

The Daily COVID-19 Literature Surveillance Summary

February 17, 2021



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Daily audio summaries of the literature in 10 minutes or less.

<https://www.covid19lst.org/podcast/>



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

Climate

- [Neurologists from AOU Mater Domini - Magna Græcia University in Italy](#) distributed a self-administered questionnaire to healthcare providers assessing facemask associated headaches. They found 26.5% (44/166) without a previous headache disorder (NHG) reported a de novo headache disorder, and that those with pre-existing migraine or tension-type headache endorsed more frequent headaches during a 4 month time frame (T0 to T1) (37.2% [51/137] and 21.3% [17/80], respectively). There was no association between duration of mask use and headache symptoms. Authors suggest wearing protective face masks may contribute to the development or worsening of headache disorders in healthcare workers, though there are a number of other potential contributing factors.

Management

- A letter to the editor from the [department of Dermatology and Venereology, Bispebjerg Hospital](#) in Copenhagen, Denmark specifies the European Task Force on Atopic Dermatitis' (ETFAD) position on COVID-19 vaccine administration in patients with atopic dermatitis (AD) being treated with systemic immuno-suppressive medication and biologics. The ETFAD state vaccines currently in use are not contraindicated in patients with AD as they do not suspect worsening of AD symptoms with its use. Although there is no clear evidence to recommend suspension of systemic AD medication before vaccine administration, the authors advise physicians to consider pausing immunosuppressants beforehand to improve the chances of vaccine response.
- Pharmacists and pediatric infectious disease physicians from 20 North American institutions [offer guidance on the use of antivirals in the setting of pediatric COVID-19 infection](#). They recommend using remdesivir only for severely or critically ill children and supportive care alone for mild cases, which compromise the majority of pediatric COVID-19. The authors stress that most pediatric patients do not need antiviral therapy and suggest their guidelines will assist in clinical decision making regarding their use.

R&D: Diagnosis & Treatments

- [A letter to the editor from University of Miami physicians](#) highlights the limitations of Lanser et al.'s 2020 article evaluating the clinical utility and sensitivity of SARS-CoV-2 antigen testing in relation to RT-PCR cycle threshold (Ct) values. Some of the limitations outlined include unreported statistical comparisons of the antigen test results for test subjects with Ct above or below 33 and no reported data regarding antigen test results in patients with negative RT-PCR swabs. With this letter, the authors hope to correctly assess a plausible correlation between antigen test results and Ct in order to properly inform infection control and public health policies.

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INCREASED DENGUE TRANSMISSIONS IN SINGAPORE ATTRIBUTABLE TO SARS-COV-2 SOCIAL DISTANCING MEASURES

Lim JT, Chew LZ, Choo ELW, Dickens BSL, Ong J, Aik J, Ng LC, Cook AR. J Infect Dis. 2021 Feb 13;223(3):399-402. doi: 10.1093/infdis/jiaa619.

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

BLUF

A retrospective study conducted at the National University of Singapore and National University Health System during early 2021 by the Saw Swee Hock School of Public Health found that, when analyzing weekly national case counts of Dengue transmissions, and while controlling for confounders, social distancing appears to increase the transmission of Dengue (Table 1), suggesting more time spent at home increases exposure to infected surfaces.

SUMMARY

- The Social Distancing Policy's effect on transmission of Dengue, though intended solely for COVID-19, is being analyzed using weekly case counts from 2003 to 2020.

- Compared to baseline, there was a 37.2% increase (95% CI, 19.9%–49.8%) in Dengue cases for those undergoing social distancing compared to those in control groups

- The equation used to calculate the difference took into account other factors which may have affected Dengue transmission with regards to public policy.

- one potential confounding effect is the lower immunity of Singapore's citizens to past novel serotype switches of the Dengue virus (DENV-1 and DENV-2).

- Future work must study what potential effects would result from exiting the SD policy with regards to Dengue transmission.

ABSTRACT

Social distancing (SD) measures aimed at curbing the spread of SARS-CoV-2 remain an important public health intervention. Little is known about the collateral impact of reduced mobility on the risk of other communicable diseases. We used pre-post differences in dengue case counts and exploited heterogeneity in SD treatment effects among different age groups in Singapore to identify the spillover effects of SD measures. SD policy caused an increased in over 37.2% of dengue cases from baseline. Additional measures to pre-emptively mitigate the risk of other communicable diseases must be considered before the implementation/re-implementation of SARS-CoV-2 SD measures.

FIGURES

Table 1.

Differences-in-Differences Specification Estimated Using Ordinary Least Squares

Dependent Variable: Weekly Reported Cases						
	(1)	(2)	(3)	(4)	(5)	(6)
Treatment effect, δ	15.865*	16.512*	15.692*	8.785*	6.612*	9.873*
Lower bound, 95% CI	12.761	12.452	12.452	5.456	4.256	7.528
Upper bound, 95% CI	18.969	19.703	18.932	12.115	8.967	12.219
No. of observations	2776	2776	2776	2776	2776	2776

Differences-in-Differences Specification Estimated Using Ordinary Least Squares

FACEMASK HEADACHE: A NEW NOSOGRAPHIC ENTITY AMONG HEALTHCARE PROVIDERS IN COVID-19 ERA

Rapisarda L, Trimboli M, Fortunato F, De Martino A, Marsico O, Demonte G, Augimeri A, Labate A, Gambardella A.. *Neurol Sci.* 2021 Jan 27. doi: 10.1007/s10072-021-05075-8. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Neurologists from AOU Mater Domini - Magna Græcia University in Italy distributed a self-administered questionnaire to healthcare providers assessing facemask associated headaches (Figure 1, Table 1). They found 26.5% (44/166) without a previous headache disorder (NHG) reported a de novo headache disorder, and that those with pre-existing migraine or tension-type headache endorsed more frequent headaches during a 4 month time frame (T0 to T1) (37.2% [51/137] and 21.3% [17/80], respectively). There was no association between duration of mask use and headache symptoms (Table 2). Authors suggest wearing protective face masks may contribute to the development or worsening of headache disorders in healthcare workers, though there are a number of other potential contributing factors.

ABSTRACT

BACKGROUND: SARS-CoV-2 is a novel infectious agent causing coronavirus disease 2019, which has been declared as pandemic in March 2020. Personal protective equipment has been mandatory for healthcare workers in order to contain the outbreak of pandemic disease. Mild neurological disturbances such as headache have been related to the extensive utilization of facemask. This study aims to examine headache variations related to the intensive utilization of facemask among a cohort of healthcare professionals in a setting of low-medium risk of exposure to SARS-CoV-2. **METHODS:** This is a cross-sectional study among healthcare providers from different hospital and clinics in Italy. Each participant completed a specifically designed self-administered questionnaire. Headache features and outcome measures' change from baseline were evaluated over a 4-month period, in which wearing facemask has become mandatory for Italian healthcare workers. **RESULTS:** A total of 400 healthcare providers completed the questionnaire, 383 of them met the inclusion criteria. The majority were doctors, with a mean age of 33.4 ± 9.2 years old. Among 166/383 subjects, who were headache free at baseline, 44 (26.5%) developed de novo headache. Furthermore, 217/383 reported a previous diagnosis of primary headache disorder: 137 were affected by migraine and 80 had tension-type headache. A proportion (31.3%) of these primary headache sufferers experienced worsening of their pre-existing headache disorder, mainly for migraine frequency and attack mean duration. **CONCLUSIONS:** Our data showed the appearance of de novo associated facemask headache in previous headache-free subjects and an exacerbation of pre-existing primary headache disorders, mostly experienced by people with migraine disease.

Fig. 1

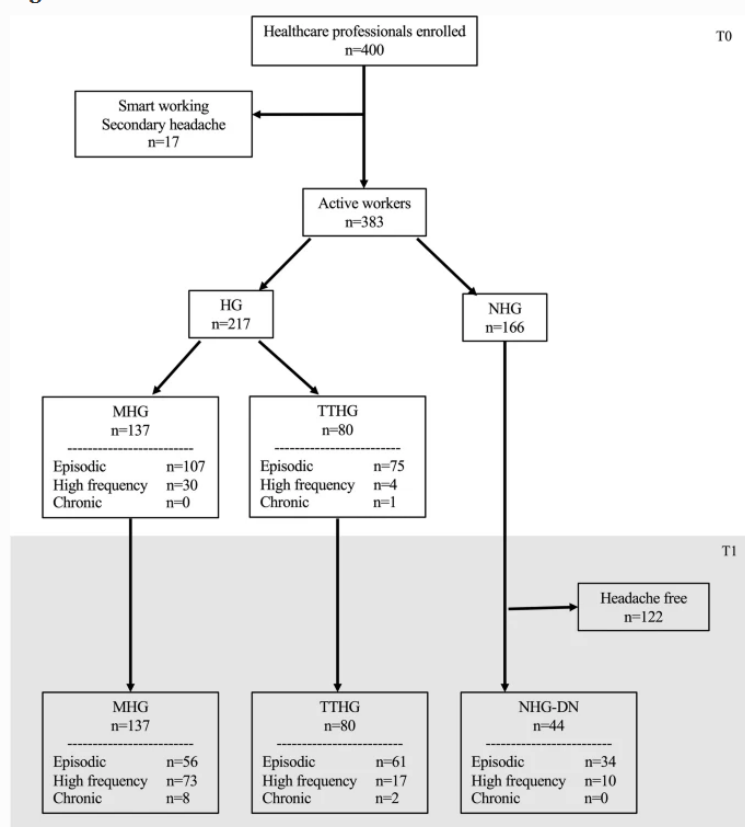


Figure 1. Flowchart of the assessment of 400 participants. HG, headache group; MHG, migraine-headache group; NHG, non-headache group; NHG-DN, non-headache group–de novo headache sufferers; TTHG, tension-type headache group. Headache frequency: (1) episodic: HD 1–4/month; (2) high frequency: HD 5–14/month; (3) chronic: HD ≥ 15/month

Table 1 Demographic features of 383 participants

From: [Facemask headache: a new nosographic entity among healthcare providers in COVID-19 era](#)

	Total (383)	NHG (166)	HG (217)	p value
Gender M/F	134/249	87/79	47/170	< 0.001
Age, years	33.4 ± 9.2	34.8 ± 10.9	32.2 ± 7.6	0.428
Healthcare professionals				
Doctors	299 (78.1%)	122 (73.5%)	177 (81.6%)	N/A
Nurses	42 (11.0%)	24 (14.5%)	18 (8.3%)	
Healthcare assistants	12 (3.1%)	10 (6.0%)	2 (0.9%)	
Technicians	23 (6.0%)	7 (4.2%)	16 (7.4%)	
Other paramedical staff	7 (1.8%)	3 (1.8%)	4 (1.8%)	
Weekly work hours				
< 20 h weekly	9 (2.3%)	1 (0.6%)	8 (3.7%)	0.653
20–38 h weekly	157 (41.0%)	70 (41.9%)	87 (40.1%)	
> 38 h weekly	217 (56.7%)	95 (57.5%)	122 (56.2%)	
Daily hours with facemask				
0–2 h a day	5 (1.3%)	2 (1.2%)	3 (1.4%)	0.566
2–4 h a day	19 (5.0%)	12 (7.2%)	7 (3.2%)	
4–6 h a day	50 (13.0%)	22 (13.3%)	28 (12.9%)	
6–8 h a day	124 (32.4%)	50 (30.1%)	74 (34.1%)	
8–10 h a day	95 (24.8%)	41 (24.7%)	54 (24.9%)	
10–12 h a day	68 (17.8%)	32 (19.3%)	36 (16.6%)	
> 12 h a day	22 (5.7%)	7 (4.2%)	15 (6.9%)	
Type of facemask				
Surgical facemask	284 (74.2%)	123 (74.1%)	161 (74.2%)	0.544
N95 facemask	96 (25%)	42 (25.3%)	54 (24.9%)	
Other type of facemask	3 (0.8%)	1 (0.6%)	2 (0.9%)	
Type of elastic head straps				
Occipital	41 (10.7%)	27 (16.3%)	14 (6.5%)	0.007
Pre-auricular	342 (89.3%)	139 (83.7%)	203 (93.5%)	

F female, M male, MHG migraine headache group, N/A not applicable, NHG non-headache group

Table 1 Demographic features of 383 participants

Table 2 Clinical features of pre-existing primary headache groups' (MHG and TTHG) subjects at T0–T1, and non-headache group–de novo (NHG-DN) subjects at T1

From: [Facemask headache: a new nosographic entity among healthcare providers in COVID-19 era](#)

	MHG (137)			TTHG (80)			NHG-DN (44)		[§] p value
	T0	T1	p value	T0	T1	p value	T1		
Headache days	3.5 ± 2.4	5.5 ± 4.5	< 0.001	2.3 ± 1.9	3.3 ± 3.4	0.167	3.5 ± 2.6		< 0.001
Headache frequency									
Episodic (1–4 days/month)	107 (78.1%)	56 (40.9%)	< 0.001	75 (93.7%)	61 (76.2%)	0.036	34 (77.3%)		0.001
High frequency (5–14 days/month)	30 (21.9%)	73 (53.3%)		4 (5.0%)	17 (21.2%)		10 (22.7%)		
Chronic (≥ 15 days/month)	0	8 (5.8%)		1 (1.3%)	2 (2.5%)		0		
Migraine days	2.5 ± 1.8	3.9 ± 3.9	0.650	0	0	N/A	0		< 0.001
Migraine-like days	N/A	N/A	N/A	0	0.6 ± 2.6	< 0.001	1.0 ± 1.5		< 0.001
Attack mean duration									
<12 h	89 (64.9%)	65 (47.4%)	0.002	60 (75.0%)	56 (70.0%)	0.287	35 (79.5%)		0.003
12–24 h	37 (27.0%)	52 (38.0%)		13 (16.2%)	17 (21.2%)		8 (18.2%)		
24–48 h	6 (4.4%)	11 (8.0%)		6 (7.5%)	5 (6.2%)		1 (2.3%)		
48–72 h	5 (3.6%)	6 (4.4%)		1 (1.3%)	1 (1.3%)		0		
> 72 h	0	3 (2.2%)		0	1 (1.3%)		0		
Average headache severity	6.0 ± 1.8	6.6 ± 1.7	0.021	5.2 ± 1.8	4.9 ± 2.3	0.717	5.8 ± 1.5		< 0.001
Allodynia (n. subjects)	58 (32.7%)	70 (40.1%)	0.182	13 (16.2%)	17 (21.2%)	0.543	17 (38.6%)		< 0.001
ASC-12	3.0 ± 3.7	2.8 ± 3.8	0.171	1.0 ± 1.9	1.3 ± 2.5	0.810	2.1 ± 2.1		< 0.001
Discomfort for elastic head straps	N/A	64 (46.7%)	N/A	N/A	22 (27.5%)	N/A	26 (59.1%)		< 0.001
HIT-6	59.1 ± 8.6	62.2 ± 8.4	0.004	51.7 ± 8.0	54.9 ± 10.0	0.010	58.5 ± 8.9		< 0.001
Pain killer use									
NSAIDS									
0 per month	19 (13.9)	16 (11.7%)	0.053	12 (15%)	20 (25%)	0.955	19 (43.4%)		< 0.001
1–9 per month	115 (83.9%)	109 (79.6%)		68 (85.0%)	56 (70.0%)		24 (54.5%)		
10–14 per month	3 (2.2%)	11 (8.0%)		0	3 (3.7%)		1 (2.3%)		
≥ 15 per month	0	1 (0.7%)		0	1 (1.2%)		0		
Triptans									
0 per month	130 (94.9%)	115 (83.9%)	0.003	79 (98.7%)	79 (98.7%)	0.663	43 (87.7%)		0.006
1–9 per month	5 (3.6%)	12 (8.8%)		1 (1.3%)	1 (1.3%)		1 (2.3%)		
≥ 10 per month	2 (1.5%)	10 (7.3%)		0	0		0		
Other									
0 per month	125 (91.2%)	120 (87.6%)	0.225	77 (96.2%)	76 (95%)	0.387	39 (88.6%)		0.072
1–9 per month	10 (7.3%)	8 (5.8%)		3 (3.8%)	4 (5.0%)		5 (11.4%)		
10–14 per month	0	2 (1.5%)		0	0		0		
≥ 15 per month	2 (1.5%)	7 (5.1%)		0	0		0		
Preventive treatment	9 (6.6%)	11 (8.0%)	0.817	0	2 (3.8%)	0.229	1 (2.3%)		0.117
Impact of facemask on headache	N/A	5.1 ± 3.1	N/A	N/A	3.8 ± 3.2	N/A	6.5 ± 2.7		0.005

[§]p value: MHG vs TTHG vs NHG-DN at T1. ASC-12, 12-item allodynia symptom checklist; MHG migraine headache group, N/A not applicable, NHG-DN non-headache group–de novo, NSAIDS non-steroidal anti-inflammatory drugs, TTHG tension-type headache group

Table 2 Clinical features of pre-existing primary headache groups' (MHG and TTHG) subjects at T0–T1, and non-headache group–de novo (NHG-DN) subjects at T1

ADULTS

MULTIPLEXED ANALYSIS OF CIRCULATING IGA ANTIBODIES FOR SARS-COV-2 AND COMMON RESPIRATORY PATHOGENS IN COVID-19 PATIENTS

Fang ZF, Sun BQ, Zhu AR, Lin LC, Zhao JC, He S, Huang SK, Zhong NS, Liu ZG.. J Med Virol. 2021 Jan 28. doi: 10.1002/jmv.26829. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Chinese respiratory disease experts evaluated serum samples from 42 patients positive for SARS-CoV-2 via RT-PCR (Table 1) for the presence of IgA for SARS-CoV-2 and other respiratory pathogens between January 26 and February 25, 2020 (see summary). They found patients with severe disease were more likely to have IgA for both SARS-CoV-2 and at least one other pathogen compared to those with milder disease (72.2% vs. 46.2%, $p=0.014$), but there was no difference in SARS-CoV-2 IgA detection between the groups (90.0% vs. 77.3%, $p=0.269$) (Table 2). Authors suggest serological testing of pathogen specific IgAs may have clinical utility for prognostication in COVID-19 patients.

SUMMARY

42 COVID-19 patients were enrolled in this study between January 26, 2020 and February 25, 2020. 20 patients (47.6%) represented severe cases and 22 (52.4%) represented non-severe cases. Authors did not provide severity definitions.

Microarray technology and quantitative measurements were used to detect specific IgAs for 8 different respiratory pathogens including adenovirus, respiratory syncytial virus, influenza virus type A, influenza virus type B, parainfluenza virus, mycoplasma pneumoniae, chlamydia pneumoniae and SARS-CoV-2. Serum specific IgA antibodies were detected for IFV-B (Influenza B), CP (chlamydia pneumoniae), IFV-A (Influenza A) and RSV (respiratory syncytial virus).

ABSTRACT

Previous studies have revealed a diagnostic role of pathogen-specific IgA in respiratory infections. However, co-detection of serum specific IgA for SARS-CoV-2 and common respiratory pathogens remains largely unexplored. This study utilizes a protein microarray technology for simultaneous and quantitative measurements of specific IgAs for 8 different respiratory pathogens including adenovirus, respiratory syncytial virus, influenza virus type A, influenza virus type B, parainfluenza virus, mycoplasma pneumoniae, chlamydia pneumoniae and SARS-CoV-2 in serum sample of COVID-19 patients. A total of 42 COVID-19 patients were included and categorized into severe cases (20 cases) and non-severe cases (22 cases). The results showed that co-detection rate of specific-IgA for SARS-CoV-2 with at least one pathogen were significantly higher in severe cases than that of non-severe cases (72.2% vs. 46.2%, $p=0.014$). Our study indicates that co-detection of IgA antibodies for respiratory pathogens might provide diagnostic value for the clinics and also be informative for risk stratification and disease management in COVID-19 patients. This article is protected by copyright. All rights reserved.

	All patients	Non-severe patients	Severe patients	p-value
Baseline variables				
No.	42	22	20	-
Age (year)*	51.9 (46.6-57.1)	46.8 (38.5-55.2)	57.4 (51.5-63.3)	0.040
Female, n (%)	15 (35.7%)	10 (45.5%)	5 (25.0%)	0.167
Type II Diabetes, n (%)	11 (26.2%)	3 (13.6%)	8 (40.0%)	0.052
Hypertension, n (%)	14 (33.3%)	6 (27.3%)	8 (40.0%)	0.382
COPD, n (%)	6 (14.3%)	2 (9.1%)	4 (20.0%)	0.313
CHB, n (%)	2 (4.8%)	1 (4.5%)	1 (5.0%)	0.945
CHD, n (%)	4 (9.5%)	2 (9.1%)	2 (10.0%)	0.920
Comorbidities#	17 (40.5%)	6 (27.3%)	11 (55.0%)	0.067

Table 1: Demographic features and positive numbers (rates) of serum specific IgAs in COVID-19 patients.

Pathogen-Specific IgAs

SARS-CoV-2, n (%)	35 (83.3%)	17 (77.3%)	18 (90.0%)	0.269
IFV-B, n (%)	16 (38.1%)	7 (31.8%)	9 (45.0%)	0.380
CP, n (%)	10 (23.8%)	2 (9.1%)	8 (40.0%)	0.019
IFV-A, n (%)	9 (21.4%)	2 (9.1%)	7 (35.0%)	0.041
RSV, n (%)	9 (21.4%)	4 (18.2%)	5 (25.0%)	0.591
ADV, (%)	0	0	0	-
PIV, (%)	0	0	0	-
MP, (%)	0	0	0	-
Co-detections*, n (%)	19 (45.2%)	6 (46.2%)	13 (72.2%)	0.014

Table 2: Pathogen specific IgAs

*Data are presented as mean (95% CI); #COVID-19 patients with at least one comorbidity. COPD: Chronic Obstructive Pulmonary disease; CHB: Chronic Hepatitis B; CHD: Coronary Heart Disease. *Denotes the co-detection of SARS-CoV-2 and at least one pathogen specific IgAs.

UNDERSTANDING THE PATHOLOGY

THE TRIUMVIRATE: WHY HYPERTENSION, OBESITY, AND DIABETES ARE RISK FACTORS FOR ADVERSE EFFECTS IN PATIENTS WITH COVID-19

Shah H, Khan MSH, Dhurandhar NV, Hegde V.. Acta Diabetol. 2021 Feb 15. doi: 10.1007/s00592-020-01636-z. Online ahead of print.

Level of Evidence: 5 - Review / Literature Review

BLUF

Researchers from the Department of Nutritional Sciences at Texas Tech University review the current understanding of the interconnection between COVID-19, hypertension, diabetes, and obesity (Table 1). Many studies have highlighted the role of the ACE2 receptor and systemic inflammation associated with these preexisting chronic metabolic comorbidities resulting in exacerbation of severity of COVID-19 (Figure 2), although the exact mechanism is still under investigation. The authors call attention to the continued need for research and better treatment options for both COVID-19, and chronic metabolic syndromes to better care for this patient population.

ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a pandemic. The cellular receptor for SARS-CoV-2 entry is the angiotensin-converting enzyme 2, a membrane-bound homolog of angiotensin-converting enzyme. Henceforth, this has brought the attention of the scientific community to study the interaction between COVID-19 and the renin-angiotensin system (RAS), as well as RAS inhibitors. However, these inhibitors are commonly used to treat hypertension, chronic kidney disorder, and diabetes. Obesity is a known risk factor for heart disease, diabetes, and hypertension, whereas diabetes and hypertension may be indirectly related to each other through the effects of obesity. Furthermore, people with hypertension, obesity, diabetes, and other related complications like cardiovascular and kidney diseases have a higher risk of severe COVID-19 infection than the general population and usually exhibit poor prognosis. This severity could be due to systemic inflammation and compromised immune response and RAS associated with these comorbid conditions. Therefore, there is an urgent need to develop evidence-based treatment methods that do not affect the severity of COVID-19 infection and effectively manage these chronic diseases in people with COVID-19.

FIGURES

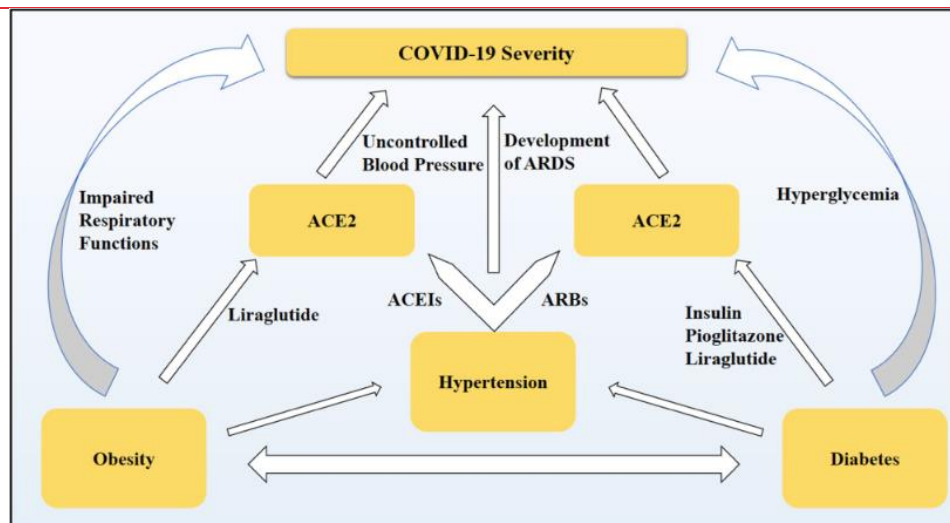


Figure 2. Proposed mechanism of disease severity in COVID-19 patients with comorbidities like hypertension, obesity, and diabetes. Hypertension, obesity, and diabetes are associated with impaired respiratory functions, uncontrolled blood pressure and development of ARDS, and hyperglycemia, respectively, which in turn leads to increased disease burden in COVID-19 patients. Moreover, medications that are used in these comorbidities (liraglutide for obesity, ACEIs, and ARBs for hypertension and insulin, pioglitazone, and liraglutide for diabetes) have been reported to affect ACE2 expression and hence may affect disease severity.*ARDS, acute respiratory distress syndrome, ACEIs, angiotensin-converting enzyme inhibitors, ARBs, angiotensin II receptor blocker.

Table 1 List of studies that show the effect of comorbidities like hypertension, diabetes, and obesity with SARS-CoV-2 infection

Study Details [Authors, Country]	Comorbidities			*p values
	Hypertension (HT) n/N (%)	Diabetes (Db) n/N (%)	Obesity (Ob) n/N (%)	
	[Use of ICU or Disease Severity or Survival—n/N (%)]*			
Chen et al. [4] China	93/274 (34%) [Survivor—39/161 (24%) Non-Survivor—54/113 (48%)]	47/274 (17%) [Survivor—24/161 (21%) Non-Survivor—23/113 (14%)]	NR	NR
Huang et al. [5] China	6/41 (15%) [ICU—2/6 (33.3%) Non-ICU—4/6 (0.67%)]	8/41 (20%) [ICU—1/8 (0.13%) Non-ICU—7/8 (0.88%)]	NR	HT—p=0.93 Db—p=0.16
Richardson et al. [8] USA	3026 (56.6%) [†]	1808 (33.8%) [†]	1737/4170 (41.7%)	NR
Petrilli et al. [9] USA	2256/5279 (42.7%) [Not Hospitalized—557/2538 (21.9%) Hospitalized—1699/2741 (62%)]	1195/5279 (22.6%) [Not Hospitalized—245/2538 (9.7%) Hospitalized—950/2741 (34.7%)]	1865/5279 (35.3%) [Not Hospital- ized—781/2538 (30.7%) Hospital- ized—1084/2741 (39.5%)]	HT, Db, Ob—p<0.001 [§]
Wang et al. [10] China	43/138 (31.2%) [ICU—21/36 (58.3%) Non-ICU—22/102 (21.6%)]	14/138 (10.1%) [ICU—8/36 (22.2%) Non-ICU—6/102 (5.9%)]	NR	HT—p<0.001 Db—p=0.009
Guan et al. [11] China	165/1099 (15%) [Severe—41/173 (23.7%) Non-severe—124/926 (13.4%)]	81/1099 (7.4%) [Severe—28/173 (16.2%) Non-severe—53/926 (5.7%)]	NR	NR
Grassilli et al. [12] Italy	509/1043 (49%) [Died—195/309 (63%) Discharged—84/212 (40%)]	180/1591 (17%)	NR	HT—p<0.001
Zhou et al. [54] China	58/191 (30%) [Survivor—32/137 (23%) Non-survivor—26/54 (48%)]	36/191 (19%) [Survivor—19/137 (14%) Non-survivor—17/54 (31%)]	NR	HT—p=0.0008 Db—p=0.0051
Wu et al. [55] China	39/201 (19.4%) [ARDS—23/84 (27.4%) No ARDS—16/117 (13.7%)]	22/201 (10.9%) [ARDS—16/84 (19%) No ARDS—6/116 (0.05%)]	NR	HT—p=0.02 Db—p=0.002
Zhang et al. [56] China	42/140(30%) [Severe—22/58 (37.9%) Non-severe—20/82 (27.4%)]	17/140 (12.1%) [Severe—8/58 (13.8%) Non-severe—9/82 (11%)]	NR	HT—p=0.85 Db—p=0.615
McMicheal et al. [57] USA	74/167 (44.3%)	38/167 (22.8%)	37/167 (22.2%)	NR
Shi et al. [101] China	127/416 (31%) [With cardiac injury—49/82 (59.8%) Without cardiac injury—78/334 (23.4%)]	60/416 (14.4%) [With cardiac injury—20/82 (24.4%) Without cardiac injury—40/334 (12%)]	NR	HT—p<0.001 Db—p=0.008
Bean et al. [102] UK	150/205 (51.2%)	62/205 (30.2%)	NR	NR

REGENERATION PROFILES OF OLFACTORY EPITHELIUM AFTER SARS-COV-2 INFECTION IN GOLDEN SYRIAN HAMSTERS

Urata S, Maruyama J, Kishimoto-Urata M, Sattler RA, Cook R, Lin N, Yamasoba T, Makishima T, Paessler S.. ACS Chem Neurosci. 2021 Feb 1. doi: 10.1021/acscchemneuro.0c00649. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Otolaryngologists and pathologists from the University of Texas Medical Branch and University of Tokyo investigated the histopathologic changes in olfactory epithelium during SARS-CoV-2 infection in golden Syrian hamsters. At 3 days post-infection, the olfactory epithelium was severely damaged in all 4 areas (nasal septum, middle, dorsal and lateral zones) but all zones recovered by 5-10 days post-infection, with fastest recovery in the nasal septal area (Figure 2). Authors suggest their findings may be attributable to variations in blood or air flow in different parts of the nose, but note limitations in a hamster model and recommend further studies to better elucidate the pathophysiology of anosmia.

ABSTRACT

Olfactory dysfunction is one of the most frequent and specific symptoms of coronavirus disease 2019 (COVID-19). Information on the damage and repair of the neuroepithelium and its impact on olfactory function after COVID-19 is still incomplete. While severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes the ongoing worldwide outbreak of COVID-19, little is known about the changes triggered by SARS-CoV-2 in the olfactory epithelium (OE) at the cellular level. Here, we report profiles of the OE after SARS-CoV-2 infection in golden Syrian hamsters, which is a reliable animal model of COVID-19. We observed severe damage in the OE as early as 3 days postinoculation and regionally specific damage and regeneration of the OE within the nasal cavity; the nasal septal region demonstrated the fastest recovery compared to other regions in the nasal turbinates. These findings suggest that anosmia related to SARS-CoV-2 infection may be fully reversible.

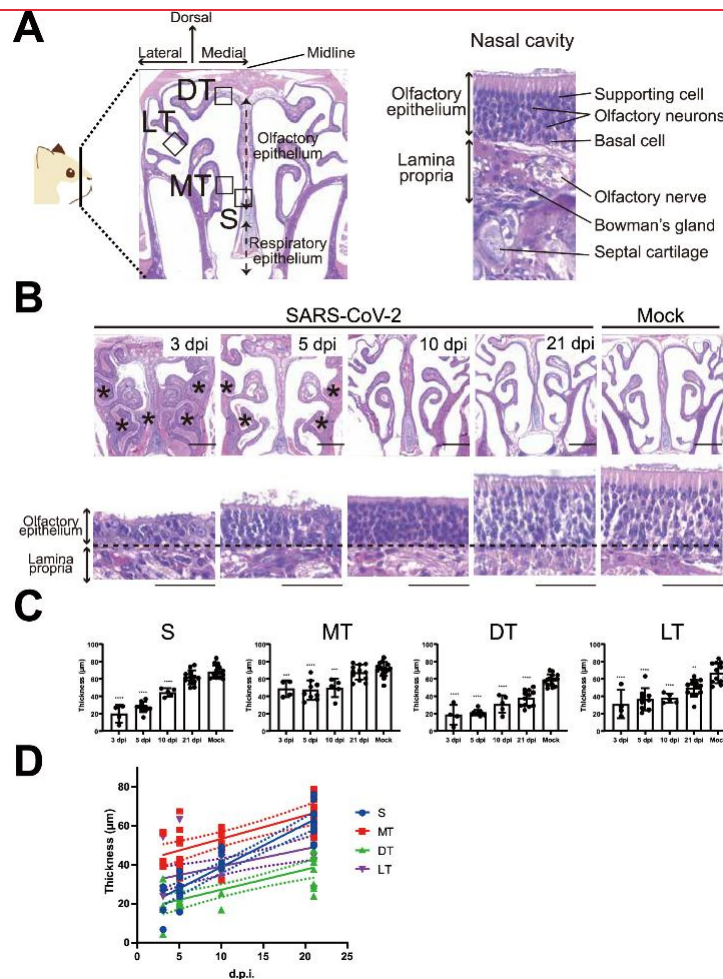


Figure 2. Regeneration of olfactory epithelium after SARS-CoV-2 infection. (A) Representative hematoxylin and eosin (H&E) staining image of the golden Syrian hamster nose. Coronal sections of the snout anterior to the eyes were used to evaluate profiles of the olfactory epithelium (left panel). The OE consists of supporting cells, olfactory sensory neurons, and basal cells (right panel). OE; olfactory epithelium, S; nasal septum, MT; medial turbinate, DT; dorsal turbinate, LT; lateral turbinate. (B) H&E staining of the golden Syrian hamster nose after SARS-CoV-2 or mock infection in low (upper panels) or high (lower panels) magnification. The asterisks represent nasal discharge in the nasal cavity. The border between the OE and lamina propria is indicated by a dashed line. The scale bar represents 1 mm (upper panels) and 50 μm (lower panels). (C) OE thickness in each region (mean ± SEM). (3 dpi, n = 4; 5 dpi, n = 9; 10 dpi, n = 5; 21 dpi, n = 12; Mock, n = 15). Statistical analysis was performed with one-way ANOVA followed by Dunnett's multiple comparison test to compare mock groups. ****: $p < 0.0001$, ***: $p < 0.001$, **: $p < 0.01$. (D) Liner regression analysis indicates that the S region features a higher rate of OE proliferation of OE than other regions.

MANAGEMENT

MEDICAL SUBSPECIALTIES

DERMATOLOGY

EUROPEAN TASK FORCE ON ATOPIC DERMATITIS (ETFAD): POSITION ON VACCINATION OF ADULT PATIENTS WITH ATOPIC DERMATITIS AGAINST COVID-19 (SARS-COV-2) BEING TREATED WITH SYSTEMIC MEDICATION AND BIOLOGICS

Thyssen JP, Vestergaard C, Barbarot S, de Bruin-Weller MS, Bieber T, Taieb A, Seneschal J, Cork MJ, Paul C, Flohr C, Weidinger S, Trzeciak M, Werfel T, Heratizadeh A, Darsow U, Simon D, Torrelo A, Chernyshov PV, Stalder JF, Gelmetti C, Szalai Z, Svensson Å, von Kobyletzki LB, De Raeye L, Fölster-Holst R, Christen-Zaech S, Jan Hijnen D, Gieler U, Gutermuth J, Bangert C, Spuls PI, Kunz B, Ring J, Wollenberg A, Deleuran M.. J Eur Acad Dermatol Venereol. 2021 Feb 15. doi: 10.1111/jdv.17167. Online ahead of print.

Level of Evidence: 5 - Guidelines and Recommendations

BLUF

A letter to the editor from the department of Dermatology and Venereology, Bispebjerg Hospital in Copenhagen, Denmark specifies the European Task Force on Atopic Dermatitis' (ETFAD) position on COVID-19 vaccine administration in patients with atopic dermatitis (AD) being treated with systemic immuno-suppressive medication and biologics. The ETFAD state vaccines currently in use are not contraindicated in patients with AD as they do not suspect worsening of AD symptoms with its use. Although there is no clear evidence to recommend suspension of systemic AD medication before vaccine administration, the authors advise physicians to consider pausing immunosuppressants beforehand to improve the chances of vaccine response.

MULTICENTER INTERIM GUIDANCE ON USE OF ANTIVIRALS FOR CHILDREN WITH CORONAVIRUS DISEASE 2019/SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Chiotos K, Hayes M, Kimberlin DW, Jones SB, James SH, Pinninti SG, Yarbrough A, Abzug MJ, MacBrayne CE, Soma VL, Dulek DE, Vora SB, Waghmare A, Wolf J, Olivero R, Grapentine S, Wattier RL, Bio L, Cross SJ, Dillman NO, Downes KJ, Oliveira CR, Timberlake K, Young J, Orscheln RC, Tamma PD, Schwenk HT, Zachariah P, Aldrich ML, Goldman DL, Groves HE, Rajapakse NS, Lamb GS, Tribble AC, Hersh AL, Thorell EA, Denison MR, Ratner AJ, Newland JG, Nakamura MM.. J Pediatric Infect Dis Soc. 2021 Feb 13;10(1):34-48. doi: 10.1093/jpids/piaa115.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

Pharmacists and pediatric infectious disease physicians from 20 North American institutions offer guidance on the use of antivirals in the setting of pediatric COVID-19 infection. They recommend using remdesivir only for severely or critically ill children (see summary for definition) and supportive care alone for mild cases, which comprise the majority of pediatric COVID-19 (Table 1, Table 2). The authors stress that most pediatric patients do not need antiviral therapy and suggest their guidelines will assist in clinical decision making regarding their use.

SUMMARY

The authors define severity as the following:

- Severe illness: supplemental oxygen requirement without need for noninvasive or invasive mechanical ventilation or ECMO
- Critical illness: requiring noninvasive or invasive mechanical ventilation or ECMO

ABSTRACT

BACKGROUND: Although Coronavirus Disease 2019 (COVID-19) is a mild infection in most children, a small proportion develop severe or critical illness. Data evaluating agents with potential antiviral activity continue to expand, such that updated guidance is needed regarding use of these agents in children. **METHODS:** A panel of pediatric infectious diseases physicians and pharmacists from 20 geographically diverse North American institutions was convened. Through a series of teleconferences and web-based surveys, a set of guidance statements was developed and refined based on review of the best available evidence and expert opinion. **RESULTS:** Given the typically mild course of COVID-19 in children, supportive care alone is suggested for most cases. For children with severe illness, defined as a supplemental oxygen requirement without need for non-invasive or invasive mechanical ventilation or extra-corporeal membrane oxygenation (ECMO), remdesivir is suggested, preferably as part of a clinical trial if available. Remdesivir should also be considered for critically ill children requiring invasive or non-invasive mechanical ventilation or ECMO. A duration of 5 days is appropriate for most patients. The panel recommends against the use of hydroxychloroquine or lopinavir-ritonavir (or other protease inhibitors) for COVID-19 in children. **CONCLUSIONS:** Antiviral therapy for COVID-19 is not necessary for the great majority of pediatric patients. For children with severe or critical disease, this guidance offers an approach for decision-making regarding use of remdesivir.

FIGURES

Table 1. Suggested Management of Coronavirus Disease 2019 by Illness Severity

Disease Category	Respiratory Support Requirement	Management
Mild	No new or increased supplemental oxygen requirement, with symptoms limited to the upper respiratory tract	Supportive care
Moderate	No new or increased supplemental oxygen requirement, with symptoms involving the lower respiratory tract, or radiographic findings on chest X ray	Supportive care
Severe	New or increase from baseline supplemental oxygen requirement <i>without</i> need for new or increase in baseline noninvasive/invasive mechanical ventilation ^a	Remdesivir is suggested for all children with severe COVID-19, unless there are contraindications
Critical	New or increased requirement for invasive or noninvasive mechanical ventilation, ^a sepsis, or multiorgan failure <i>OR</i> rapidly worsening clinical trajectory that does not yet meet these criteria	Remdesivir should be considered for all children with critical COVID-19, unless there are contraindications

Abbreviation: COVID-19, coronavirus disease 2019.

^aNoninvasive mechanical ventilation includes high-flow nasal canula, continuous positive airway pressure, or bilevel positive airway pressure.

Table 2. Remdesivir Dosing and Administration

Pediatric Dose/Duration	Contraindications	Warnings
Pediatric and adult dosing 3.5–40 kg: 5 mg/kg IV loading dose on day 1, followed by 2.5 mg/kg IV every 24 hours of lyophilized powder only ≥40 kg: 200 mg IV loading dose on day 1, followed by 100 mg IV every 24 hours; lyophilized powder or solution may be used	Hepatic impairment: Remdesivir should not be administered to patients with ALT ≥5 times the upper limit of normal <i>OR</i> to patients with ALT elevations associated with elevated conjugated bilirubin, alkaline phosphatase, or international normalized ratio	Potential adverse events include elevation in hepatic transaminases and hypersensitivity reactions; hepatic function tests should be monitored daily
Recommended duration Severe disease: up to 5 days Critical disease: 5–10 days	Renal insufficiency: Remdesivir is not recommended for patients aged >28 days with an eGFR <30 mL/min or term neonates (7 to 28 days of life) with a serum creatinine ≥1 mg/dL, unless the benefit outweighs the risk; no dose adjustments have been performed for patients with eGFR >30 mL/min	Coadministration of hydroxychloroquine may reduce antiviral activity of remdesivir [52]

Abbreviations: ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; IV, intravenous. Source: Fact sheet for healthcare providers: emergency use authorization (EUA) of remdesivir (GS-5734) [50].

ROOMING-IN FOR WELL-TERM INFANTS BORN TO ASYMPTOMATIC MOTHERS WITH COVID-19: CORRESPONDENCE

Kest H, Kaushik A, Skroce L, Bogusz J, Datta-Bhutada S. J Pediatric Infect Dis Soc. 2021 Feb 13;10(1):60-61. doi: 10.1093/jpids/piaa120.

Level of Evidence: 4 - Cohort study or control arm of randomized trial

BLUF

Pediatricians from St. Joseph's Children's Hospital in New Jersey evaluated the outcomes of rooming-in in well term infants of 49 SARS-CoV-2 positive mothers, only four of whom were mildly symptomatic. Infection control precautions were maintained (see summary), and 48/49 infants tested negative for SARS-CoV-2 by PCR at 24 hours, with all testing negative by 48 hours. Mothers reported all infants were feeding well and active on post-discharge telehealth followup. Authors suggest SARS-CoV-2 positive asymptomatic mothers can safely care for their well term infants if following infection prevention guidelines.

SUMMARY

The hospital followed guidelines from the American Association of Pediatrics for rooming-in in a single room:

- "maintain[ed] a distance of at least 6-feet between mother and infant with a curtain barrier"
- mothers were required to wear a mask
- mothers "perform[ed] hand hygiene while providing hands-on care for the baby"
- mothers performed "breast hygiene before breastfeeding"

ABSTRACT

There is an ongoing debate about rooming-in for neonates born to mothers with COVID-19 disease. Rooming-in promotes bonding and leads to better outcomes for both mother and baby. The unprecedented nature of COVID-19 has led to practices aimed at protecting newborns but may come with risks of losing the momentum of rooming-in that has been achieved over past decade. In this pilot study, well neonates born at or near term (>36 weeks gestational-age) were roomed in with their mothers who were positive for SARS-Co-V-2 infection, in a single room with infection control education according to American Academy of Pediatrics (AAP) recommendations and followed weekly through telehealth for 2 weeks after discharge. Of the 49 infants, none developed any symptoms of COVID-19. One out of 49 infants tested positive for SARS-Co-V-2 by reverse transcription polymerase chain reaction (RT-PCR) but repeat testing at 48-hours was negative. Our pilot study showed that rooming-in may be considered for term/near term infants with asymptomatic mothers with COVID19, while limiting transmission risk through infection control and education measures.

CLINICAL APPLICATIONS OF DETECTING IGG, IGM, OR IGA ANTIBODY FOR THE DIAGNOSIS OF COVID-19: A META-ANALYSIS AND SYSTEMATIC REVIEW

Chen M, Qin R, Mei J, Yang Z, Wen W, Li J. *Int J Infect Dis.* 2021 Jan 12:S1201-9712(21)00026-6. doi: 10.1016/j.ijid.2021.01.016. Online ahead of print.

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

BLUF

Otolaryngologists and immunologists from several institutions in Guangzhou, China conducted a meta-analysis of 68 articles published between December 2019 and June 2020 comparing the performance of serologic tests detecting SARS-CoV-2 antibodies (Figure 1, summary). Though they note high heterogeneity in the included studies, they found test results showing IgM+IgG+/-, IgG+IgM+/-, and IgM+ or IgG+ had the highest sensitivity (68%, 73%, and 79%, respectively), while pooled specificities ranged from 98 to 100% (Tables 1, 3). Test accuracy was higher 2 weeks post-symptom onset than earlier. Authors suggest serological tests (IgG, IgM, IgA) are promising supplementary diagnostic tests to RT-PCR for COVID-19 diagnosis, though note their utility may be limited early in infection.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 is a global pandemic. Serological antibody test is one important diagnostic method increasingly used in the clinic, although its clinical application is still under investigation. **METHODS:** We conducted a meta-analysis to compare the diagnostic performances of severe acute respiratory syndrome coronavirus 2 specific antibody tests in COVID-19 patients. Test results analyzed included (1) IgM-positive but IgG-negative (IgM+IgG-), (2) IgG-positive but IgM-negative (IgG+IgM-), (3) both IgM and IgG-positive (IgM+IgG+), (4) IgM-positive without IgG information (IgM+IgG+/-), (5) IgG-positive without IgM information (IgG+IgM+/-), (6) either IgM or IgG-positive (IgM+ or IgG+), and (7) IgA-positive (IgA+). **RESULTS:** Sixty-eight studies were included. The pooled sensitivities of IgM+IgG-, IgG+IgM-, IgM+IgG+, IgM+IgG+/-, IgG+IgM+/-, and IgM+ or IgG+ were 6%, 7%, 53%, 68%, 73%, and 79% respectively. The pooled specificity ranged from 98% to 100%. The IgA+ had a pooled sensitivity of 78%, but a relatively low specificity of 88%. Tests conducted two weeks after symptom onset provided improved diagnostic accuracy. Chemiluminescence immunoassay and detection of S protein as the antigen could offer a more accurate diagnostic result. **DISCUSSION:** Our findings support the supplemental role of serological antibody tests in COVID-19 diagnosis. However, their capacity to diagnose COVID-19 early in the disease course could be limited.



Figure 1: " Prisma Flow Chart".

Types of antibody	Number of studies and samples	Sensitivity with 95% CI (%)	Specificity with 95% CI (%)	AUROC with 95% CI (%)
IgM ⁺ IgG ⁻	28 studies, 6161 samples	6, [4, 8]	99, [98,99]	0.64, [1.00, 0.00]
IgG ⁺ IgM ⁻	58 studies, 12751 samples	7, [5, 11]	99, [99,99]	0.91, [1.00, 0.00]
IgM ⁺ IgG ⁺	63 studies, 13344 samples	53, [46, 60]	100, [99,100]	0.94, [1.00, 0.00]
IgM ⁺ IgG ^{±/-}	87 studies, 18924 samples	68, [62, 73]	98, [97,99]	0.96, [0.19, 1.00]
IgG ⁺ IgM ^{±/-}	88 studies, 18597 samples	73, [69, 77]	99, [98,99]	0.97, [0.19, 1.00]
IgM ⁺ or IgG ⁺	76 studies, 20065 samples	79, [76, 83]	98, [98,99]	0.97, [0.19, 1.00]
IgA ⁺	6 studies, 934 samples	78, [67, 85]	88, [82,92]	0.91, [0.88, 0.93]

Table 1: "Pooled sensitivity, pooled specificity, and area under the receiver operating characteristic curve (AUROC) of serological tests".

Category	PPV5	PPV10	PPV20	NPV5	NPV10	NPV20
Overall	67.52%	81.44%	90.80%	98.88%	97.67%	94.92%
Days 0–7	40.63%	59.09%	76.47%	96.80%	93.47%	86.41%
Days 8–14	66.67%	80.85%	90.48%	98.73%	97.35%	94.23%
Days >14	70.99%	80.85%	90.48%	99.63%	99.21%	98.25%
CLIA	81.90%	90.53%	95.56%	99.26%	98.45%	96.59%
ELISA	81.37%	90.22%	95.40%	99.10%	98.13%	95.88%
LFIA	56.82%	73.53%	86.21%	98.66%	97.22%	93.95%
N antigen	58.09%	74.53%	86.81%	98.87%	97.65%	94.87%
S Antigen	82.57%	90.91%	95.74%	99.47%	98.89%	97.54%
N and S	69.84%	83.02%	91.67%	99.36%	98.66%	97.03%

Table 3: "The positive predictive value (PPV) and negative predictive value (NPV) of the serological test for IgM+ or IgG+".

ANTIGEN TESTING AND NON-INFECTIOUS SHEDDING OF SARS-COV-2

Raveh Y, Simkins J, Nicolau-Raducu R.. Infection. 2021 Feb 10. doi: 10.1007/s15010-021-01579-9. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

A letter to the editor from University of Miami physicians highlights the limitations of Lanser et al.'s 2020 article evaluating the clinical utility and sensitivity of SARS-CoV-2 antigen testing in relation to RT-PCR cycle threshold (Ct) values. Some of the limitations outlined include unreported statistical comparisons of the antigen test results for test subjects with Ct above or below 33 and no reported data regarding antigen test results in patients with negative RT-PCR swabs (see summary). With this letter, the authors hope to correctly assess a plausible correlation between antigen test results and Ct in order to properly inform infection control and public health policies.

SUMMARY

Additional limitations include:

- overestimation of the true sensitivity of the antigen assay
- strongly biased study findings toward severe illness
- lack of reported data regarding the days from onset of symptoms to testing.

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