospital chronic statin therapy had no effect (RR 1.18, 95% CI 0.79–1.77, p = 0.415; I2: 68.6%, p = 0.013) (Figure 3). Authors suggest in-hospital use of statins may reduce of mortality risk among patients with COVID-19 though recognize limitations of the retrospective and non-randomized methodology included in this analysis.

ABSTRACT

BACKGROUND AND AIMS: The idea of treating COVID-19 with statins is biologically plausible, although it is still controversial. The systematic review and meta-analysis aimed to address the association between the use of statins and risk of mortality in patients with COVID-19. METHODS: Several electronic databases, including PubMed, SCOPUS, EuropePMC, and the Cochrane Central Register of Controlled Trials, with relevant keywords up to 11 November 2020, were used to perform a systematic literature search. This study included research papers containing samples of adult COVID-19 patients who had data on statin use and recorded mortality as their outcome of interest. Risk estimates of mortality in statin users versus non-statin users were pooled across studies using inverse-variance weighted DerSimonian-Laird random-effect models. RESULTS: Thirteen studies with a total of 52,122 patients were included in the final qualitative and quantitative analysis. Eight studies reported in-hospital use of statins; meanwhile, the remaining studies reported pre-admission use of statins. In-hospital use of statin was associated with a reduced risk of mortality (RR 0.54, 95% CI 0.50-0.58, p < 0.00001; I2: 0%, p = 0.87), while pre-admission use of statin was not associated with mortality (RR 1.18, 95% CI 0.79-1.77, p = 0.415; I2: 68.6%, p = 0.013). The funnel plot for the

association between the use of statins and mortality were asymmetrical. CONCLUSION: This meta-analysis showed that in-hospital use of statins was associated with a reduced risk of mortality in patients with COVID-19.

FIGURES

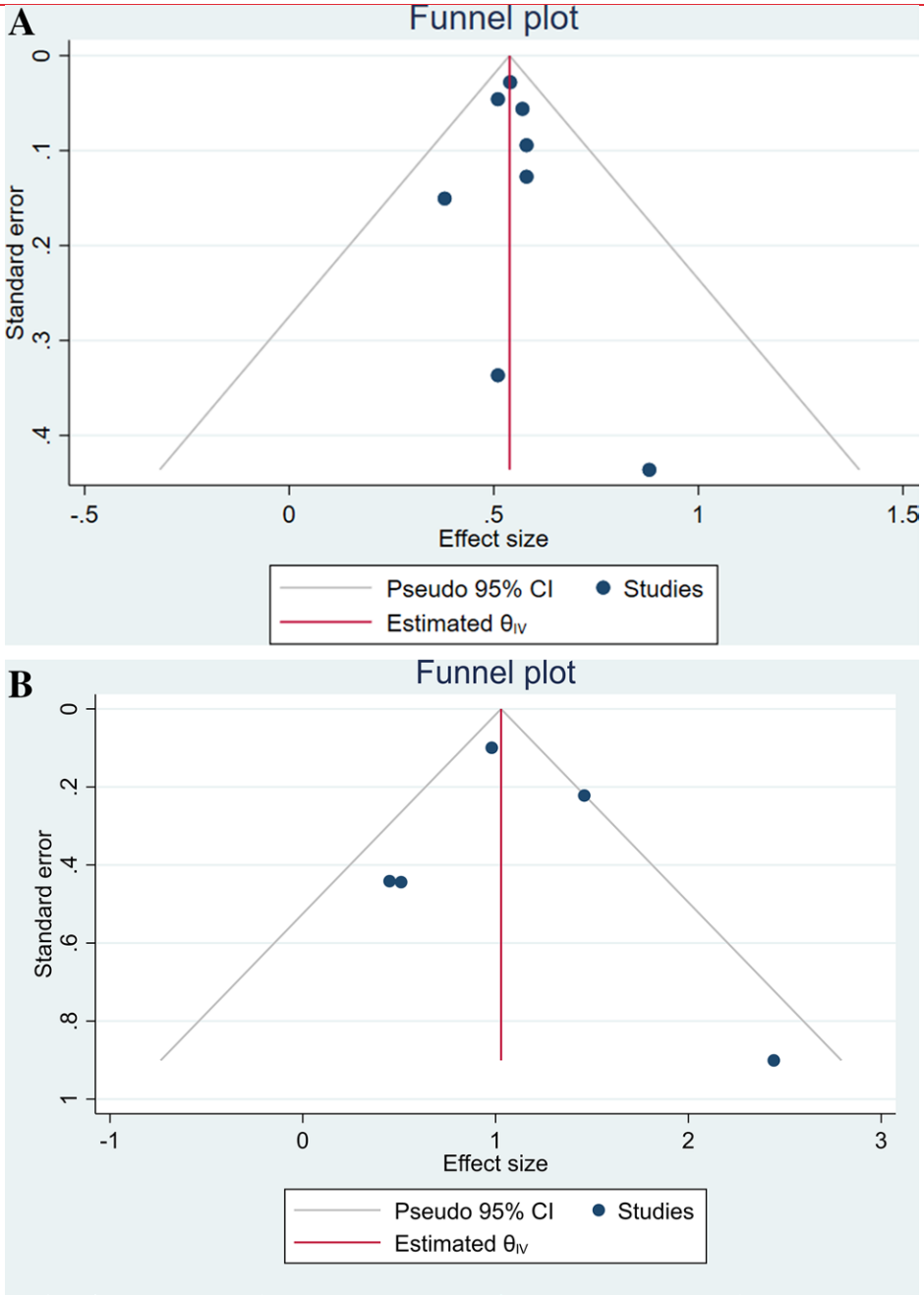
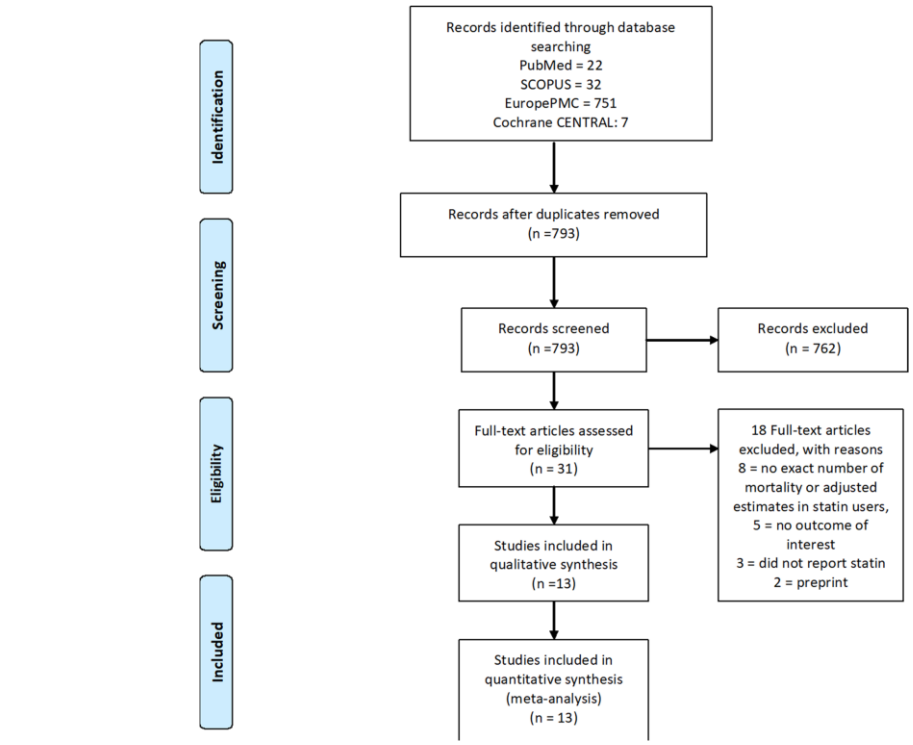


Fig. 2 Forest plot showing overall effect estimates of in-hospital use of statins and mortality in patients with COVID-19. RR Relative Risk, CI Confidence Interval



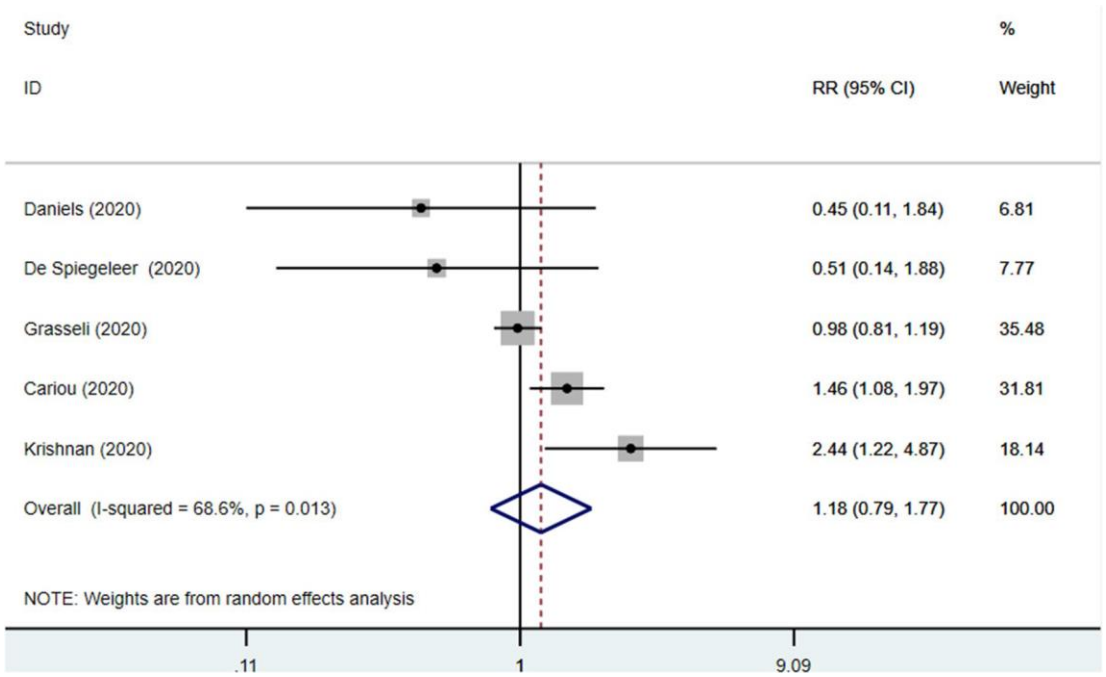


Fig. 3 Forest plot showing overall effect estimates of pre-admission use of statins and mortality in patients with COVID-19. RR Relative Risk, CI Confidence Interval

COVID-19-ASSOCIATED COAGULOPATHY: THROMBOEMBOLISM PROPHYLAXIS AND POOR PROGNOSIS IN ICU

Zheng R, Zhou J, Song B, Zheng X, Zhong M, Jiang L, Pan C, Zhang W, Xia J, Chen N, Wu W, Zhang D, Xi Y, Lin Z, Pan Y, Liu X, Li S, Xu Y, Li Y, Tan H, Zhong N, Luo X, Sang L.. Exp Hematol Oncol. 2021 Feb 1;10(1):6. doi: 10.1186/s40164-021-00202-9.

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

BLUF

A group of physicians and scientists from Wuhan, China conducted a retrospective study of 180 COVID-19-positive patients in the intensive care unit of Jinyintan Hospital from March 30, 2019 - March 31, 2020 and found that a D-dimer concentration of > 0.5 mg/L on admission was a risk factor for severe disease, and an SIC (sepsis-induced coagulopathy) score of > 4 and DIC (disseminated intravascular coagulation) score of > 5 may be used to predict mortality (Figure 1, Figure 2, Table 3). They also found that prophylactic enoxaparin can reduce mortality only in patients with a D-dimer concentration of > 2 mg/L or DIC score of ≥ 5, allowing for informed decision-making for when to administer thromboembolism prophylaxis and better prediction of mortality.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) is associated with coagulation abnormalities which are indicators of higher mortality especially in severe cases. METHODS: We studied patients with proven COVID-19 disease in the intensive care unit of Jinyintan Hospital, Wuhan, China from 30 to 2019 to 31 March 2020. RESULTS: Of 180 patients, 89 (49.44 %) had died, 85 (47.22 %) had been discharged alive, and 6 (3.33 %) were still hospitalised by the end of data collection. A D-dimer concentration of > 0.5 mg/L on admission was significantly associated with 30 day mortality, and a D-dimer concentration of > 5 mg/L was found in a much higher proportion of non-survivors than survivors. Sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) scoring systems were dichotomised as < 4 or >= 4 and < 5 or >= 5, respectively, and the mortality rate was significantly different between the two stratifications in both scoring systems. Enoxaparin was administered to 68 (37.78 %) patients for thromboembolic prophylaxis, and stratification by the D-dimer concentration and DIC score confirmed lower mortality in patients who received enoxaparin when the D-dimer concentration was > 2 than < 2 mg/L or DIC score was >= 5 than < 5. A low platelet count and low serum calcium concentration were also related to mortality. CONCLUSIONS: A D-dimer concentration of > 0.5 mg/L on admission is a risk factor for severe disease. A SIC score of > 4 and DIC score of > 5 may be used to predict mortality. Thromboembolic prophylaxis can reduce mortality only in patients with a D-dimer concentration of > 2 mg/L or DIC score of >= 5.

FIGURES

Prognostic factors	Survivors		Non-survivors		*P* value
	No.	%	No.	%	
$Temperature_{max}$ (°C)					0.291
≥39	45	25.00	51	28.33	
<39	46	25.56	38	21.11	
Duration of Low BP (h)					0.000*
0	83	46.11	25	13.89	
<72	1	0.56	25	13.89	
≥72	7	3.89	39	21.67	
Blood transfusion (ml)					0.037*
0	73	40.56	55	30.56	
≤800	13	7.22	20	11.11	
>800	6	3.33	13	7.22	
Lymphocyte					0.000*
$\geq 1.0 \times 10^9$/L	33	18.33	7	3.89	
$<1.0 \times 10^9$/L	58	32.22	82	45.56	
Platelet count					0.001*
$\geq 150 \times 10^9$/L	77	42.78	56	31.11	
$<150 \times 10^9$/L	14	7.78	33	18.33	
SIC score					0.002*
<4	85	47.22	69	38.33	
≥4	6	3.33	20	11.11	
DIC score					0.000*
<5	78	43.33	48	26.67	
≥5	13	7.22	41	22.78	
Overt DIC					0.000*
Yes	4	2.22	59	32.78	
No	87	48.33	30	16.67	
Prolongation of PT (s)					0.785
>3	6	3.33	5	2.78	
≤3	85	47.22	84	46.67	
Prolongation of aPTT (s)					0.632
>10	2	1.11	3	1.67	
≤10	89	49.44	86	47.78	
Fbg (g/L)					0.160
1.5–4	32	17.78	21	11.67	
>4	58	32.22	65	36.11	
<1.5	1	0.56	3	1.67	
D-dimer (mg/L)					0.000*
≤0.5	25	13.89	1	0.56	
>0.5 and ≤2	34	18.89	27	15.00	
>2 and <5	13	7.22	18	10.00	
>5	19	10.56	43	23.89	
FDP (mg/L)					0.000*
≤5	52	28.89	10	5.56	
>5 and ≤20	12	6.67	21	11.67	
>20	9	5.00	34	18.89	
Antithrombin (%)					0.147
≥80	20	11.11	37	20.56	
<80	29	16.11	31	17.22	
Serum calcium levels (mmol/L)					0.002*
≥1.8	70	38.89	73	40.56	
<1.8	2	1.11	16	8.89	
VTE prophylaxis					0.098
Yes	29	16.11	39	21.67	
No	62	34.44	50	27.78	

BP blood pressure, *SIC* sepsis-induced coagulopathy, *DIC* disseminated intravascular coagulation, *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *Fbg* fibrinogen, *FDP* fibrin degradation products, *VTE* venous thromboembolism

Blood transfusion: red blood cells, platelet or fresh-frozen plasma

*Statistically significant

Table 3: Coagulation abnormalities/clinical prognostic factors and mortality

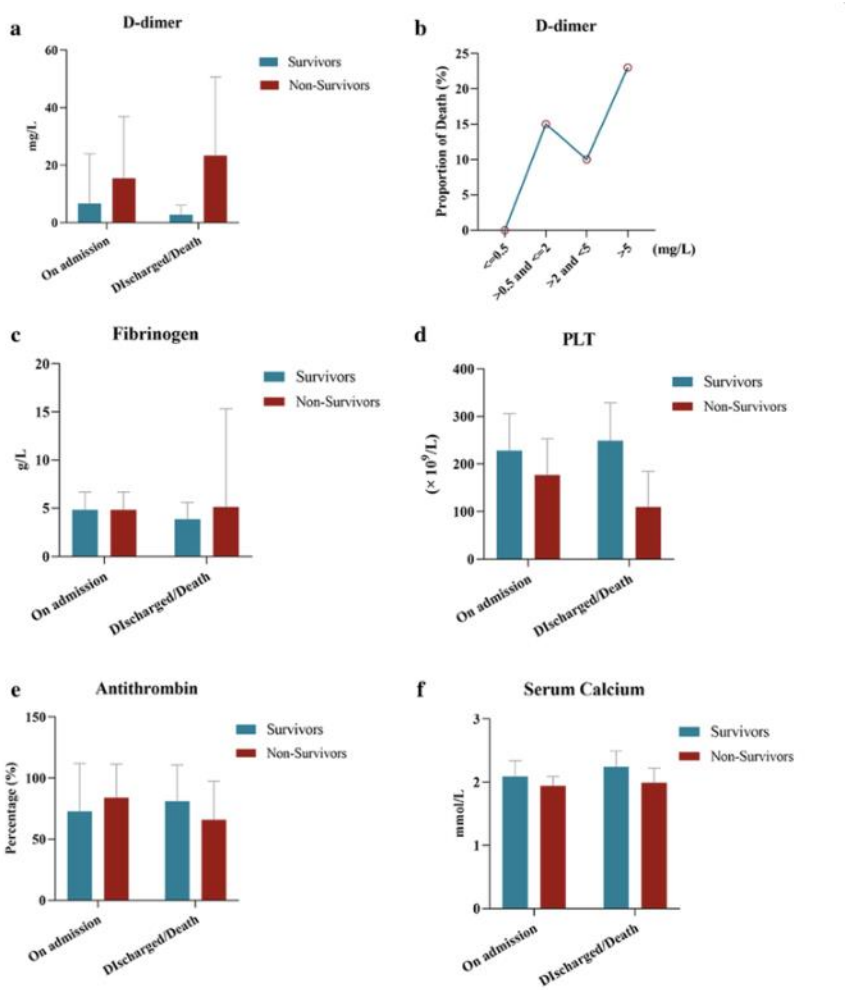


Figure 1: Comparison of coagulation parameters on the day of ICU admission versus the day of ICU discharge or death.

a The D-dimer concentration was significantly increased in non-survivors on the day of death (p = 0.004).
b The D-dimer concentration was stratified into four levels. The mortality rate was increased when the D-dimer concentration was > 0.5 mg/L and peaked when the D-dimer concentration was > 5 mg/L.
c The fibrinogen concentration was increased in non-survivors and decreased in survivors on the day of ICU discharge or end of data collection (p = 0.001, 0.000).
d The platelet count was decreased in non-survivors on the day of death but increased as patients recovered (p = 0.000, 0.024).
e The antithrombin concentration was significantly decreased in non-survivors on the day of death (p = 0.000).
f The serum calcium concentration was decreased in non-survivors on the day of death (p = 0.031).

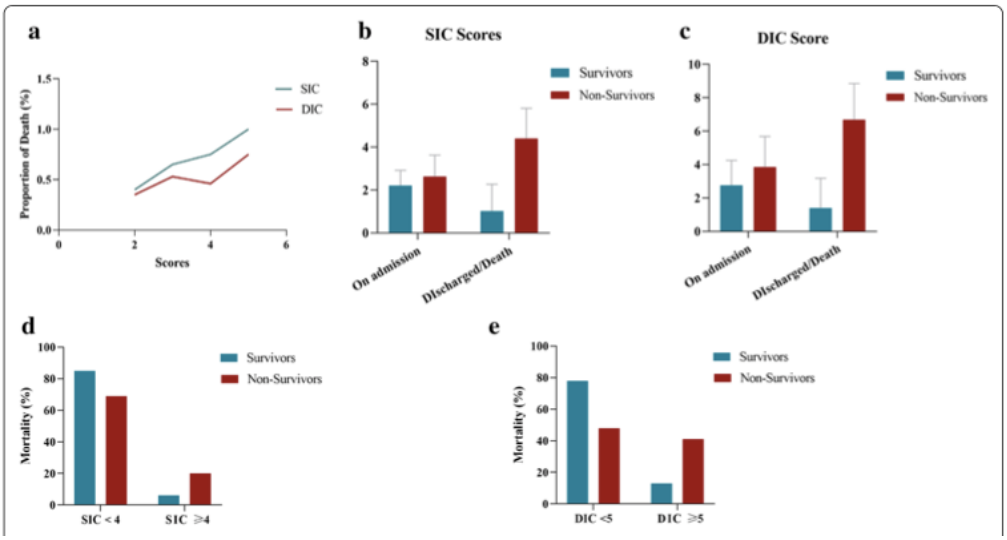


Figure 2: SIC and DIC scores in predicting mortality of patients with COVID-19.

a. Both the SIC and DIC scores of non-survivors were much higher than those of survivors.
b, c. The SIC and DIC scores were significantly higher in non-survivors on the day of death than on the day of admission to the intensive care unit (p = 0.000).
d.The mortality rate was significantly higher in patients with an SIC score of ≥ 4 than in those with an SIC score of< 4 (p = 0.002).
e. The mortality rate was significantly higher in patients with a DIC score of ≥ 5 than in those with a DIC score of < 5 (p = 0.000). SIC, sepsis-induced coagulopathy; DIC, disseminated intravascular coagulation

ORTHOPEDICS

MANAGEMENT OF REGIONAL BONE BANK DURING DECLARATION OF A STATE OF EMERGENCY CONCERNING THE COVID-19 IN JAPAN

Uchida K, Mukai M, Miyagi M, Fukushima K, Uchiyama K, Nakayama A, Matsumoto M, Takahira N, Urabe K, Takaso M, Inoue G.. Cell Tissue Bank. 2021 Feb 20. doi: 10.1007/s10561-021-09908-w. Online ahead of print.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

Researchers from the Kitasato University School of Medicine Department of Orthopedic Surgery and the Kitasato University Bone Bank found that changes were needed in the management of the bone bank in order to prevent the transmission of COVID-19 (Figure 3). They suggest screening donors and recipients for COVID-19 with PCR and implementation of biological inactivation methods, including heat treatment of bone grafts.

SUMMARY

In response to COVID-19, the Bank stopped all dead donor donations. All living donors were pre-operatively screened for COVID-19 with PCR, only allograft bone from COVID-19 negative donors were used. The allograft bone was cryopreserved at -80 degrees C as transplantable tissue and underwent heat treatment at 60 degrees C prior to bone grafting (Figure 1). Three COVID-19 negative recipients received the transplantable tissue, were monitored for four weeks after bone allograft and remained asymptomatic. This study was limited by a small sample size of only three participants and a short follow-up period of only 4 weeks after bone allograft.

ABSTRACT

Bone banks are necessary for providing biological allografts for a series of orthopedic procedures. As nations cope with new realities driven by the 2019 coronavirus disease (COVID-19) pandemic, health-care providers, institutions, and patients share a particular concern about the effect of COVID-19 on organ donation and transplantation. Here, we describe the management of the Kitasato University Bone Bank during the state of emergency declared in response to COVID-19. Living donors received pre-operative screening by PCR, and allograft bone from COVID-19-negative donors was cryopreserved as transplantable tissues. The weekly rate of infection gradually increased from February 2-9 to April 5-11 in the dead donor-derived allograft bone-harvesting region covered by the Bank. It is becoming clear that the virus can be transmitted by asymptomatic patients, and that this route may have facilitated the spread of COVID-19. Therefore, the Bank stopped dead donor donation to consider the safety of medical staff. Three recipients received bone allografts following pre-operative COVID-19 screening by PCR. All patients were asymptomatic after bone allograft. Our experience may provide helpful information for the management of tissue banks.

FIGURES

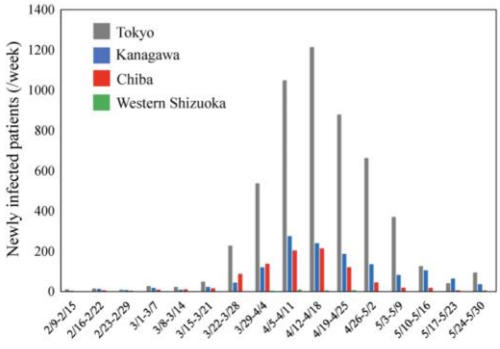


Fig. 3 Number of patients newly infected with COVID-19 in the allograft bone-harvesting region covered by Kitasato University Bone Bank

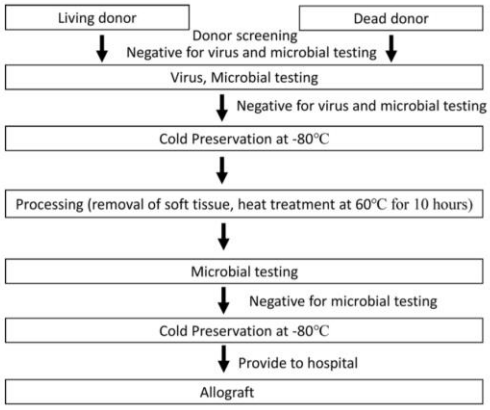


Fig. 1 Role of KUBB

PEDIATRICS

'STAY AT HOME': IS IT GOOD OR NOT FOR HOUSE DUST MITE SENSITIZED CHILDREN WITH RESPIRATORY ALLERGIES?

Yucel E, Suleyman A, Hizli Demirkale Z, Guler N, Ulker Tamay Z, Ozdemir C.. Pediatr Allergy Immunol. 2021 Feb 18. doi: 10.1111/pai.13477. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Pediatricians from Istanbul evaluated the effect of lockdown on 165 pediatric patients diagnosed with mild-moderate asthma between March and May 2020 and compared to the same months of 2019. In 2020, incidence of upper respiratory tract infections and use of asthma control medications decreased (both p<.001) while asthma control test scores increased (p<.001)(Table 1). However, nasal symptoms for patients with known house dust mite (HDM) sensitivity worsened (p<0.001)(Table 3). Authors suggest while prolonged indoor activities may improve asthma control in pediatric patients, patients with HDM sensitization may have worse symptoms during indoor lockdowns and require different management strategies.

ABSTRACT

BACKGROUND: Lockdown was imposed for children for 75 days in Turkey to limit the spread of COVID-19. During this period children have to stay indoors, which might probably increase their exposures to indoor allergens and pollutants. Besides, reduced exposures to respiratory tract infections and outdoor pollutants might be favorable outcomes of this lockdown period. We evaluated the effects of the lockdown on house dust mite (HDM) sensitized children with respiratory allergies. METHODS: Three-month clinical and medication data of 165 mild-moderate asthmatic children with or without allergic rhinitis (AR), who were grouped according to their HDM sensitization status were retrieved from patient records. Demographics, asthma control tests, nasal visual analog scores and outdoor air-quality monitoring data were used for assessments in comparisons to the same period in the previous year. RESULTS: Eighty-four patients had asthma and 81 patients had asthma with AR. Sensitization to HDM was present in 61.8% of the children. Patients experienced reduced numbers of upper-respiratory tract infections (p=0.008) and reduced asthma exacerbations (p<0.001) compared to the same period in the previous year. Asthma control tests were significantly improved (p<0.001) and cumulative inhaled corticosteroid usages were significantly reduced (p<0.001). Noteworthily, nasal symptoms were significantly worsened in HDM-sensitized asthmatics with AR (p<0.001). CONCLUSIONS: This study highlighted that reduction in respiratory tract infections and outdoor pollution may play roles in asthma control and prevent exacerbations despite continuous indoor allergen exposure. Besides, worsening of nasal symptoms in HDM-sensitized asthmatics with AR implies importance of indoor avoidance measures for AR control.

FIGURES

Table 1- Comparison of the frequencies of upper respiratory tract infections, asthma exacerbations and antibiotic usage between March-April-May 2019 and March-April-May 2020.

	March-April-May 2019 *median (min-max) n=165*	March-April-May 2020 *median (min-max) n=165*	p value*
Upper respiratory tract infections	0 (0-2)	0 (0-1)	**0.008**
Asthma exacerbations	0 (0-10)	0 (0-2)	**<0.001**
Antibiotic usage	0 (0-4)	0 (0-2)	**<0.001**

**Wilcoxon test*

** p value highlighted as bold: statistically significant*

Table 3- Comparison of the cumulative medication requirements in patients with asthma and allergic rhinitis according to HDM sensitivity between March-April-May 2019 and March-April-May 2020.

	House dust mite sensitized asthmatics with allergic rhinitis n=74			House dust mite-non-sensitized asthmatics with allergic rhinitis n=7		
	March-April-May 2019 *median (min- max)*	March-April-May 2020 *median (min- max)*	p value	March-April-May 2019 *median (min- max)*	March-April-May 2020 *median (min- max)*	p value
ACT	22 (15-25)	25 (17-25)	**<0,001**	20 (18-22)	25 (20-25)	**0.016**
Cumulative INS dose (µg)	0 (0-6000)	0 (0-12000)	0.887	0 (0-6000)	0	0.102
Cumulative ICS dose (µg)	7500 (0-7500)	6000 (0-15000)	**<0.001**	7500 (2500-7500)	5000 (0-7500)	0.066
Cumulative AH dose (mg)	100 (0-300)	75 (0-300)	0.110	0 (0-150)	0 (0-150)	1
Cumulative LTRA dose (mg)	120 (0-360)	120 (0-300)	**0.014**	150(50-150)	150 (0-150)	0.180
Cumulative SABA dose (µg)	0 (0-20000)	0 (0-10000)	**<0.001**	0 (0-12000)	0	0.180

ACT; asthma control test, AH; antihistamine (cetirizine), ICS; inhaled corticosteroids (fluticasone propionate), LTRA; leukotriene receptor antagonists (montelukast), SABA; short-acting beta2 mimetics (salbutamol)

** p value highlighted as bold: statistically significant*

DOES FAMOTIDINE REDUCE THE RISK OF PROGRESSION TO SEVERE DISEASE, DEATH, AND INTUBATION FOR COVID-19 PATIENTS? A SYSTEMIC REVIEW AND META-ANALYSIS

Sun C, Chen Y, Hu L, Wu Y, Liang M, Ayaz Ahmed M, Bhan C, Guo Z, Yang H, Zuo Y, Yan Y, Zhou Q.. Dig Dis Sci. 2021 Feb 24. doi: 10.1007/s10620-021-06872-z. Online ahead of print.
Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

Internists and epidemiologists from several American and Chinese institutions conducted a systematic review and meta-analysis of five articles (Table 1, Figure 1) assessing the use of famotidine in COVID-19 patients. They found famotidine use produced no statistically significant effect in decreasing progression to severe disease, intubation, or death (RR: 0.82 [95% CI = 0.52–1.30], P = 0.40) (Table 2). Patients who received famotidine had lower reported median ferritin (P = 0.030), CRP (P = 0.002), and procalcitonin (P = 0.004) levels. Authors suggest though famotidine does not appear to decrease poor outcomes in COVID-19 patients, there still may be some potential benefit to its use given their observation of lower serum markers thought to be associated with COVID-19 prognosis.

Table 1 Characteristics of studies included in this meta-analysis

From: Does Famotidine Reduce the Risk of Progression to Severe Disease, Death, and Intubation for COVID-19 Patients? A Systemic Review and Meta-Analysis

First author	Country	Sample size		Exposure	Dosage	Outcome	OR/HR (95% CI)	Adjustment	Study design	NOS scores
		Famotidine use	Non-famotidine use							
Cheung [16]	China	23	929	On the day of admission	NA	Critical complication [respiratory failure, septic shock, and/or multiple organ dysfunction], ventilatory support, intensive care unit admission, and/or death	OR: 1.34(0.24–7.48)	Adjusted[a]	Cohort	9
Freedberg [6]	USA	84	1536	Within 24 h of hospital admission	10, 20, or 40 mg/d IV a median 5.8 days of drug for a total median dose of 136 mg (63–233 mg)	A composite of death or endotracheal intubation from hospital day 2 to day 30 (intubation-free survival)	HR: 0.43(0.21–0.88)	Propensity score matching[b]	Cohort	8
Mather [15]	USA	83	795	Within +/− 7 days of COVID-19 screening and/or hospital admission	20,40 mg/d IV 20 mg/2 ml oral median total dose was 80 mg (40–160 mg) median of 4 days (2–8 days)	(1) In-hospital death, requirement for mechanical ventilation, and the composite of death or requirement for ventilation (2) Mortality	(1) HR: 0.51(0.31–0.79) (2) HR: 0.39(0.20–0.74)	Propensity score matching[c]	Cohort	8
Shoaibi [32]	USA	1623	24,404	On the day of admission	20 or 40 mg oral and/or IV	(1) Death and death or intensive services (combined). Intensive services were defined as any condition, procedure, or observation code indicative of mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation (2) Mortality	(1) HR: 1.00(0.86–1.16) (2) HR: 1.03(0.86–1.24)	Propensity score matching[d]	Cohort	9
Yeramaneni [33]	USA	1127	6031	Within 24 h of admission	A median 6.0 days and median cumulative dose of 160 mg (IQR, 80–300 mg)	30-day mortality	OR: 1.59(0.94–2.71)	Adjusted[e]	Cohort	7

NA not applicable

[a]Adjusted for age, sex, comorbidities (diabetes mellitus, hypertension, ischemic heart disease, stroke, and atrial fibrillation), other medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aspirin, statins, and prednisolone), and laboratory parameters (leukocyte, platelet, C-reactive protein, urea, creatinine, sodium, potassium, bilirubin, alkaline phosphatase, alanine aminotransferase, albumin, globulin, and lactate dehydrogenase)

[b]The variables used for the propensity score calculation including age, sex, race, body mass index (BMI), comorbidities (diabetes, hypertension, coronary artery disease, heart failure, end-stage renal disease or chronic kidney disease, chronic pulmonary disorders), Initial oxygen requirement (room air, nasal cannula, non-rebreather, or similar)

[c]The variables used for the propensity score calculation including age, sex, smoking status, body mass index (BMI), comorbidities (atrial fibrillation, asthma, coronary artery disease, cancer, chronic obstructive pulmonary disease, diabetes, heart failure, hypertension, obesity, kidney disease)

[d]The variables used for the propensity score calculation including age, gender, general medical history (acute respiratory disease, attention deficit hyperactivity disorder, chronic liver disease, chronic obstructive lung disease, Crohn's disease, dementia, depressive disorder, diabetes mellitus, gastroesophageal reflux disease, gastrointestinal hemorrhage, human immunodeficiency virus infection, hyperlipidemia, hypertensive disorder, lesion of liver, obesity, osteoarthritis, pneumonia, psoriasis, renal impairment, rheumatoid arthritis, schizophrenia, ulcerative colitis, urinary tract infectious disease, viral hepatitis C, visual system disorder), cardiovascular medical history (atrial fibrillation, cerebrovascular disease, coronary arteriosclerosis, heart disease, heart failure, ischemic heart disease, peripheral vascular disease, pulmonary embolism, venous thrombosis), neoplasms history (hematologic neoplasm, malignant lymphoma, malignant neoplasm of anorectum, malignant neoplastic disease, malignant tumor of breast, malignant tumor of colon, malignant tumor of urinary bladder, primary malignant neoplasm of prostate)

[e]Adjusted for baseline World Health Organization severity, smoking and use of other medications

Table 1 Characteristics of studies included in this meta-analysis
NA not applicable
aAdjusted for age, sex, comorbidities (diabetes mellitus, hypertension, ischemic heart disease, stroke, and atrial fibrillation), other medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aspirin, statins, and prednisolone), and laboratory parameters (leukocyte, platelet, C-reactive protein, urea, creatinine, sodium, potassium, bilirubin, alkaline phosphatase, alanine aminotransferase, albumin, globulin, and lactate dehydrogenase)
bThe variables used for the propensity score calculation including age, sex, race, body mass index (BMI), comorbidities (diabetes, hypertension, coronary artery disease, heart failure, end-stage renal disease or chronic kidney disease, chronic pulmonary disorders), Initial oxygen requirement (room air, nasal cannula, non-rebreather, or similar)
cThe variables used for the propensity score calculation including age, sex, smoking status, body mass index (BMI), comorbidities (atrial fibrillation, asthma, coronary artery disease, cancer, chronic obstructive pulmonary disease, diabetes, heart failure, hypertension, obesity, kidney disease)
dThe variables used for the propensity score calculation including age, gender, general medical history (acute respiratory disease, attention deficit hyperactivity disorder, chronic liver disease, chronic obstructive lung disease, Crohn's disease, dementia, depressive disorder, diabetes mellitus, gastroesophageal reflux disease, gastrointestinal hemorrhage, human immunodeficiency virus infection, hyperlipidemia, hypertensive disorder, lesion of liver, obesity, osteoarthritis, pneumonia, psoriasis, renal impairment, rheumatoid arthritis, schizophrenia, ulcerative colitis, urinary tract infectious disease, viral hepatitis C, visual system disorder), cardiovascular medical history (atrial fibrillation, cerebrovascular disease, coronary arteriosclerosis, heart disease, heart failure, ischemic heart disease, peripheral vascular disease, pulmonary embolism, venous thrombosis), neoplasms history (hematologic neoplasm, malignant lymphoma, malignant neoplasm of anorectum, malignant neoplastic disease, malignant tumor of breast, malignant tumor of colon, malignant tumor of urinary bladder, primary malignant neoplasm of prostate)
eAdjusted for baseline World Health Organization severity, smoking and use of other medications

Table 2 Association between famotidine use and COVID-19 outcomes

From: Does Famotidine Reduce the Risk of Progression to Severe Disease, Death, and Intubation for COVID-19 Patients? A Systemic Review and Meta-Analysis

Analysis	Number of studies	OR (95% CI)	P	Heterogeneity	
				$P_{Heterogeneity}$	I^2 (%)
Severity, mortality and intubation	5	0.82(0. 52–1.30)	0.400	0.003	76
Mortality and intubation	3	0.63(0.35–1.16)	0.140	0.002	84
Mortality only	3	0.90(0.49–1.65)	0.730	0.003	82

Table 2 Association between famotidine use and COVID-19 outcomes

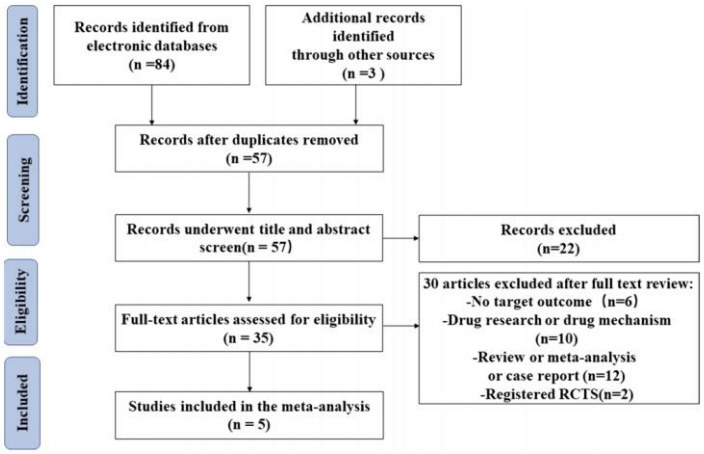


Fig. 1 PRISMA flowchart

CURRENT DIAGNOSTICS

DIAGNOSTIC PERFORMANCE OF COVID-19 SEROLOGICAL ASSAYS DURING EARLY INFECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF 11 516 SAMPLES

Zhang JJY, Lee KS, Ong CW, Chan MY, Ang LW, Leo YS, Chen MI, Lye DCB, Young BE.. Influenza Other Respir Viruses. 2021 Feb 20. doi: 10.1111/irv.12841. Online ahead of print.

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

BLUF

This systematic review and meta-analysis by researchers from the National University of Singapore analyzes the diagnostic performances of COVID-19 IgM and IgG serological assays during early infection in 55 studies with virologically confirmed SARS-CoV-2. Results showed the overall sensitivity and specificity to be 0.727 and 0.918 for IgM testing and 0.788 and 0.948 for IgG. They also found test accuracy significantly rose for both assays using enzyme-linked immunosorbent assay (ELISA) after Day 14 (Figure 3). The authors conclude that because seroconversion of IgM and IgG (Figure 1) were found to be low during the first week of infection (37.5% and 35.4%, respectively) and rose around Day 21 (81.3% and 93.3%, respectively), these assays are most practical later after symptom onset, and this understanding should be considered when choosing diagnostic testing for COVID-19.

ABSTRACT

OBJECTIVE: The use of coronavirus disease 2019 (COVID-19) serological testing to diagnose acute infection or determine population seroprevalence relies on understanding assay accuracy during early infection. We aimed to evaluate the diagnostic performance of serological testing in COVID-19 by providing summary sensitivity and specificity estimates with time from symptom onset. METHODS: A systematic search of Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed was performed up to May 13, 2020. All English language, original peer-reviewed publications reporting the diagnostic performance of serological testing vis-a-vis virologically confirmed SARS-CoV-2 infection were included. RESULTS: Our search yielded 599 unique publications. A total of 39 publications reporting 11 516 samples from

8872 human participants met eligibility criteria for inclusion in our study. Pooled percentages of IgM and IgG seroconversion by Day 7, 14, 21, 28 and after Day 28 were 37.5%, 73.3%, 81.3%, 72.3% and 73.3%, and 35.4%, 80.6%, 93.3%, 84.4% and 98.9%, respectively. By Day 21, summary estimate of IgM sensitivity was 0.872 (95% CI: 0.784-0.928) and specificity 0.973 (95% CI: 0.938-0.988), while IgG sensitivity was 0.913 (95% CI: 0.823-0.959) and specificity 0.960 (95% CI: 0.919-0.980). On meta-regression, IgM and IgG test accuracy was significantly higher at Day 14 using enzyme-linked immunosorbent assay (ELISA) compared to other methods. CONCLUSIONS: Serological assays offer imperfect sensitivity for the diagnosis of acute SARS-CoV-2 infection. Estimates of population seroprevalence during or shortly after an outbreak will need to adjust for the delay between infection, symptom onset and seroconversion.

FIGURES

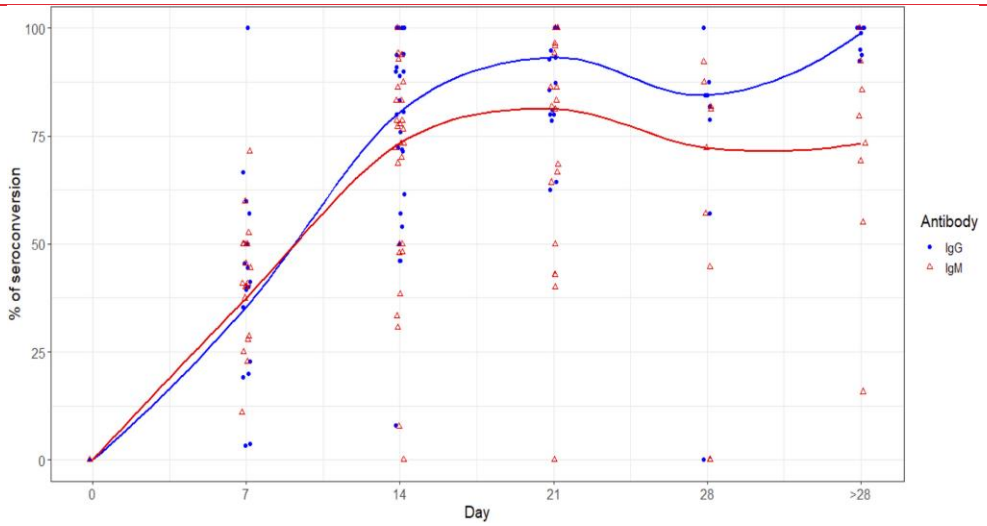


Figure 1. Graph of IgM and IgG seroconversion against time from symptom onset

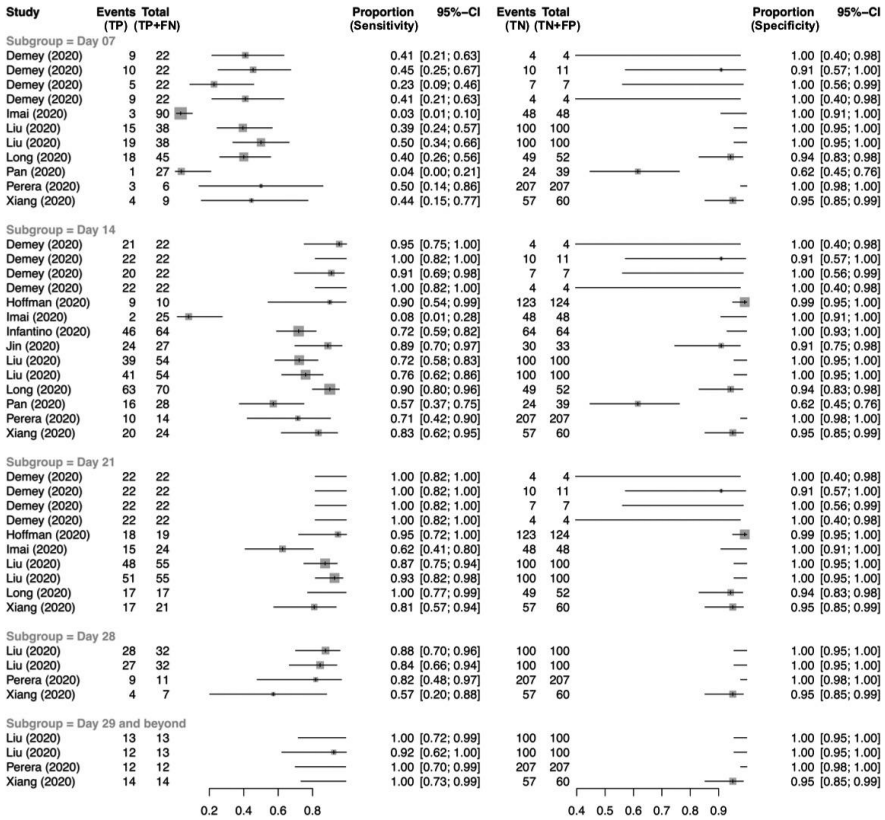


Figure 3. Coupled forest plot showing sensitivity and specificity of IgG testing stratified by time from symptom onset

Table S2. Inclusion and exclusion criteria used to assess eligibility of studies.

Inclusion criteria	Exclusion criteria
• Any peer-reviewed publication reporting the diagnostic performance of rapid serological assays in patients with COVID-19 • Diagnosis of COVID-19 made with virologic testing • At least 5 human samples from patients of any age	• Not written in English • No original research data e.g. narrative and systematic reviews, editorials, commentaries, opinion papers, letters[a], education papers, conference abstracts, protocols, reports, theses or book chapters • Case reports and case series with fewer than 5 patients reported • Non-human samples (e.g. murine, porcine studies) • Purely seroepidemiological with no outcomes of diagnostic test accuracy

[a]Letters to Editors with original research data reported were included.

SALIVA SAMPLES FOR DETECTION OF SARS-COV-2 IN MILDLY SYMPTOMATIC AND ASYMPTOMATIC PATIENTS

Ediz Tutuncu E, Ozgur D, Karamese M.. J Med Virol. 2021 Jan 26. doi: 10.1002/jmv.26821. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

Investigators from Kafkas University in Kars, Turkey conducted a cohort study of 53 patients with confirmed SARS-CoV-2 infection by nasopharyngeal RT-PCR in May 2020, consisting of both asymptomatic (n=28) and mildly symptomatic (n=25) patients with dry cough, sore throat, fatigue or anosmia. An additional saliva RT-PCR test was positive in 90.56% of patients and the mean cycle threshold values between the two testing modalities were significantly correlated (p = 0.016) (Figure 1), suggesting that saliva sampling is a reliable and less invasive alternative for screening asymptomatic individuals.

ABSTRACT

BACKGROUND: The ongoing Covid-19 pandemic has been rapidly spreading throughout the world with confirmed case numbers already exceeding 75 millions. Although nasopharyngeal swabs are the most commonly utilized samples for based SARS-CoV-2 RNA detection, collecting these specimens requires healthcare workers and necessitates the use of personal protective equipment since it presents a nosocomial transmission risk. We aimed to assess the diagnostic value of saliva samples in mildly symptomatic and asymptomatic patients with confirmed Covid-19. METHODS: We did a cohort study to validate the use of saliva for SARS-CoV-2 detection in mildly symptomatic and asymptomatic patients with confirmed diagnosis of Covid-19. Saliva samples of the patients were analyzed by RT-PCR. RESULTS: In May 2020, 28 asymptomatic and 25 mildly symptomatic patients were enrolled in the study. The median age was 37 years (range 4-70). None of the patients had fever on presentation. Among 53 patients with SARS-CoV-2 detected in the nasopharyngeal sample, the real-time RT-PCR was positive in the saliva specimens in 48 (90.56%) patients. The mean cycle threshold (CT) values for nasopharyngeal and saliva specimens (27.80+-3.44 and 30.64+-2.83, respectively) were significantly correlated between the two sample types (p=0.016). The mean CT values of nasopharyngeal and saliva samples in mildly symptomatic and asymptomatic patients (27.18+-3.53 and 30.24+-3.29 vs. 28.36+-3.31 and 30.98+-2.39, respectively) were not significantly different (p=0.236 and p=0.733, respectively). CONCLUSIONS: Saliva specimens can be considered as a reliable and less resource intensive alternative to nasopharyngeal specimens for screening asymptomatic SARS-CoV-2 infections. This article is protected by copyright. All rights reserved.

FIGURES

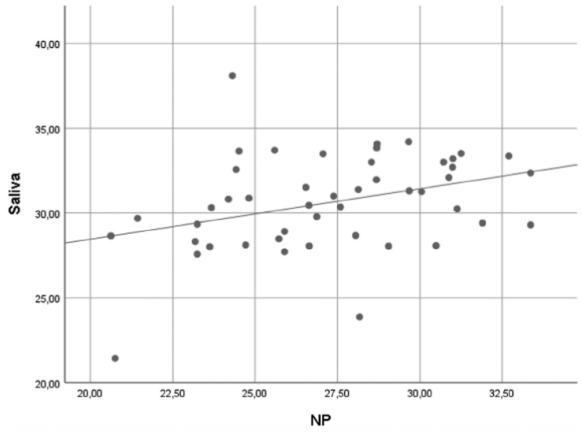


Figure 1. Scatter graph for correlation between the mean cycle threshold values for NP and saliva specimens. NP, nasopharyngeal.

DEVELOPMENTS IN DIAGNOSTICS

EARLY ANTI-SARS-COV-2 IMMUNOGLOBULIN G RESPONSE MAY BE ASSOCIATED WITH DISEASE SEVERITY IN PATIENTS WITH COVID-19

Maeda T, Kashiwagi K, Yoshizawa S, Sato T, Aoki K, Ishii Y, Tateda K.. Jpn J Infect Dis. 2021 Feb 26. doi: 10.7883/yoken.JJID.2020.799. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

A prospective study conducted at the Toho University School of Medicine in Tokyo, Japan found that 7 of 21 patients who tested positive by PCR produced an early SARS-CoV-2 IgG response (See Figure 1a). This response was associated with higher severity of disease, elevated CRP and D-dimer levels upon admission and higher respiratory rate and lower lymphocyte percentage on Day 7 of hospitalization (See Figure 1b) compared to late SARS-CoV-2 IgG responders. It was also determined that early-IgG response was associated with lower viral load, which is contrary to previous studies that have associated increasing COVID-19 infection severity with higher viral load. These results suggest potential for early production of IgG to be used as a clinical indicator for disease severity, however further studies are needed to analyze and differentiate early vs. late IgG responses in regards to clinical presentation.

FIGURES

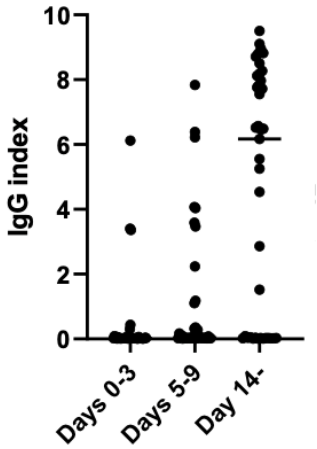


Figure 1a. IgG Index of the coronavirus disease patients in the early phase of the disease.
Specific anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG in the serum of coronavirus disease (COVID-19) patients was measured using Abbott ARCHITECT i2000SR. Sequential measurements of the IgG index were evaluated

among 44 COVID-19 patients. The IgG index was calculated, which is defined as the relative luminescence value of sample when the calibrator sample is set to 1. The "Day" is the number of days after the onset of symptoms. An IgG index above 1.4 was considered positive. The bars indicate the median. The horizontal dashed line indicates the IgG index cutoff value of 1.4.

Abbreviations: CRP, C-reactive protein; DD, D-dimer; IgG, immunoglobulin G; Ly%, lymphocyte %; RR, respiratory rate; VL, SARS-CoV-2 viral load; CTRX, ceftriazone; AZM, azithromycin; PIPC/TAZ, piperacillin/tazobactam

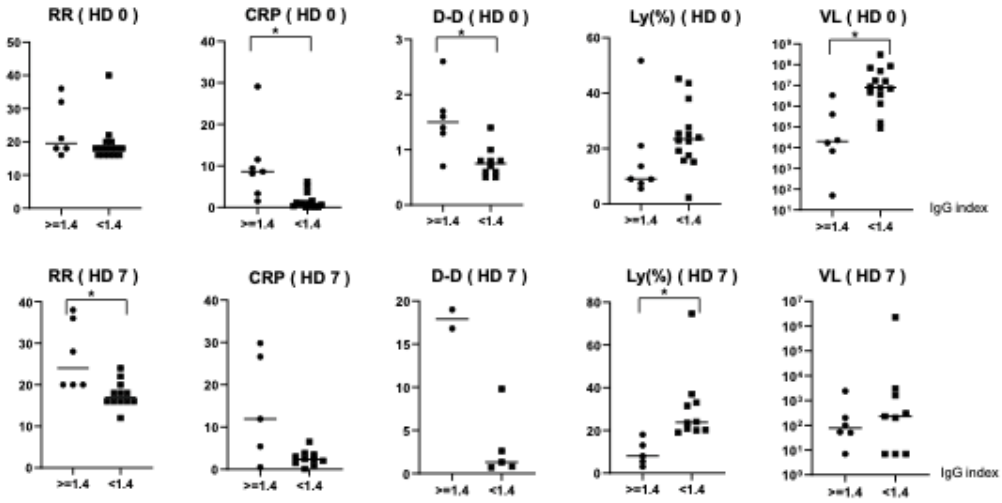


Figure 1b. Severity markers were compared between early-IgG and late-IgG responders.
Severity markers were compared according to the increase in IgG antibodies (based on an IgG index cutoff of 1.4) between early-IgG responders and late-IgG responders. HD 0: day of admission; HD7: 7 days +/- 2 days after admission. The bars indicate the median values. The Mann-Whitney U test was used to determine whether differences between the two groups were statistically significant (*P<0.05). The columns on the left of each scatterplot represent the early-IgG responders (IgG index >1.4, N=7) and the columns on the right represent the late-IgG responders (IgG index < 1.4, N=14). There was one case of intubation after admission. Due to the ventilator setting, the case was excluded from the RR (HD7) review.

Abbreviations: CRP, C-reactive protein; DD, D-dimer; IgG, immunoglobulin G; Ly%, lymphocyte %; RR, respiratory rate; VL, SARS-CoV-2 viral load;

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