

The Daily COVID-19 Literature Surveillance Summary

April 30, 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

- [IL-33 expression in response to SARS-CoV-2 correlates with seropositivity in COVID-19 convalescent individuals:](#) Immunologists from the Max Planck Institute in Germany and Bloomberg-Kimmel Institute in the United States evaluated immune responses to SARS-CoV-2 in 155 individuals with professional exposure and found anti-Spike IgG/IgM titers remain elevated 60 days post-infection and the only clinical symptom associated with high titers was fever. Additionally, they found that SARS-CoV-2 peptide stimulation of peripheral blood monocytes from seropositive individuals stimulates interleukin-33 (IL-33) production which was associated with CD4 T-cell activation. Because IL-33 is known to be involved in the pathophysiology of asthma and COPD, the authors suggest more research to better understand the role of IL-33 in the pathogenesis of COVID-19.

Transmission & Prevention

- [Age- and gender-dependent antibody responses against SARS-CoV-2 in health workers and octogenarians after vaccination with the BNT162b2 mRNA vaccine:](#) Cell biologists and clinical biochemists from the University of Athens evaluated SARS-CoV-2 antibody responses in 255 health workers from Alexandra General Hospital in Athens, Greece (group 1) and 112 octogenarians (group 2) after receiving BNT162b2 mRNA vaccination. They found Anti-Spike-RBD IgG antibodies and NAbs against SARS-CoV-2 increased after vaccination before plateauing two weeks after the second dose, with a more robust response in younger individuals compared to the older cohort and female octogenarians compared to male. The authors suggest humoral responses to the BNT162b2 mRNA vaccine are age and gender dependent and that administration of a timely second vaccine is critical to maximizing the immune response.
- [Open Schools, Covid-19, and Child and Teacher Morbidity in Sweden:](#) Swedish pediatricians used a nationwide intensive care registry to study SARS-CoV-2 infections among children and teachers between March 1 and June 30, 2020, where schools remained opened and masking was not mandatory. Fifteen children with COVID-19 were admitted to an ICU (0.77 per 100,000 children), four of whom had an underlying chronic coexisting condition; none died. Fewer than 10 preschool teachers and 20/103,596 schoolteachers in Sweden received intensive care for COVID-19 (age-adjusted relative risk 1.10 [95%CI 0.49-2.49] for preschool teachers and 0.43 [95% CI 0.28-0.68] for schoolteachers). Authors suggest SARS-CoV-2 transmission in school settings is low, though acknowledge lack of data about household transmission and wide confidence intervals.

R&D: Diagnosis & Treatments

- [Are sniffer dogs a reliable approach for diagnosing SARS-CoV-2 infection?:](#) A biochemist, public health expert, and pediatric intensivist from the University of Verona and Cincinnati Children's Hospital performed a critical review and pooled analysis of three studies analyzing the efficacy of dogs trained to identify patients infected with SARS-CoV-2. In 17 dogs, the diagnostic sensitivity was 0.88 (95% CI, 0.84–0.91; I₂, 85.3%) - above that of tested nasopharyngeal swab samples seen in some other studies - and specificity was 0.99 (95% CI, 0.99–0.99; I₂, 97.4%). Due to the time needed to train the dogs, the dependency on the state of the dog, and potentially confounding odors from comorbidities, authors suggest the use of dogs should be further investigated at a larger scale to better determine its practical applications for SARS-CoV-2 testing.

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EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

EVOLVING CHANGES IN MORTALITY OF 13,301 CRITICALLY ILL ADULT PATIENTS WITH COVID-19 OVER 8 MONTHS

Kurtz P, Bastos LSL, Dantas LF, Zampieri FG, Soares M, Hamacher S, Salluh JIF, Bozza FA.. Intensive Care Med. 2021 Apr 14. doi: 10.1007/s00134-021-06388-0. Online ahead of print.

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

BLUF

Critical care neurologists and infectious disease physicians from the D'Or Institute for Research and Education in Brazil, among others, conducted a multicenter cohort study of 13,301 patients admitted to 126 ICU's with COVID-19 between February and October 2020. They found mortality rates declined over time and that younger age, absence of frailty, and the use of non-invasive respiratory support as the first means of treatment were independently associated with improved survival (Figure 2). Because their findings are inferential and do not establish a causal relationship, authors suggest further research to clarify best practices for respiratory support.

ABSTRACT

PURPOSE: Clinical characteristics and management of COVID-19 patients have evolved during the pandemic, potentially changing their outcomes. We analyzed the associations of changes in mortality rates with clinical profiles and respiratory support strategies in COVID-19 critically ill patients. **METHODS:** A multicenter cohort of RT-PCR-confirmed COVID-19 patients admitted at 126 Brazilian intensive care units between February 27th and October 28th, 2020. Assessing temporal changes in deaths, we identified distinct time periods. We evaluated the association of characteristics and respiratory support strategies with 60-day in-hospital mortality using random-effects multivariable Cox regression with inverse probability weighting.

RESULTS: Among the 13,301 confirmed-COVID-19 patients, 60-day in-hospital mortality was 13%. Across four time periods identified, younger patients were progressively more common, non-invasive respiratory support was increasingly used, and the 60-day in-hospital mortality decreased in the last two periods. 4188 patients received advanced respiratory support (non-invasive or invasive), from which 42% underwent only invasive mechanical ventilation, 37% only non-invasive respiratory support and 21% failed non-invasive support and were intubated. After adjusting for organ dysfunction scores and premorbid conditions, we found that younger age, absence of frailty and the use of non-invasive respiratory support (NIRS) as first support strategy were independently associated with improved survival (hazard ratio for NIRS first [95% confidence interval], 0.59 [0.54-0.65], $p < 0.001$). **CONCLUSION:** Age and mortality rates have declined over the first 8 months of the pandemic. The use of NIRS as the first respiratory support measure was associated with survival, but causal inference is limited by the observational nature of our data.

FIGURES

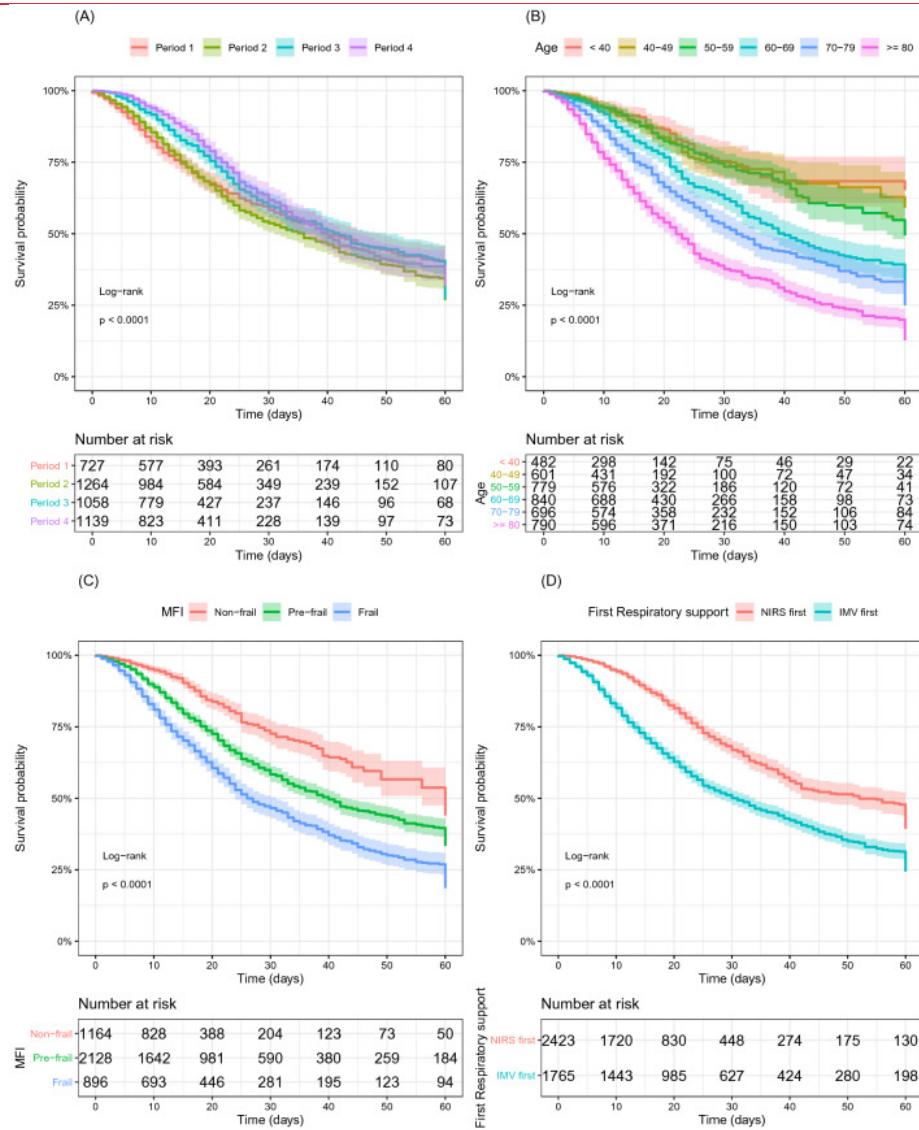


Figure 2. Univariable survival curves (Kaplan-Meier) of factors related to the 60-day outcome in critically ill patients who underwent advanced respiratory support. a Time periods estimated with the breakpoints of structure change (Period 1: February 27th to April 25th; Period 2: April 26th to June 6th; Period 3: June 7th to August 10th; Period 4: August 11th to October 28th); b age (< 40, 40-49, 50-59, 60-69, 70-79, and ≥ 80); c Modified Frailty Index (MFI) at the admission, with groups non-frail (MFI = 0), pre-frail (MFI = 1-2) and frail (MFI ≥ 3); and d initial respiratory support considering non-invasive (NIRS first) invasive (IMV first). Differences among curves were assessed using the log-rank test with a confidence level of 0.05.

UNDERSTANDING THE PATHOLOGY

IL-33 EXPRESSION IN RESPONSE TO SARS-COV-2 CORRELATES WITH SEROPOSITIVITY IN COVID-19 CONVALESCENT INDIVIDUALS

Stanczak MA, Sanin DE, Apostolova P, Nerz G, Lampaki D, Hofmann M, Steinmann D, Krohn-Grimbergh M, Thimme R, Mittler G, Waller CF, Pearce EJ, Pearce EL.. Nat Commun. 2021 Apr 9;12(1):2133. doi: 10.1038/s41467-021-22449-w.

Level of Evidence: 3 - Local non-random sample

BLUF

Immunologists from the Max Planck Institute in Germany and Bloomberg-Kimmel Institute in the United States evaluated immune responses to SARS-CoV-2 in 155 individuals with professional exposure. They found anti-Spike IgG/IgM titers remain elevated 60 days post-infection and the only clinical symptom associated with high titers was fever (Figure 1). Additionally, they found that SARS-CoV-2 peptide stimulation of peripheral blood monocytes from seropositive individuals stimulates interleukin-33 (IL-33) production which was associated with CD4 T-cell activation (Figure 3). Because IL-33 is known to be involved in the pathophysiology of asthma and COPD, the authors suggest more research to better understand the role of IL-33 in the pathogenesis of COVID-19.

ABSTRACT

Our understanding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still developing. We perform an observational study to investigate seroprevalence and immune responses in subjects professionally exposed to SARS-CoV-2 and their family members (155 individuals; ages 5-79 years). Seropositivity for SARS-CoV-2 Spike glycoprotein aligns with PCR results that confirm the previous infection. Anti-Spike IgG/IgM titers remain high 60 days post-infection and do not strongly associate with symptoms, except for fever. We analyze PBMCs from a subset of seropositive and seronegative adults. TLR7 agonist-activation reveals an increased population of IL-6+TNF-IL-1beta+ monocytes, while SARS-CoV-2 peptide stimulation elicits IL-33, IL-6, IFNa2, and IL-23 expression in seropositive individuals. IL-33 correlates with CD4+ T cell activation in PBMCs from convalescent subjects and is likely due to T cell-mediated effects on IL-33-producing cells. IL-33 is associated with pulmonary infection and chronic diseases like asthma and COPD, but its role in COVID-19 is unknown. Analysis of published scRNAseq data of bronchoalveolar lavage fluid (BALF) from patients with mild to severe COVID-19 reveals a population of IL-33-producing cells that increases with the disease. Together these findings show that IL-33 production is linked to SARS-CoV-2 infection and warrant further investigation of IL-33 in COVID-19 pathogenesis and immunity.

FIGURES

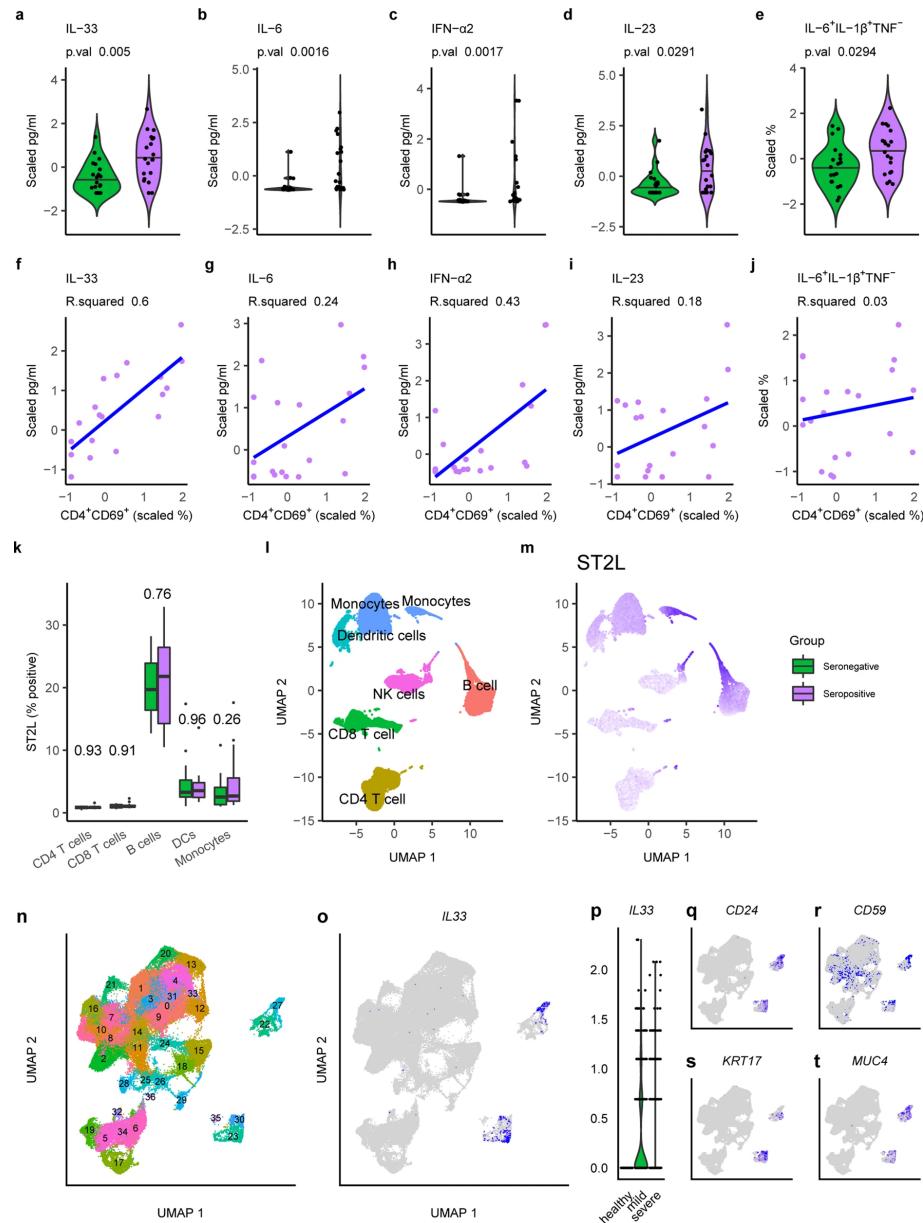


Figure 3. IL-33 production correlates with T cell activation and disease severity in SARS-CoV-2 infected subjects.

a-e Cytokine production measured in the media of cultured PBMCs (a-d) or via intracellular staining of CD14hiCD16-low monocytes from seropositive (purple) and seronegative (green) subjects are shown as scaled values. Two-tailed Mann-Whitney U tests were calculated and the resulting p-value is reported. Values for subjects are shown as dots, the sample distribution is presented as a violin plot and the population median is a black line. f-j Scaled cytokine production versus corresponding CD4 T cell activation (CD4+CD69+) in PBMC cultures of seropositive individuals are shown. Linear regression curves fitted to these data (blue) alongside R² values are provided. k-m ST2L expression as a percentage of positive cells was measured in the indicated cell populations via flow cytometry in PBMCs from seropositive (purple) and seronegative (green) subjects (n = 40). Two-tailed Mann-Whitney U tests were calculated and resulting p values are reported. Boxplots indicating the mean (black line), 25th and 75th quantiles (edges), and interquartile ranges (whiskers), as well as outliers (dots), are shown. Flow cytometry staining is presented in a dimensional reduction projection (UMAP), showing immune cell clusters (l) and ST2L median fluorescence intensity (MFI) (m). Scaled MFI is indicated on a gradient from low (gray) to high (purple). n-t Single-cell RNA sequencing data from the bronchoalveolar lavage fluid of 3 healthy individuals compared to 9 SARS-CoV-2 infected subjects with different disease severities (3 milds; 6 severe) was retrieved from a public database (GSE145926), grouped into cell clusters (n) and analyzed for the expression of IL-33 (o). Relative expression levels are indicated on a gradient from low (light gray) to high (blue). p IL-33 expression in clusters 23, 27, and 30 presented as a violin plot grouped by disease status. q-t, Key surface (q-r), and lineage-specific (s-t) genes expressed in IL-33 producing cells. Relative expression levels are indicated on a gradient from low (light gray) to high (blue).

The figure illustrates the correlation between IL-33 production and T cell activation, as well as the relationship between IL-33 expression and disease severity. Panel (k) shows ST2L expression in various cell types, with higher expression in seropositive individuals. Panels (l) and (m) show UMAP projections and MFI for ST2L, respectively, with distinct clusters for different cell types. Panel (n) shows a UMAP projection of cell clusters with numbered points corresponding to individual subjects. Panel (o) shows IL-33 expression in these clusters. Panels (p-t) show the relative expression of IL-33 and other genes (CD24, CD59, KRT17, MUC4) in healthy, mild, and severe disease states. Panels (f-j) show the correlation between scaled cytokine production and CD4+CD69+ activation, with linear regression curves and R-squared values. Panels (a-e) show the comparison of cytokine production between seropositive and seronegative subjects using violin plots.

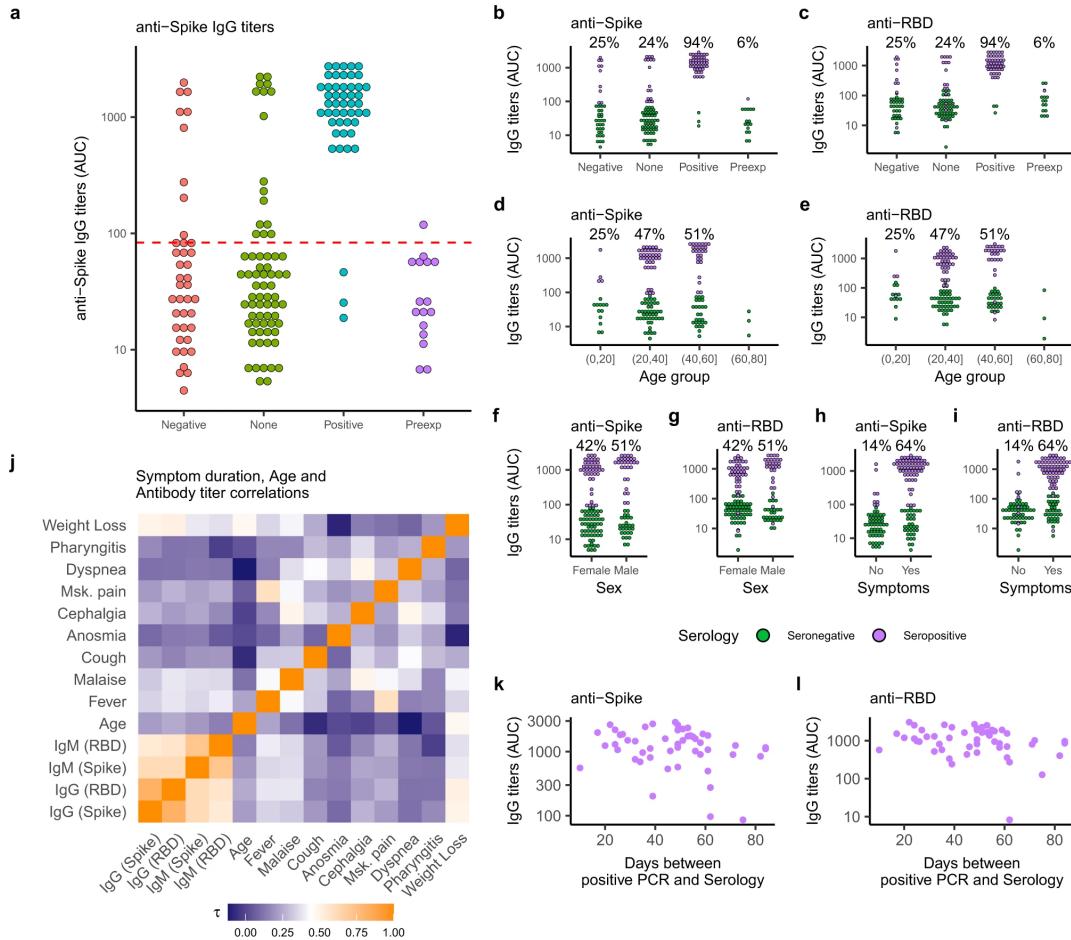


Figure 1. Serological characterization of the study population.

a Anti-Spike IgG titers shown as area under titration curve (AUC) in sera from investigated subjects grouped by SARS-CoV-2 PCR status (Negative-red circles, None-green circles, Positive-blue circles) plus pre-pandemic historical sera (Preexp, magenta circles). The dotted line illustrates the estimated threshold above which subjects were classified as "Seropositive" (mean + 2xSD-red). Mean and SD was calculated for all IgG titers below the maximum value measured from Preexp sera ($n = 63$). b-i Anti-Spike (b, d, f, h) and anti-RBD (c, e, g, i) IgG titers shown as AUC for investigated subjects grouped by SARS-CoV-2 PCR status (b-c), age group (d-e), sex (f-g) and reported symptoms (h-i). Subjects are colored by anti-Spike IgG serology results (seropositive-purple circles, seronegative-green circles). Percentage seropositive subjects within each category are indicated. j Detected antibody titers from seropositive subjects were correlated to each other, symptom duration, and subject age using a Kendall rank correlation. A heatmap of the Kendall rank correlation coefficient (τ) is shown for each pair of variables. k-l, Anti-Spike (k), and anti-RBD (l) IgG titers shown as a function of time for seropositive subjects. The approximate time of infection was taken as the day of positive SARS-CoV-2 PCR status.

TRANSMISSION & PREVENTION

AGE- AND GENDER-DEPENDENT ANTIBODY RESPONSES AGAINST SARS-COV-2 IN HEALTH WORKERS AND OCTOGENARIANS AFTER VACCINATION WITH THE BNT162B2 mRNA VACCINE

Terpos E, Trougakos IP, Apostolakou F, Charitaki I, Skliroú AD, Mavrianou N, Papanagnou ED, Liacos CI, Gumeni S, Rentziou G, Korompoki E, Papassotiriou I, Dimopoulos MA.. Am J Hematol. 2021 Apr 10. doi: 10.1002/ajh.26185. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Cell biologists and clinical biochemists from the University of Athens evaluated SARS-CoV-2 antibody responses in 255 health workers from Alexandra General Hospital in Athens, Greece (group 1) and 112 octogenarians (group 2) after receiving BNT162b2 mRNA vaccination (see summary). They found Anti-Spike-RBD IgG antibodies and NAbs against SARS-CoV-2 increased after vaccination before plateauing two weeks after the second dose, with a more robust response in younger individuals compared to the older cohort and female octogenarians compared to male. The authors suggest humoral responses to the BNT162b2 mRNA vaccine are age and gender dependent and that administration of a timely second vaccine is critical to maximizing the immune response.

SUMMARY

Group 1 consisted of 92 males and 163 females. The age ranged from 25 to 70 years, with the median age being 49 years. Group 2 consisted of 51 males and 61 females. The age ranged from 80 to 95 years, with the median age being 85 years.

Participants in this study had to be over 18 years old, properly consented, and eligible to receive the vaccine. They were excluded if they had end-stage renal disease, active malignant disease, or an autoimmune disease under immunosuppressive therapy.

Anti-Spike-RBD IgG antibodies and NAbs against SARS-CoV-2 were measured using the Elecsys Anti-SARS-CoV-2 S assay and the cPass™ SARS-CoV-2 NAb Detection Kit (which are both FDA approved).

Blood was collected at day 1 (D1; first BNT162b2 dose), D8, D22 (second dose), D36 and D50 for health workers. It was collected at D1, D22 and D50 for octogenarians.

After venipuncture, serum was separated and stored within 4 hours at -80°C until measurement day.

PREVENTION IN THE COMMUNITY

OPEN SCHOOLS, COVID-19, AND CHILD AND TEACHER MORBIDITY IN SWEDEN

Ludvigsson JF, Engerström L, Nordenhäll C, Larsson E.. N Engl J Med. 2021 Feb 18;384(7):669-671. doi: 10.1056/NEJMc2026670. Epub 2021 Jan 6.

Level of Evidence: 3 - Local non-random sample

BLUF

Swedish pediatricians used a nationwide intensive care registry to study SARS-CoV-2 infections among children and teachers between March 1 and June 30, 2020, where schools remained opened and masking was not mandatory. Fifteen children with COVID-19 (see summary) were admitted to an ICU (0.77 per 100,000 children), four of whom had an underlying chronic coexisting condition; none died (Table 1). Fewer than 10 preschool teachers and 20/103,596 schoolteachers in Sweden received intensive care for COVID-19 (age-adjusted relative risk 1.10 [95%CI 0.49-2.49] for preschool teachers and 0.43 [95% CI 0.28-0.68] for schoolteachers). Authors suggest SARS-CoV-2 transmission in school settings is low, though acknowledge lack of data about household transmission and wide confidence intervals.

SUMMARY

Cases were diagnosed by PCR, antibody testing, or clinically (Table 1).

FIGURES

Table 1

Characteristics of the Children with Covid-19, Including Those with MIS-C, Admitted to Swedish ICUs in March–June 2020.*

Age	Sex	SARS-CoV-2 Test Result	Days in ICU†	No. of Admissions	BP and Laboratory Measures at Admission‡	Organ Support	Complications
		PCR Antibodies					
1 yr§	F	Negative Positive	5	1	Systolic BP, 70 mm Hg; SaO ₂ , 99%; BE, +0.6 mmol/liter; lactate, 1.6 mmol/liter	—	MIS-C, septic shock, renal failure
3 yr	F	Positive ND	38	3	Systolic BP, 75 to 143 mm Hg; SaO ₂ , 96%; lactate, 1.2 mmol/liter	Invasive mechanical ventilation	Clostridium difficile infection
4 yr	F	Positive Positive	6	1	Systolic BP, 87 mm Hg; SaO ₂ , 99%	—	MIS-C, renal failure, coagulation disorder
5 yr	F	Positive Positive	3	1	Systolic BP, 83 mm Hg; SaO ₂ , 98%; BE, -0.7 mmol/liter	—	MIS-C
7 yr¶	M	Negative ND	<1	1	Systolic BP, 85 mm Hg, SaO ₂ , 97%; BE, -0.7 mmol/liter	—	Iron deficiency, coma, fever
7 yr	F	Positive Positive	35	2	Systolic BP, 115 mm Hg; SaO ₂ , 90%; lactate, 0.8; BE, +5 mmol/liter	Invasive mechanical ventilation, renal replacement therapy	—
10 yr§	F	Negative Positive	1	1	Systolic BP, 95 mm Hg; SaO ₂ , 99%; lactate, 1.1 mmol/liter; BE, -1.5 mmol/liter	—	MIS-C, cardiomyopathy
12 yr	M	Positive ND	<1	1	Systolic BP, 100 mm Hg; SaO ₂ , 98%; BE, -6 mmol/liter	—	—
12 yr	M	Positive ND	2	1	—	—	Viral pneumonia
13 yr	M	Positive ND	11	2	Systolic BP, 123 to 137 mm Hg; SaO ₂ , 92%; lactate, 0.9 mmol/liter; BE, +3.2 mmol/liter	—	—
13 yr	F	Positive Positive	7	2	Systolic BP, 80 mm Hg; SaO ₂ , 98%; lactate, 3.7 mmol/liter; BE, -9 mmol/liter	Invasive mechanical ventilation	MIS-C, heart failure
14 yr§	M	Negative Positive	4	1	Systolic BP, 57 mm Hg; SaO ₂ , 98%; lactate, 3.4 mmol/liter; BE, -1.5 mmol/liter	—	MIS-C, myocarditis, sepsis
14 yr	M	Positive ND	4	2	Systolic BP, 90 to 100 mm Hg; SaO ₂ , 83%; lactate, 2.7 mmol/liter; BE, +4 mmol/liter	Invasive mechanical ventilation	—
16 yr	M	Positive Positive	9	1	—	—	—
16 yr¶	M	Negative Positive	5	1	—	—	MIS-C, myocarditis with heart failure

*Four children had underlying conditions: 2 had cancer, 1 had chronic kidney disease, and 1 had hematologic disease and had undergone stem-cell transplantation. Two children had additional conditions: 1 had alcohol intoxication, and 1 had sustained a traumatic injury; coronavirus disease 2019 (Covid-19) was diagnosed in these 2 children only when they underwent screening for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the intensive care unit (ICU) (they did not have Covid-19 symptoms). BE denotes base excess, BP blood pressure, MIS-C multisystem inflammatory syndrome in children, ND not done, PCR polymerase chain reaction, and SaO₂ oxygen saturation.

†For patients with multiple admissions, the total duration is reported.

‡For patients with multiple admissions, the most aberrant value is reported.

§The patient was identified through the presence of MIS-C according to the Swedish Pediatric Rheumatology Quality Register.

Covid-19 was not diagnosed during ICU care, but the results of subsequent antibody testing were positive.

¶Covid-19 was diagnosed clinically (i.e., SARS-CoV-2 was not detected during the ICU admission).

CHARACTERISTICS OF SARS-COV-2 TRANSMISSION AMONG MEAT PROCESSING WORKERS IN NEBRASKA, USA, AND EFFECTIVENESS OF RISK MITIGATION MEASURES

Herstein JJ, Degarege A, Stover D, Austin C, Schwedhelm MM, Lawler JV, Lowe JJ, Ramos AK, Donahue M.. Emerg Infect Dis. 2021 Feb 16;27(4). doi: 10.3201/eid2704.204800. Online ahead of print.

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

BLUF

Epidemiologists from the University of Nebraska Medical Center and Nebraska Department of Health and Human Services evaluated SARS-CoV2 transmission among meat-processing workers in Nebraska who were noted to be subject to a disproportionate high attack rates (19%) between April 1 and July 31, 2020. They found 8/13 facilities had a statistically significant reduction in SARS-CoV-2 incidence within 10 days of implementing universal masking and physical barrier interventions (Tables 2, 3). Authors suggest that interventions such as multilayered infection prevention strategies, rapid contact tracing, and accessible testing can mitigate the disproportionately high risk of transmission in this population.

ABSTRACT

The coronavirus disease (COVID-19) pandemic has severely impacted the meat processing industry in the United States. We sought to detail demographics and outcomes of severe acute respiratory syndrome coronavirus 2 infections among workers in Nebraska meat processing facilities and determine the effects of initiating universal mask policies and installing physical barriers at 13 meat processing facilities. During April 1-July 31, 2020, COVID-19 was diagnosed in 5,002 Nebraska meat processing workers (attack rate 19%). After initiating both universal masking and physical barrier interventions, 8/13 facilities showed a statistically significant reduction in COVID-19 incidence in <10 days. Characteristics and incidence of confirmed cases aligned with many nationwide trends becoming apparent during this pandemic: specifically, high attack rates among meat processing industry workers, disproportionately high risk of adverse outcomes among ethnic and racial minority groups and men, and effectiveness of using multiple prevention and control interventions to reduce disease transmission.

FIGURES

Table 2

Comparisons of the incidence of severe acute respiratory syndrome coronavirus 2 infection before and after mask or physical barrier interventions or both among employees in 13 meatpacking facilities in Nebraska, April–July 2020*

Facility	Incidence /1,000 persons /d		
	<10 d after final intervention	10 d after final intervention	p value for difference
Facilities that initiated a universal mask policy ≥ 10 d before physical barriers			
A	7.27	0.33	<0.001
B	3.21	0.69	<0.001
C	3.46	0.27	<0.001
D	3.64	0.15	0.072
E	0.48	2.09	0.008
Facilities that initiated a universal mask policy and physical barriers <10 d of each other			
F	17.16	0.58	<0.001
G	2.49	1.27	0.002
H	4.08	0.78	<0.001
I	6.82	1.40	<0.001
J	2.19	0.059	<0.001
K	0.65	1.90	0.180
Facilities that only initiated a universal mask policy			
L	3.2	2.87	0.745
M	3.29	3.178	0.944

*For facilities that initiated both a universal mask policy and physical barriers, date of last intervention was defined as start date of latter intervention (i.e., if physical barriers were initiated first, final intervention date was date of mask policy initiation). For facilities that initiated only masking, final intervention date was the initiation date.

Table 3

Comparisons of the incidence of severe acute respiratory syndrome coronavirus 2 infection among meat processing workers before mask intervention, between mask and physical barrier intervention, and after physical barrier intervention in meatpacking facilities, Nebraska, April–July 2020

Facility	Incidence /1,000 persons /d			p value for difference*
	<10 d after mask intervention	Between day 10 after mask and day 10 after physical barrier intervention	>10 d after physical intervention	
A	3.46	3.23	0.26	<0.001
B	11.13	42.2	0.58	<0.001
C	2.63	0.26	0.32	<0.001

*p value difference represents difference in incidence before initiation of mask intervention and after physical barrier intervention.

PREVENTION IN THE HOSPITAL

ABDOMINAL AND TESTICULAR PAIN: AN ATYPICAL PRESENTATION OF COVID-19

Kim J, Thomsen T, Sell N, Goldsmith AJ.. Am J Emerg Med. 2020 Jul;38(7):1542.e1-1542.e3. doi: 10.1016/j.ajem.2020.03.052. Epub 2020 Mar 31.

Level of Evidence: 5 - Case Report

BLUF

Researchers associated with Harvard Medical School present a case study of a 42-year-old man presenting with abdominal, testicular, and back pain who was diagnosed with pneumonia and colitis of the sigmoid and distal descending colon via CT. He was treated with cefpodoxime and azithromycin for both of these conditions. Two days later, he tested positive for COVID-19 meaning he potentially exposed over 25 patients and healthcare workers who were not wearing PPE during his initial ED visit due to the lack of respiratory symptoms. The authors recommend consideration of full PPE in case of atypical COVID-19 presentations.

ABSTRACT

The outbreak of a novel coronavirus disease (COVID-19) has been of concern to health care workers (HCW's) in the emergency department (ED) due to potential exposure and transmission. This case report describes a man who was referred to the ED for abdominal and testicular pain who was subsequently found to test positive for COVID-19. Due to the lack of respiratory symptoms, proper protective equipment (PPE) was not donned, and it led to several patients and health care workers being exposed. Given recent new descriptions of patients who present atypically, full PPE for all patients may be considered as community spread increases.

ADJUSTING PRACTICE DURING COVID-19

PEDIATRICS

IMPACT OF COVID-19 ON SERUM MELATONIN LEVELS AND SLEEP PARAMETERS IN CHILDREN

Yayıcı Köken Ö, Gültutan P, Güngören MS, Bayhan GI, Yilmaz D, Gürkaş E, Özyürek H, Çitak Kurt AN.. Turk J Med Sci. 2021 Apr 12. doi: 10.3906/sag-2012-361. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Pediatricians of Ankara City Hospital (Turkey) conducted a cross-sectional study to compare the melatonin level of 106 children, ages 6-16 years old, who had been admitted between June to August of 2020 with the diagnosis either non-COVID-19 upper respiratory infection (n=26) or mild to moderate COVID-19 (cases, n=80). They additionally evaluated the impact of COVID-19 on sleep patterns for two specific time frames for comparison (last week of disease onset and six months before disease onset) using the Sleep Disturbance Scale for Children (SDSC) questionnaire. They did not find any statistically significant difference in median melatonin levels between the 2 groups ($p=0.16$, Table 1), and there was no appreciable relationship between disease and changes in sleep pattern ($p=0.99$, Appendix). Authors suggested that there is no association between COVID-19 and melatonin or sleep pattern change in children.

ABSTRACT

BACKGROUND/AIM: This study aimed to analyze the serum melatonin levels and changes in sleep patterns in pediatric patients with coronavirus disease 2019 (COVID-19). **MATERIALS AND METHODS:** This study was designed as a descriptive, cross-sectional study. Serum melatonin levels and sleep parameters of children with the diagnosis of COVID-19 who had mild and moderate disease (i.e., COVID-19 group) were compared with those of children admitted with non-COVID-19 non-specific upper respiratory tract infection (i.e., control group). The Sleep Disturbance Scale for Children (SDSC) questionnaire was applied to the participants' primary caregivers to analyze their sleep patterns at present and six months before symptom onset and to investigate the impact of COVID-19 on sleep patterns. **RESULTS:** The entire study cohort consisted of 106 patients. The COVID-19 group included 80 patients, while the control group consisted of 26 patients. The mean serum melatonin levels were 136.72 pg/mL and 172.63 pg/mL in the COVID-19 and control groups, respectively ($p=0.16$). There was no significant difference between the groups in terms of 6 subcategories of the SDSC questionnaire regarding the present time and six months before symptom onset. The total SDSC scores were also similar in two different evaluation time points described above ($p=0.99$). **CONCLUSIONS:** We conclude that COVID-19 did not impact the sleep parameters of children. Serum melatonin levels of all patients were higher than the reference range; however, they were higher in the non-COVID-19 patient group than the COVID-19 group. Since serum melatonin levels were higher than the reference values in children with COVID-19, and this disease is significantly less morbid in children, melatonin may have protective effects against COVID-19.

FIGURES

		COVID-19-positive (n: 58)	COVID-19-negative (n: 26)	P-value
Gender (n,%)	Male	34 (58.6%)	20 (76.9%)	0.11
	Female	24 (41.4%)	6 (23.1%)	
Age (mo, mean± SD)		156.42 ± 42.33	155.12 ± 38.30	0.13
Serum Melatonin (pg/ml,median,min-max)		136.72 (48.09 – 1217.13)	172.63 (59.16 – 1171.09)	0.16

Table 1. Age, gender, and serum melatonin levels of the participants

	COVID-19-positive (n: 65)	COVID-19- negative (n: 20)	P-value
SDSC where the sleep features of the last week of infection were evaluated			
Disorders of initiating and maintaining sleep	9 (7–16)	8 (7–15)	0.992
Sleep-wake transition disorders	4 (3–8)	4 (4–8)	0.829
Sleep breathing disorders	3 (3–9)	3 (3–7)	0.350
Sleep hyperhidrosis	2 (2–7)	2 (1–4)	0.583
Disorders of excessive somnolence	5 (4–8)	5 (5–13)	0.956
Disorders of arousal	3 (3–7)	3 (3–7)	0.451
SDSC where the sleep features at 6 months prior to onset were evaluated			
Disorders of initiating and maintaining sleep	9 (7–17)	10.5 (7–17)	0.109
Sleep-wake transition disorders	4 (3–9)	4 (4–8)	0.618
Sleep breathing disorders	3 (3–9)	3 (3–7)	0.654
Sleep hyperhidrosis	2 (2–7)	2 (1–5)	0.685
Disorders of excessive somnolence	5 (4–13)	5 (5–13)	0.405
Disorders of arousal	3 (3–8)	3 (3–7)	0.698

Appendix SDSC scores of the participants at 6 months prior to onset and the last week of infection

R&D: DIAGNOSIS & TREATMENTS

DEVELOPMENTS IN DIAGNOSTICS

ARE SNIFFER DOGS A RELIABLE APPROACH FOR DIAGNOSING SARS-COV-2 INFECTION?

Lippi G, Mattuzzi C, Henry BM.. Diagnosis (Berl). 2021 Apr 20. doi: 10.1515/dx-2021-0034. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

A biochemist, public health expert, and pediatric intensivist from the University of Verona and Cincinnati Children's Hospital performed a critical review and pooled analysis of three studies analyzing the efficacy of dogs trained to identify patients infected with SARS-CoV-2. In 17 dogs, the diagnostic sensitivity was 0.88 (95% CI, 0.84–0.91; I₂, 85.3%) - above that of tested nasopharyngeal swab samples seen in some other studies - and specificity was 0.99 (95% CI, 0.99–0.99; I₂, 97.4%) (Figure 1). Due to the time needed to train the dogs, the dependency on the state of the dog, and potentially confounding odors from comorbidities, authors suggest the use of dogs should be further investigated at a larger scale to better determine its practical applications for SARS-CoV-2 testing.

SUMMARY

For all included studies nucleic acid amplification testing was the reference technique to define positivity for sensitivity/specificity calculations.

ABSTRACT

OBJECTIVES: Despite inter-individual variations in their diagnostic efficiency, dogs have been trained to investigate many human pathologies, especially cancer, diabetes, migraine, seizures and even infectious diseases. To this end, we performed a critical review and pooled analysis of current scientific literature on the performance of dogs trained for identifying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive human specimens. **METHODS:** We carried out an electronic search in PubMed, Scopus and Web of Science with the keywords "dog(s)" AND "sniffer" OR "scent" OR "smell" AND "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus disease 2019" OR "COVID-19" within all fields, without date or language restrictions, to identify studies describing dogs' performance for identifying SARS-CoV-2 infected material. **RESULTS:** Three studies could be finally included in pooled analysis, totaling 17 dogs (47% females), aged between 0.5 and 12 years. The pooled diagnostic sensitivity was 0.88 (95% CI, 0.84–0.91; I₂, 85.3%), the diagnostic specificity 0.99 (95% CI, 0.99–0.99; I₂, 97.4%), whilst the area under the summary receiver operating characteristic curve (SROC) was 0.979 (standard error, 0.003). **CONCLUSIONS:** The notable performance observed in this pooled analysis would persuade us to suggest that adequately trained dogs could represent an intriguing and sustainable resource for purposes of rapid SARS-CoV-2 mass screening.

FIGURES

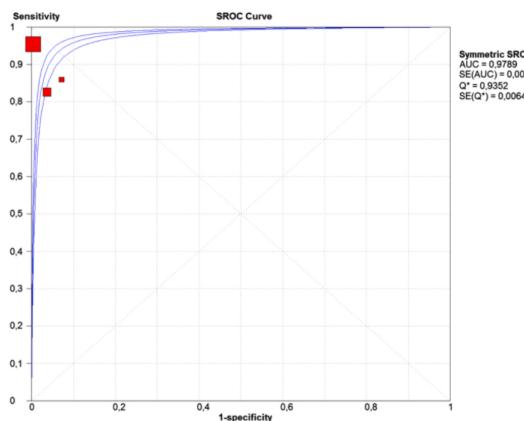


Figure 1. Pooled diagnostic sensitivity, specificity and accuracy (summary receiver operating characteristic curve; SROC) of dogs trained to identify severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in human samples.

DEVELOPMENTS IN TREATMENTS

IN VITRO ANTIVIRAL ACTIVITY OF THE ANTI-HCV DRUGS DACLATASVIR AND SOFOSBUVIR AGAINST SARS-COV-2, THE AETIOLOGICAL AGENT OF COVID-19

Sacramento CQ, Fintelman-Rodrigues N, Temerozo JR, Da Silva APD, Dias SDSG, da Silva CDS, Ferreira AC, Mattos M, Pão CRR, de Freitas CS, Soares VC, Hoelz LVB, Fernandes TVA, Branco FSC, Bastos MM, Boechat N, Saraiva FB, Ferreira MA, Jockusch S, Wang X, Tao C, Chien M, Xie W, Patel D, Garzia A, Tuschl T, Russo JJ, Rajoli RKR, Pedrosa CSG, Vitória G, Souza LRQ, Goto-Silva L, Guimarães MZ, Rehen SK, Owen A, Bozza FA, Bou-Habib DC, Ju J, Bozza PT, Souza TML.. *J Antimicrob Chemother.* 2021 Apr 21:dkab072. doi: 10.1093/jac/dkab072. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Immunologists and pharmacologists from Instituto Oswaldo Cruz and National Institute for Science and Technology on Innovation in Diseases of Neglected Populations in Brazil, among others, conducted an in vitro, cell-based analysis of daclatasvir and sofosbuvir against SARS-CoV-2. Daclatasvir inhibited replication of the virus in Vero, HuH-7 and Calu-3 cells, with potencies of 0.8, 0.6 and 1.1 μM, respectively (Table 1), while Sofosbuvir was only effective at inhibiting apoptosis and RNA synthesis in combination with Daclatasvir (Figure 4). Authors suggest daclatasvir may be useful in the treatment of COVID-19 and recommend human studies to investigate its real-life effects and dosing.

ABSTRACT

BACKGROUND: Current approaches of drug repurposing against COVID-19 have not proven overwhelmingly successful and the SARS-CoV-2 pandemic continues to cause major global mortality. SARS-CoV-2 nsp12, its RNA polymerase, shares homology in the nucleotide uptake channel with the HCV orthologue enzyme NS5B. Besides, HCV enzyme NS5A has pleiotropic activities, such as RNA binding, that are shared with various SARS-CoV-2 proteins. Thus, anti-HCV NS5B and NS5A inhibitors, like sofosbuvir and daclatasvir, respectively, could be endowed with anti-SARS-CoV-2 activity. **METHODS:** SARS-CoV-2-infected Vero cells, HuH-7 cells, Calu-3 cells, neural stem cells and monocytes were used to investigate the effects of daclatasvir and sofosbuvir. In silico and cell-free based assays were performed with SARS-CoV-2 RNA and nsp12 to better comprehend the mechanism of inhibition of the investigated compounds. A physiologically based pharmacokinetic model was generated to estimate daclatasvir's dose and schedule to maximize the probability of success for COVID-19. **RESULTS:** Daclatasvir inhibited SARS-CoV-2 replication in Vero, HuH-7 and Calu-3 cells, with potencies of 0.8, 0.6 and 1.1 μM, respectively. Although less potent than daclatasvir, sofosbuvir alone and combined with daclatasvir inhibited replication in Calu-3 cells. Sofosbuvir and daclatasvir prevented virus-induced neuronal apoptosis and release of cytokine storm-related inflammatory mediators, respectively. Sofosbuvir inhibited RNA synthesis by chain termination and daclatasvir targeted the folding of secondary RNA structures in the SARS-CoV-2 genome. Concentrations required for partial daclatasvir in vitro activity are achieved in plasma at Cmax after administration of the approved dose to humans. **CONCLUSIONS:** Daclatasvir, alone or in combination with sofosbuvir, at higher doses than used against HCV, may be further fostered as an anti-COVID-19 therapy.

FIGURES

Table 1. Pharmacological parameters of SARS-CoV-2-infected cells in the presence of daclatasvir and sofosbuvir

Drugs	Vero			HuH-7			Calu-3		
	EC ₅₀ (μM)	CC ₅₀ (μM)	SI	EC ₅₀ (μM)	CC ₅₀ (μM)	SI	EC ₅₀ (μM)	CC ₅₀ (μM)	SI
DCV	0.8±0.3	31±8	39	0.6±0.2	28±5	47	1.1±0.3	38±5	34
SFV	>10	360±43	ND	5.1±0.8	381±34	74	7.3±0.5	512±34	70
SFV/DCV (1:0.15)	ND	ND	ND	ND	ND	ND	0.7±0.2 ^a	389±12	555
SFV/DCV (1:1)	ND	ND	ND	ND	ND	ND	0.5±0.1 ^a	389±10	778
GS-331007	>10	512±24	ND	>10	421±18	ND	9.3±0.2	630±34	68
RBV	ND	ND	ND	6.5±1.3	142±12	13	7.1±0.5	160	16
CQ	1.3±0.4	268±23	206	ND	ND	ND	ND	ND	ND
LPV/RTV	5.3±0.5	291±32	54	2.9±0.2	328±16	113	8.2±0.3	256±17	31

DCV, daclatasvir; SFV, sofosbuvir; GS-331007, sofosbuvir's nucleoside; RBV, ribavirin; CQ, chloroquine; LPV/RTV, lopinavir/ritonavir; ND, not determined.

^aP<0.05 comparing sofosbuvir/daclatasvir combination with sofosbuvir alone.

Table 1. Pharmacological parameters of SARS-CoV-2-infected cells in the presence of daclatasvir and sofosbuvir

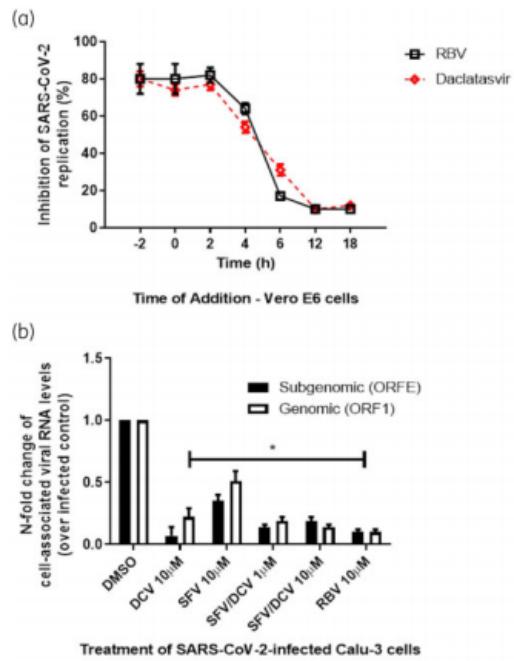


Figure 4. Daclatasvir and sofosbuvir reduced SARS-CoV-2-associated RNA synthesis. (a) To initially understand the temporal pattern of inhibition promoted by daclatasvir, we performed time-of-addition assays. Vero cells were infected with an MOI of 0.01 of SARS-CoV-2 and treated with daclatasvir or ribavirin (RBV) at 2 times their EC50 values at different times after infection, as indicated; 24 h post-infection, culture supernatant was harvested and SARS-CoV-2 replication was measured by plaque assay. (b) Next, Calu-3 cells (5% 105 cells/well in 48-well plates) were infected with SARS-CoV-2 at an MOI of 0.1, for 1 h at 37C. An inoculum was removed and cells were washed and incubated with fresh DMEM containing 2% FBS and the indicated concentration of daclatasvir (DCV), sofosbuvir (SFV), sofosbuvir/ daclatasvir (SFV/DCV) (proportion of 1:0.15) or ribavirin (RBV). After 48 h, cell monolayers were lysed, total RNA extracted and quantitative RT-PCR performed for detection of ORF1 and ORFE mRNA. The data represent means±SEM of three independent experiments. *P< 0.05 for comparisons with vehicle (DMSO). #P< 0.05 for differences in genomic and sub-genomic RNA. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

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