The Daily COVID-19 Literature Surveillance Summary

November 09, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
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

Adjusting Practice During COVID-19

- Using medical records from 3 hospitals, researchers at Duke University Health System developed a Clinical Decision Support (CDS) tool, which determines urgency of surgical procedures based on general length of stay, ICU length of stay, ventilator need, and skilled nursing facility (SNF) need. They note the tool is limited by lack of external validity and inability to consider factors like daily or seasonal case load variation. Given the consideration for case prioritization regarding elective producers during the COVID-19 pandemic, authors suggest clinical tools such as CDS could be useful for resource allocation, but further research is needed to confirm their effectiveness in a hospital setting.

R&D: Diagnosis & Treatments

- Investigators at the University of Maryland examined the estimated sensitivity and specificity of several SARS-CoV-2 antibody tests and found in-house ELISAs to have better outcomes. The study tested 3 in-house ELISAs (one detecting anti-trimer IgG antibodies, one anti-trimer IgA antibodies, and another IgG anti-capsid antibodies), 4 commercial ELISAs (EDI Novel Coronavirus COVID-19 IgG and IgM, Euroimmun SARS-CoV-2 IgG and IgA), and one lateral flow immunoassay (DPP COVID-19 IgM/IgG). When analyzing 300 pre-epidemic samples (including 66 HIV infected samples) and 100 RT-PCR confirmed SARS-CoV-2 positive samples, the in-house ELISAs generally showed the greatest sensitivity and specificity. While the in-house ELISAs appear to demonstrate an improvement in antibody detection against SARS-CoV-2, the authors relate that creating testing algorithms with more than 1 assay may be needed to eliminate false positives.

- A randomized Phase III trial conducted by researchers affiliated with AIM Immunotech Inc. in Philadelphia investigated use of rintatolimod (a selective TLR3 agonist) in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and found a subset of patients with symptom duration of 2-8 years who received treatment (n=75) had ≥2 fold increased exercise response, with 51.2% showing >25% increase in exercise tolerance. Among patients with a disease duration window of 2-8 years, this is a significant improvement when compared to 5 FDA-approved drugs, leading to clinically significant quality of life enhancement. Authors advocate for investigation of rintatolimod as a potential therapeutic agent in patients with COVID-19 "long-hauler" post-viral syndrome to reduce lingering brain-fog and fatigue.

- 5-Alpha-Reductase Inhibitors are Associated with Reduced Frequency of COVID-19 Symptoms in Males with Androgenetic Alopecia according to a retrospective cohort study of SARS-CoV-2 positive male patients with androgenetic alopecia (n=113) presenting to outpatient clinics in Brazil. They found men taking dutasteride (a 5-alpha-reductase inhibitor; n=48) had a significantly reduced frequency of 20/29 COVID-19 symptoms ($P<0.05$) compared to men not taking dutasteride (n=65). Authors suggest androgens may play a role in COVID-19 severity and more studies are needed to investigate possible benefits of 5-alpha-reductase inhibitors.

TABLE OF CONTENTS

ADULTS

CLINICAL AND MICROBIOLOGICAL FEATURES OF ASYMPTOMATIC SARS-COV-2 INFECTION AND MILD COVID-19 IN SEVEN CREWMEMBERS OF A CRUISE SHIP

Hoshiyama T, Wada T, Nihonyanagi S, Kameda R, Yamaoka-Tojo M, Fukuda M, Ako J, Yamaoka K, Takayama Y.. Intern Med. 2020 Nov 2. doi: 10.2169/internalmedicine.5601-20. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Physicians from Kitasato University Hospital in Japan conducted a retrospective cohort study including seven crew members (aged 23-47) of Diamond Princess cruise ship hospitalized between February 24 and March 7, 2020 with asymptomatic or mild SARS-CoV-2 infection (Table 1). All recovered, but the only overweight patient (BMI 28.6) developed a ground glass opacity (Figure 1), elevated CRP of 1.29 (Table 2), and was hospitalized longer than the others (12 vs. 8 days). Authors suggest that being overweight may be a risk factor for more severe SARS-CoV-2 infection and disease complications in otherwise healthy young adults with mild disease.

ABSTRACT

Objective To describe the clinical features and clinical course of individuals diagnosed with asymptomatic SARS-CoV-2 infection or mild COVID-19. Patients The study participants consisted of 7 crewmembers of the passenger cruise-liner, Diamond Princess, who were admitted to our hospital after becoming infected with SARS-CoV-2 aboard the ship. Methods The data on patient background and biochemical test results were obtained from the patients' medical records. All patients had a chest X-ray, and a throat swab and sputum samples were sent for culture on admission. Results The median age of the 7 patients, of whom 4 were male and 3 were female, was 39 years (range: 23-47 years). On admission, none of them had fever, but 4 (57%) had a cough. None of them showed any signs of organ damage on laboratory testing. Chest X-ray showed pneumonia in one individual, which resolved spontaneously, while the other 6 had normal chest X-ray findings. Culture of throat swabs and sputum samples revealed that 4 patients (57%) had bacterial upper respiratory infections (Haemophilus influenzae, Klebsiella pneumoniae, and Staphylococcus aureus). The period from a positive PCR test to negative conversion ranged from 5 to 13 days, with a median of 8 days. Conclusion Healthy young adults without risk factors who acquire SARS-CoV-2 infection may have an asymptomatic infection or may experience mild COVID-19. In addition to obesity, an older age, underlying illness, and being overweight can lead to a risk of exacerbation; thus, hospital management for such individuals may be desirable. Culturing respiratory samples may be useful for diagnosing secondary bacterial pneumonia.

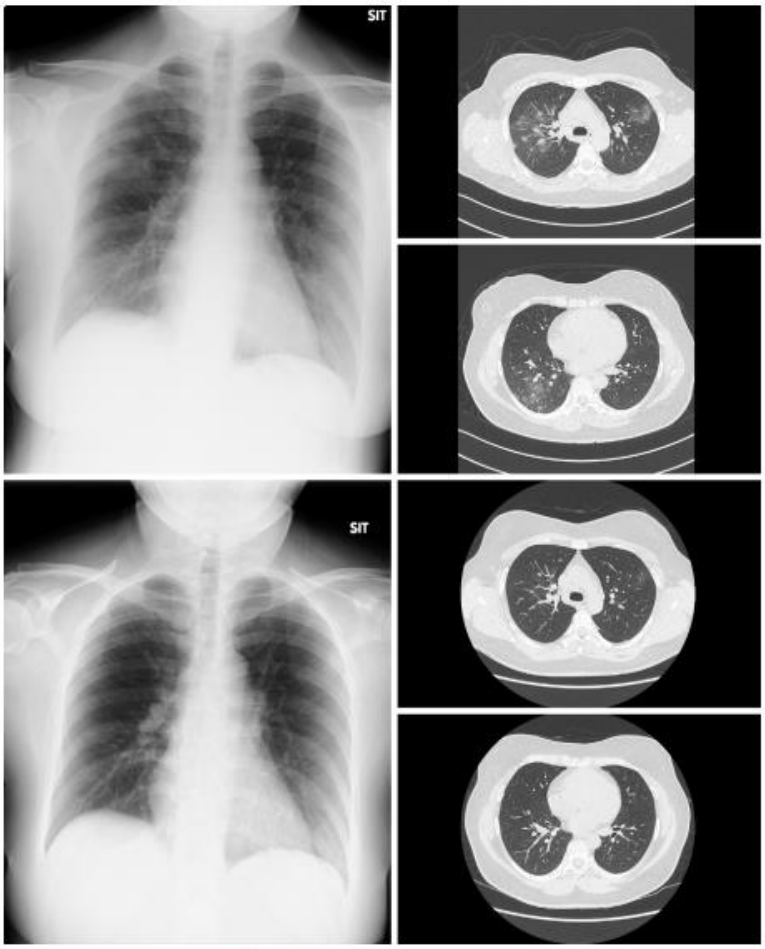


Figure. **Changes in the lungs of Patient 7 on chest X-ray and a chest computed tomography (CT) scan. A patchy ground-glass opacification was found in the upper lobes of both lungs superiorly and lower lung margin dorsal superiorly on hospital day 3. On hospital Day 10, the chest CT scan showed a marked improvement in the ground-glass shadow. A: Chest X-ray on hospital Day 2; B and C: A chest CT scan on hospital Day 3; D: Chest X-ray on hospital Day 9; E and F: Chest CT scans on hospital Day 10.**

Table 1. **Patient Characteristics, Clinical Features, and Imaging Findings.**

Patient	Age (years)	Sex	Over-weight†	Smoking history	BT >37.5°C	Respiratory symptoms	Past medical history	CXR	Days to negative PCR†††	Days to discharge
1	45	M	-	-	No	Cough	Hyperuricemia	-	6	7
2	47	M	-	-	No	Cough	Cerebral hemorrhage	-	8	8
3	23	M	-	-	No	Cough	-	-	8	8
4	39	M	-	-	No	-	Hypertension	-	8	8
5	32	F	-	-	No	-	-	-	6	8
6	28	F	-	-	No	-	Interstitial nephritis	-	5	8
7	39	F	+	-	No	Cough	Dyslipidemia	+††	13	12

BT: body temperature, CXR: chest X-ray

† Overweight is defined as a BMI>25.

††Patient 7's chest X-rays and chest computed tomography images are shown in Figure 1.

††† The day of a positive PCR test is defined as day 1.

Table 2. **Patients' Complete Blood Count and Blood Biochemistry Results.**

Patient	WBC (/μL)	Neut (/μL)	Lymph (/μL)	AST (U/L)	ALT (U/L)	BUN (mg/dL)	Cr (mg/dL)	CRP (mg/dL)	IgG (mg/dL)	FER (ng/mL)
1	6,100	3,142	2,385	17	27	14	0.99	0.03	-	-
2	7,800	4,376	2,660	22	34	11	0.92	0.22	1,269	**674†**
3	8,100	3,386	2,997	27	53	13	1.04	0.17	-	-
4	7,200	3,859	2,333	28	37	11	0.88	0.04	1,110	130
5	6,300	3,893	1,997	12	17	14	0.79	<0.03	1,488	27
6	6,200	3,776	1,829	37	41	3	0.60	<0.03	1,127	<4
7	7,500	4,448	2,415	29	27	9	0.61	**1.29‡**	-	-

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, FER: ferritin, IgG: immunoglobulin G, Lymph: lymphocytes, Neut: neutrophils, WBC: white blood cells

All values are normal unless indicated otherwise.

† Above the normal range. The normal range for ferritin is 5–152(ng/mL).

‡ Above the normal range. The normal range for C-reactive protein is less than 0.14(mg/dL).

Table 3. **Patients' Throat Swab and Sputum Culture Results.**

Patient	Throat swab	Sputum
1	-	-
2	*Staphylococcus aureus*<10^3	*Staphylococcus aureus* 10^5
3	-	-
4	*Staphylococcus aureus* 10^5 *Streptococcus agalactiae* (Group B) 10^5	*Staphylococcus aureus* <10^3
5	-	Group C*Streptococcus* 10^6 *Haemophilus influenzae* 10^6
6	-	-
7	*Enterobacteria* species 10^4	*Klebsiella pneumoniae* 10^6

ARE MIGRAINE PATIENTS AT INCREASED RISK FOR SYMPTOMATIC CORONAVIRUS DISEASE 2019 DUE TO SHARED COMORBIDITIES?

Bolay H, Özge A, Uludüz D, Baykan B.. Headache. 2020 Oct 30. doi: 10.1111/head.13998. Online ahead of print.
Level of Evidence: 2 - Review / Literature Review

BLUF

This literature review by investigators affiliated with the departments of neurology and algology at several Turkish universities examines the comorbidities to COVID-19, including vascular comorbidities (Table 1) and migraines (Table 2). They found shared inflammation pathways involving the NLRP3 inflammasome and the angiotensin system (Figure 3) between migraines and COVID-19, suggesting that patients with migraines and related comorbidities might be more susceptible to COVID-19.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has rapidly transformed the whole world and forced us to look through comorbid diseases and risk factors from a different perspective. COVID-19 shows some inherent risk factors like cardiovascular comorbidities independent from age, gender, and geographic location. One of the most peculiar features of the COVID-19 pandemic is that severe acute respiratory syndrome coronavirus 2 respiratory infections disproportionately impact patients with hypertension, diabetes, and other cardiovascular comorbidities rather than those with allergic respiratory diseases and immune-compromised conditions. Migraine is a complex neuro-vasculo-inflammatory disorder that is also packed frequently with certain medical conditions including vascular disorders, hypertension, allergic diseases such as asthma and systemic inflammatory disorders. Accordingly, 2 different questions arise during the pandemic: (1) Do share comorbidities of cardiovascular diseases and hypertension increase the risk of symptomatic COVID-19 for migraine patients? (2) Do comorbid allergic and atopic diseases, including asthma act as opposite influencers alongside with female gender? This paper focuses on the co-existence of comorbidities of COVID-19, in comparison with migraine, based on a wide clinical dataset and available reports. Discussed mechanisms include potential strategic roles of angiotensin-converting enzyme 2, angiotensin-II, and nucleotide oligomerization domain-like receptor family, pyrin domain containing 3 inflammasome, playing remarkable parts in the pathogenesis of COVID-19 and migraine. There are also some clues about the importance of endothelial and pericyte dysfunction and neuroinflammation in COVID-19 infection, related to complications and survival of the patients. The large epidemiological studies as well as basic research, focusing on migraine patients with COVID-19 will clarify these vital questions during the upcoming periods.

FIGURES

First Author Year	Country	Study Design	Sample Size	Gender % Male	Allergy Asthma %	Hyper-Tension %	CAD %	DM %
Lodigiani[5] 2020	Italy	Cohort study	388	68	NA	47.2	13.9	22.7
Zhou[6] 2020	China	Cohort study	191	62	NA	30 OR: 3.05	8 OR: 21.4	19 OR: 2.85
Bhatraju[7] 2020	USA	Hospital based	24	63	18	NA	NA	58
Mao[8] 2020	China	Hospital based	214	40.7	NA	23.8	7	14
Guan[9] 2020	China	Nation-wide	1099	58.1	NA	15	2.5	7.4
Wang[10] 2020	China	Hospital based	138	54.3	NA	31.2	14.5	10.1
Zhang[11] 2020	China	Hospital based	140	50.7	0	30	5	12.1
Mo[12] 2020	China	Hospital based	155	55.5	NA	23.9	9.7	9.7
Chen[13] 2020	China	Hospital based	274	62	NA	34	8	17
Helms[14] 2020	France	Hospital based	150	81.3	14	NA	48	20
Aggarwal[15] 2020	USA	Hospital based	16	75	NA	57	19	31
Grasselli[16] 2020	Italy	Regional network based	1591	82	4	49	21	17
Guo[17] 2020	China	Hospital based	187	48.7	2.1	32.6	11.2	15
Wu[18] 2020	China	Hospital based	201	63.7	2.5	19.4	4	10.9
Gold[19] 2020	USA	Hospital based	305	49.5	10.5	67.5	11.5	39.7
Garg[20] 2020	USA	Network based	178	NA	17	49.7	14.2	28.3
Hu[21] 2020	China	Hospital based	323	51.4	9	32.5	12.7	14.6
Lagi[22] 2020	Italy	Hospital based	84	65.5	NA	36.9	14.3	14.3
Lovell[23] 2020	UK	Hospital based	101	64	22	54	NA	36
Cui[24] 2020	China	Hospital based	81	54	NA	25	12	10
Richardson[25] 2020	USA	Hospital based	5700	60.3	9	56.6	11.1	33.8

CAD = coronary artery disease; CVD = cardiovascular disease; DM = diabetes mellitus; NA = not available; OR = odds ratio.

Table 1. Clinical Reports on COVID-19-Associated Vascular and Allergic Comorbidities

First Author Year	Country	Study Design	Diagnosis	Sample Size	Gender % Female	Allergy Asthma %	HT %	CAD %	DM %
Yildirim[27] 2018	Turkey	Tertiary headache center data	ICHD-3β	2037 MwA: 225	86.9	9.9	22.9	15.8	17.0
Nuyen[28] 2006	Denmark	Primary care data setting	ICHD-II	3067 MwA: NA	78.7	8.4	10.5	1.9	1.8
McLean[29] 2017	UK	Cross-sectional primary care data	ICHD-3β	9370 MwA: NA	85	12.4	19.2 AHR: 1.18	0.7 AHR: 1.21	6.1 AHR: 1.23
Adelborg[30] 2018	Denmark	Cohort – 18 years follow-up	ICHD-3β	51,032 MwA: 13,076	70.6 71.3	NA NA	3.0 3.0	NA NA	1.4 1.2%
Gudmundsson[31] 2010	Iceland	Population based cohort study	ICHD-II	2023 MwA: 1397	71.7 68.3	NA NA	NA NA	AHR: 1.27 AHR: 1.28	NA NA
Kurth[32] 2006	USA	Cohort – 108 mos follow-up	ICHD-II	3610 MwA: 1434	100 100	NA NA	26 25.5	NA NA	1.6 1.8
Kurth[33] 2007†	USA	Cohort – 188 mos follow-up	ICHD-I	1449 MwA: NA	0	NA	34.2	AHR: 1.24	3.0
Kurth[34] 2020	USA	Cohort- 16 yrs follow-up	ICHD-3	27,858 MwA: 1435	100	NA	AHR: 2.80 AHR: 4.46	AHR: 2.11 AHR: 3.36	AHR: 4.35 AHR: 6.92
Martin[35] 2016¶	USA	Cohort	ICHD-3β	4446 MwA: NA	80.8	17	NA	NA	NA
Chen[36] 2012¶	Taiwan	Retrospective matched cohort	ICHD-II	4738 MwA: NA	78.5	3.52 AHR = 1.77	16.8 AHR: 1.64	8.37 AHR: 1.73	4.7 AHR: 1.08
Buse[37] 2020	USA	Web-based survey	ICHD-3β	15,133 MwA: NA	73	OR: 2.49	OR: 1.51	OR: 1.66	OR: 1.37
Lipton[38] 2018‡	USA	Web-based survey	ICHD-3β	12,810 MwA: NA	76	32	24	NA	9
Martin[39] 2014§	USA	Mailed questionnaire	ICHD-II	17,892 MwA: NA	77.8	OR: 3.75	OR: 1.28	NA	OR: 1.22
Mahmoud[40] 2018	USA	Meta-analysis	ICHD	394,942 MwA: NA	NA	NA	NA	AHR: 1.23 AHR: 1.56	AHR: 1.23
Bigal[41] 2010	USA	Case control	ICHD-II	6102 MwA: 270	80.3 NA	NA NA	33.1 NA	OR: 2.19 OR: 2.99	12.6 NA

†The study included only men using a multivariable model that adjusted for age, history of hypertension, diabetes mellitus, smoking status, exercise, body mass index, alcohol consumption, a high cholesterol level, parental history of MI before age 60 years, and randomized treatment assignments.
‡The cardiovascular comorbidity had more men (22%) had a later age of onset (median, 22 years), and were associated with the least severe phenotype of migraine.
§66.8% of the patients with allergic rhinitis, OR: 1.18 (0.95-1.46). The frequency and headache-related disability of migraine are higher in persons with rhinitis overall.
¶Asthma is associated with an increased risk of new-onset CM, with the highest risk being among those with the greatest number of respiratory symptoms.
††CM sufferers (n = 948) had significantly increased risks of CVD, sinusitis, asthma, gastrointestinal ulcers, vertigo, and psychiatric disorders by 1.6- to 3.9-fold.
AHR = adjusted hazard ratio; CAD = coronary artery disease; CM = chronic migraine; CVD = cardiovascular disease; DM = diabetes mellitus; HT = hypertension; MwA = migraine with aura; NA = not available; OR = odds ratio.

Table 2. Clinical Reports of Migraine-Associated Comorbidities Based on Cohorts

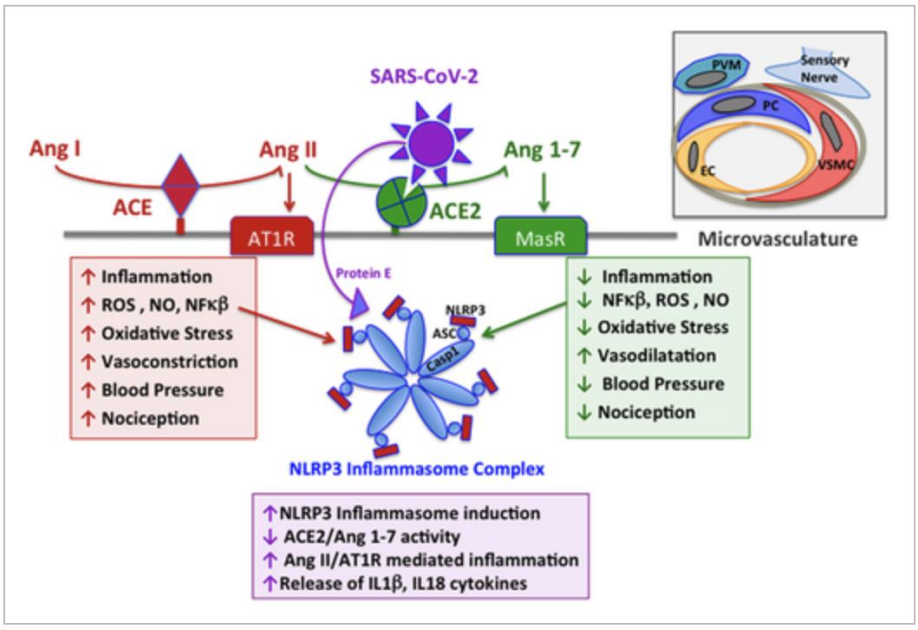


Figure 3. The diagram summarizing the hypothetical mechanisms of the inflammatory activation in the microvasculature in COVID-19. Vascular cells involved in regulating microvascular circulation and inflammatory responses are shown in the upper right part; endothelial cells (EC), pericytes (PC), vascular smooth muscle cell (VSMC), perivascular macrophages (PVM), and sensory nerve ending. Angiotensin II/(Ang II) that is produced by angiotensin-converting enzyme (ACE), and its downstream effect via AT1 receptor (AT1R) are the main players in the pathogenesis of hypertension, cardiovascular diseases, and inflammation, tissue damage, and nociception. Conversion of Ang II by ACE2 into Ang 1-7 yields protective functions via Mas receptor (MasR) against detrimental effects of Ang II/AT1R, including vasodilation, blood pressure decrease, vascular and tissue protection, anti-nociception, and anti-inflammatory properties. SARS-CoV binding to the ACE2 and internalization of the complex is the entry route for the virus, which leads to exaggerated inflammatory responses not only through the unbalanced AT1R pathway, but also via direct impact of virus protein E on inflammasome complex. Functional NLRP3 inflammasome complex consists of caspase 1, ASD (apoptosis-associated speck-like protein containing a caspase-recruitment domain), and NLRP3 primed by NF-κβ. The important key regulator of the suggested pathogenesis is the activation of the NLRP3 inflammasome complex, which leads to the release of proinflammatory cytokines of IL-1β, IL-18 recruiting other immune-competent cells and cell injury implicated in a variety of disorders.

THE DETECTION OF SARS-COV-2 VIRUS IN THE VAGINAL FLUID OF FEMALES WITH SEVERE COVID-19 INFECTION: SCIENTIFIC FACTS

Ahmad MF, Mahakkanukrauh P, Das S.. Clin Infect Dis. 2020 Oct 21:ciaa1608. doi: 10.1093/cid/ciaa1608. Online ahead of print.
Level of Evidence: 4 - Expert Opinion

BLUF

A letter to the editor by researchers at University Kebangsaan Malaysia Medical Centre in Kuala Lumpur, Malaysia and Chiangmai University in Thailand discusses a recent study which found no evidence of SARS-CoV-2 virus on vaginal swabs when taken on average 17 days post-infection. From this, they discuss further study in quantifying amount of virus present, menopausal status of women, and effect of cervical and vaginal atrophy on ACE2 receptor expression among post-menopausal women. They discuss future studies are needed to investigate reproductive-aged females within 7 days post-infection, potential for association with HPV infection, and for the presence of SARS-CoV-2 in both vaginal and cervical samples.

SARS-COV-2 RNA SHEDDING IN RECOVERED COVID-19 CASES AND THE PRESENCE OF ANTIBODIES AGAINST SARS-COV-2 IN RECOVERED COVID-19 CASES AND CLOSE CONTACTS, THAILAND, APRIL-JUNE 2020

Chirathaworn C, Sripramote M, Chalongviriyalert P, Jirajariyavej S, Kiatpanabhikul P, Saiyarin J, Soudon C, Thienfaidee O, Palakawong Na Ayuthaya T, Brukesawan C, Chaiwanichsiri D, Intharasongkroh D, Wanlapakorn N, Chansaenroj J, Puenpa J, Yorsaeng R, Thitithanyanont A, Kitphati R, Mungaomklang A, Nagavajara P, Poovorawan Y.. PLoS One. 2020 Oct 29;15(10):e0236905. doi: 10.1371/journal.pone.0236905. eCollection 2020.
Level of Evidence: 3 - Local non-random sample

BLUF

Investigators from Thailand analyzed samples from 217 recovered COVID-19 patient from Bangkok Metropolitan Administration (BMA) associated medical centers admitted from April-June 2020, as well as close contacts to those patients (Table 1). The results revealed 6.6% of recovered patients still had detectable SARS-CoV-2 RNA by RT-PCR 105 days after onset of symptoms, and 4.9% of close contacts tested positive for IgG antibodies using ELISA (Figure 3). Although the authors acknowledge limits of their study, they suggest this data provides insight to guide evolving public health polices for reducing viral transmission throughout Thailand.

ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although Thailand has been fairly effective at controlling the spread of COVID-19, continued disease surveillance and information on antibody response in recovered patients and their close contacts remain necessary in the absence of approved vaccines and antivirals. Here, we examined 217 recovered COVID-19 patients to assess their viral RNA shedding and residual antibodies against SARS-CoV-2. We also evaluated antibodies in blood samples from 308 close contacts of recovered COVID-19 patients. We found that viral RNA remained detectable in 6.6% of recovered COVID-19 cases and up to 105 days. IgM, IgG, and IgA antibodies against SARS-CoV-2 were detected in 13.8%, 88.5%, and 83.4% of the recovered cases 4-12 weeks after disease onset, respectively. Higher levels of antibodies detected were associated with severe illness patients experienced while hospitalized. Fifteen of the 308 contacts (4.9%) of COVID-19 cases tested positive for IgG antibodies, suggesting probable exposure. Viral clearance and the pattern of antibody responses in infected individuals are both crucial for effectively combating SARS-CoV-2. Our study provides additional information on the natural history of this newly emerging disease related to both natural host defenses and antibody duration.

Table 1. Recovered COVID-19 cases and close contacts included in this study and the results of antibody detection.

	Recovered cases	Close contacts
Total number	217	308
Median age in years (IQR)	33 (25–47)	35 (26–48)
Gender		
Number of males (%)	92 (42.4)	159 (51.6)
and median age in years (IQR)	36 (29–48)	34 (25–47)
Number of females (%)	125 (57.6)	149 (48.4)
and median age in years (IQR)	31 (25–45)	37 (27.5–51)
Clinical History		
Asymptomatic (%)	4 (1.8)	NA
Mild symptoms (%)	151 (69.6)	
Pneumonia (%)	59 (27.2)	
Pneumonia requiring intubation (%)	3 (1.4)	
Time from patient symptom onset to sample collection (days)	range 28–142	NA
	median 54 (IQR 45–61)	
Time from the last contact with patient to sample collection (days)	NA	range 1–128
		median 61.5
		(IQR 47.5–67)
IgM antibody detection		
Number of positive cases (%)	30/217 (13.8)	ND
Time from patient symptom onset to	range 34–67	
sample collection for positive cases (days)	median 51 (IQR 39–57.3)	
IgG antibody detection		
Number of positive cases (%)	192/217 (88.5)	15/308 (4.9)
Time from symptom onset to	range 28–142	
sample collection for positive case (days)	median 53 (IQR 44–60)	
IgA antibody detection		
Number of positive cases (%)	181/217 (83.4)	ND
Time from symptom onset to	range 28–142	
sample collection for positive cases (days)	median 53 (IQR 44–60)	

NA, not applicable; ND, not done.

Table 1. Recovered COVID-19 cases and close contacts included in this study and the results of antibody detection.

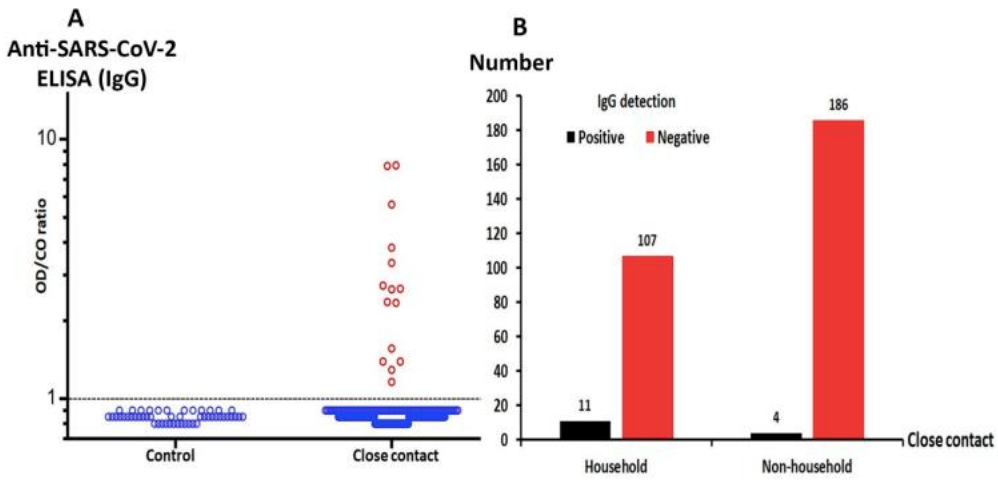


Figure 3. IgG antibody against SARS-CoV-2 among close contacts of COVID-19 cases. (A) IgG antibodies against SARS-CoV-2 in blood samples from 308 close contacts of COVID-19 cases compared to 50 healthy controls collected in 2018 (prior to the emergence of COVID-19). (B) IgG detection among household and non-household close contacts.

CLINICAL CARE OF PREGNANT AND POSTPARTUM WOMEN WITH COVID-19: LIVING RECOMMENDATIONS FROM THE NATIONAL COVID-19 CLINICAL EVIDENCE TASKFORCE

Vogel JP, Tendal B, Giles M, Whitehead C, Burton W, Chakraborty S, Cheyne S, Downton T, Fraile Navarro D, Gleeson G, Gordon A, Hunt J, Kitschke J, McDonald S, McDonnell N, Middleton P, Millard T, Murano M, Oats J, Tate R, White H, Elliott J, Roach V, Homer CSE; National COVID-19 Clinical Evidence Taskforce.. Aust N Z J Obstet Gynaecol. 2020 Oct 29. doi: 10.1111/ajo.13270. Online ahead of print.
Level of Evidence: 1 - Guidelines and Recommendations

BLUF

The National COVID-19 Clinical Evidence Taskforce reviewed 81 guidelines from 48 Australian organizations on antenatal, intrapartum, and postpartum care of women during the COVID-19 pandemic. Several highlighted recommendations on pregnancy and prenatal care include per usual care for mode of birth, skin to skin contact, breastfeeding, and administration of antenatal corticosteroids for women with preterm birth risk (Table 2). Recommendations on disease-modifying therapies (dexamethasone, remdesivir, etc.) for pregnant or postpartum COVID-19-positive females were also summarized (Table 3). These findings provide a more synchronized set of recommendations to guide care of pregnant women during the COVID-19 pandemic.

SUMMARY

Please note, recommendations within this article are current as of September 17, 2020. Please refer to https://covid19evidence.net.au/ for the latest updates on the recommendations.

ABSTRACT

To date, 18 living recommendations for the clinical care of pregnant and postpartum women with COVID-19 have been issued by the National COVID-19 Clinical Evidence Taskforce. This includes recommendations on mode of birth, delayed umbilical cord clamping, skin-to-skin contact, breastfeeding, rooming-in, antenatal corticosteroids, angiotensin-converting enzyme inhibitors, disease-modifying treatments (including dexamethasone, remdesivir and hydroxychloroquine), venous thromboembolism prophylaxis and advanced respiratory support interventions (prone positioning and extracorporeal membrane oxygenation). Through continuous evidence surveillance, these living recommendations are updated in near real-time to ensure clinicians in Australia have reliable, evidence-based guidelines for clinical decision-making. Please visit https://covid19evidence.net.au/ for the latest recommendation updates.

Intervention	Recommendation and remarks
Mode of birth	For pregnant women with COVID-19, mode of birth should remain as per usual care *(conditional recommendation, very low certainty evidence)* • There is currently no evidence to indicate that caesarean section for women with COVID-19 reduces the risk of vertical transmission to the newborn. Mode of birth should continue as per usual care. Respiratory deterioration due to COVID-19 may prompt urgent delivery on an individual basis.
Delayed umbilical cord clamping	Delayed umbilical cord clamping is supported as part of standard care, independent of the presence of COVID-1 *(consensus recommendation)* • There is currently no evidence that delayed umbilical cord clamping affects the risk of vertical transmission of COVID-19.
Skin-to-skin contact	Early skin-to-skin contact after birth and during the postnatal period is supported, irrespective of the presence of COVID-19. However, parents with COVID-19 should use infection prevention and control measures (mask and hand hygiene) *(consensus recommendation)* • Early skin-to-skin contact refers to placing the naked baby prone on the parent's bare chest immediately after birth. • Skin-to-skin contact should be encouraged and continue as per usual practice in other postnatal and neonatal settings, such as neonatal intensive care unit and postnatal wards, providing infection prevention and control measures are maintained.
Breastfeeding	Breastfeeding is supported irrespective of the presence of COVID-19. However, women with COVID-19 who are breastfeeding should use infection prevention and control measures (mask and hand hygiene) while infectious *(conditional recommendation, very low certainty evidence)* • There is currently no evidence to indicate that breastfeeding increases the risk of vertical transmission to the newborn. As there are substantial known benefits for breastfeeding, women should be supported to initiate or continue breastfeeding. If the baby is being fed with expressed breastmilk or formula, these same infection prevention and control measures should be used.
Rooming-in	For women with COVID-19 who have given birth, support rooming-in of mother and newborn in the birth suite and on the postnatal ward when both mother and baby are well. However, women with COVID-19 should use infection prevention and control measures (mask and hand hygiene) *(conditional recommendation, very low certainty evidence)* • There is currently no evidence to indicate that a woman with a known COVID-19 infection should be separated from her newborn to prevent transmission. As there are substantial known benefits for keeping mother and newborn together postpartum, women should be supported to be with their newborn as per usual care. • Women with COVID-19 should be encouraged and supported in using good hand hygiene before and after handling their baby, and using a mask while in close contact with their baby. To the extent possible, these women should practice physical distancing when not feeding or caring for the baby.
Antenatal corticosteroids	The use of antenatal corticosteroids for women at risk of preterm birth is supported as part of standard care, independent of the presence of COVID-19 *(consensus recommendation)* • There are clear benefits to using antenatal corticosteroids for women at risk of preterm birth at less than 34 weeks gestation. There is currently no evidence to suggest that antenatal corticosteroids cause additional maternal or fetal harm in the setting of COVID-19 when used for this indication. They should therefore be given where indicated. • The Taskforce has separate recommendations regarding the use of dexamethasone as a disease-modifying treatment in pregnant or breastfeeding women for COVID-19. Women with COVID-19 who are on oxygen and receiving dexamethasone do not require additional doses of corticosteroids for fetal lung maturation.
ACE inhibitors for postpartum women with hypertension requiring drug treatment	In postpartum women with COVID-19 who have hypertension requiring treatment with ACE inhibitors, there is currently no evidence to deviate from usual care. These medications should be initiated or continued unless otherwise contraindicated *(consensus recommendation)* • ACE inhibitors are contraindicated in the antenatal period due to risk of fetal and neonatal harm.

†Recommendations were current at the time of writing. Please visit The National COVID-19 Clinical Evidence Taskforce (https://covid19evidence.net.au/) for the latest updates to the recommendations. ACE, angiotensin-converting enzyme

Table 2. Pregnancy and perinatal care recommendations for women with COVID-19†

Dexamethasone as treatment for COVID-19	1. Use dexamethasone 6 mg daily intravenously or orally for up to ten days in pregnant or breastfeeding women with COVID-19 who are receiving oxygen (including mechanically ventilated patients) *(strong recommendation, low certainty evidence)*. 2. Do not routinely use dexamethasone to treat COVID-19 in pregnant or breastfeeding women who do not require oxygen *(strong recommendation, low certainty evidence)*. • Antenatal corticosteroids should still be used for fetal lung maturation in pregnant women at risk of preterm birth who also have COVID-19. Dexamethasone should still be used for other evidence-based indications in pregnant and breastfeeding women who have COVID-19.
Remdesivir as treatment for COVID-19	Use of remdesivir for pregnant or breastfeeding women with COVID-19 outside of a trial setting should not be considered routinely *(conditional recommendation, very low certainty evidence)*. • As pregnant and breastfeeding women are often excluded from clinical trials, use of remdesivir in this population would be outside a clinical trial setting. Pregnant and breastfeeding women receiving remdesivir should nonetheless be enrolled in national COVID-19 registries. Currently, there is no direct evidence of the effects of remdesivir in pregnant and breastfeeding women. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab. • Due to antagonism observed *in vitro*, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended.[90]
Hydroxychloroquine as treatment for COVID-19	Do not use hydroxychloroquine for the treatment of COVID-19 *(strong recommendation, moderate certainty evidence)*. • This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. • Use of hydroxychloroquine may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include hydroxychloroquine.
Hydroxychloroquine for post-exposure prophylaxis	For people exposed to individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, do not use hydroxychloroquine for post-exposure prophylaxis outside of randomised trials with appropriate ethical approval *(strong recommendation, low certainty evidence)*. Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use hydroxychloroquine for post-exposure prophylaxis in these populations unless they are eligible to be enrolled in trials.
Other disease-modifying treatments	For people with COVID-19, do not use the other disease-modifying treatments‡ outside of randomised trials with appropriate ethical approval *(strong recommendation, very low certainty evidence)*. • Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use in these populations unless they are eligible to be enrolled in trials.

†Recommendations were current at the time of writing. Please visit The National COVID-19 Clinical Evidence Taskforce (https://covid19evidence.net.au/) for the latest updates to the recommendations.
‡The treatments include: aprepitant, baloxavir marboxil, calcifediol, chloroquine, colchicine, convalescent plasma, darunavir-cobicistat, favipiravir, human mesenchymal stem cells, immunoglobulin plus methylprednisolone, interferon β-1a, interferon β-1b, interferon gamma, lopinavir-ritonavir, ruxolitinib, sofosbuvir-daclatasvir, telmisartan and umifenovir.

Table 3. Recommendations on use of disease-modifying treatments for pregnant or postpartum women with COVID-19†

ADJUSTING PRACTICE DURING COVID-19

FOR HEALTHCARE PROFESSIONALS

SARS-COV-2 AND THE NOSE: RISKS AND IMPLICATIONS FOR PRIMARY CARE

Campbell RG.. Aust J Gen Pract. 2020 Nov;49(11):728-732. doi: 10.31128/AJGP-05-20-5452.
Level of Evidence: 5 - Opinion

BLUF

An otolaryngologist from Australia reviews the pathophysiology of the SARS-CoV-2 virus and explains that the upper respiratory tract (nose and oropharynx) may be an especially vulnerable area for viral replication and thus transmission to healthcare providers performing physical examinations (highlights summarized). They suggest that General Practitioners (GPs) are more at risk to become infected and recommend GPs take extra precaution against COVID-19 especially after performing ear, nose, and throat examinations.

SUMMARY

This otolaryngologist explains that two early symptoms of COVID-19 are sudden loss of smell and loss of taste and such signs should be included in screening protocols for the virus.

For GPs known to perform procedures such as “applying nasal prong oxygen, spraying the nose, taking nasal and/or oral swabs, using nebulisers and performing nasendoscopy and spirometry,” PPE is of utmost importance, “studies have shown that no nosocomial transmission occurred when appropriate PPE was worn.”

“Appropriate PPE for aerosol-generating procedures includes a surgical or N95 mask, goggles or a visor, a waterproof gown with full length sleeves (ideally with thumb hooks)” and “if significant aerosolisation is expected, gloves that cover the sleeves of the gown and a cover for the hair.”

“It is also recommended to avoid asking a patient with a known tympanic membrane perforation to perform a Valsalva manoeuvre, as SARS-CoV-2 has been detected in the middle ear and mastoid cavity.”

ABSTRACT

BACKGROUND: General practitioners (GPs) have some of the highest rates of mortality from COVID-19 among healthcare workers. SARS-CoV-2 has unique properties that place GPs at particular risk. OBJECTIVE: The aim of this article is to discuss the nose-related features of SARS-CoV-2 that place GPs at risk, and to make recommendations pertinent to the safety and protection of primary healthcare physicians. DISCUSSION: The highest viral load of SARS-CoV-2 is in the nose and nasopharynx. It is often highest early in the illness, before the development of symptoms. Further, SARS-CoV-2 replicates and continues to shed in the nasopharynx long after the virus is no longer detectable in the lower respiratory tract. This places any physician performing examinations on, or procedures involving, the upper respiratory tract at risk for contracting COVID-19. New-onset hyposmia and dysgeusia are indicators for COVID-19 and should be included in screening protocols.

SURGICAL SUBSPECIALTIES

DEVELOPMENT AND PERFORMANCE OF A CLINICAL DECISION SUPPORT TOOL TO INFORM RESOURCE UTILIZATION FOR ELECTIVE OPERATIONS

Goldstein BA, Cerullo M, Krishnamoorthy V, Blitz J, Mureebe L, Webster W, Dunston F, Stirling A, Gagnon J, Scales CD Jr.. JAMA Netw Open. 2020 Nov 2;3(11):e2023547. doi: 10.1001/jamanetworkopen.2020.23547.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Researchers at Duke University Health System conducted a prognostic study using medical records from 3 hospitals between 2017-2020 to develop a Clinical Decision Support (CDS) tool which determines urgency of surgical procedures based on general length of stay, ICU length of stay, ventilator need, and skilled nursing facility (SNF) need (Figure 1, Table 2). They note

the tool is limited by lack of external validity and inability to consider factors like daily or seasonal case load variation. Given the consideration for case prioritization regarding elective producers during the COVID-19 pandemic, authors suggest clinical tools such as CDS could be useful for resource allocation, but further research is needed to confirm their effectiveness in a hospital setting.

ABSTRACT

Importance: Hospitals ceased most elective procedures during the height of coronavirus disease 2019 (COVID-19) infections. As hospitals begin to recommence elective procedures, it is necessary to have a means to assess how resource intensive a given case may be. Objective: To evaluate the development and performance of a clinical decision support tool to inform resource utilization for elective procedures. Design, Setting, and Participants: In this prognostic study, predictive modeling was used on retrospective electronic health records data from a large academic health system comprising 1 tertiary care hospital and 2 community hospitals of patients undergoing scheduled elective procedures from January 1, 2017, to March 1, 2020. Electronic health records data on case type, patient demographic characteristics, service utilization history, comorbidities, and medications were and abstracted and analyzed. Data were analyzed from April to June 2020. Main Outcomes and Measures: Predicitons of hospital length of stay, intensive care unit length of stay, need for mechanical ventilation, and need to be discharged to a skilled nursing facility. These predictions were generated using the random forests algorithm. Predicted probabilities were turned into risk classifications designed to give assessments of resource utilization risk. Results: Data from the electronic health records of 42 199 patients from 3 hospitals were abstracted for analysis. The median length of stay was 2.3 days (range, 1.3-4.2 days), 6416 patients (15.2%) were admitted to the intensive care unit, 1624 (3.8%) received mechanical ventilation, and 2843 (6.7%) were discharged to a skilled nursing facility. Predictive performance was strong with an area under the receiver operator characteristic ranging from 0.76 to 0.93. Sensitivity of the high-risk and medium-risk groupings was set at 95%. The negative predictive value of the low-risk grouping was 99%. We integrated the models into a daily refreshing Tableau dashboard to guide decision-making. Conclusions and Relevance: The clinical decision support tool is currently being used by surgical leadership to inform case scheduling. This work shows the importance of a learning health care environment in surgical care, using quantitative modeling to guide decision-making.

FIGURES

Table 2. Top Predictor Variables From Each of the Models

Outcome	Length of stay	Need for ICU	ICU length of stay	Need for ventilator	Discharge to SNF
Top predictor					
1	Age	Specialty	Age	Age	Procedure type: coronary artery bypass grafting
2	No. of previous hospital encounters	Service	No. of previous outpatient encounters	No. of previous outpatient encounters	Procedure type: endoscopic video of harvest vein bypass
3	No. of previous outpatient encounters	Procedure type: microsurgery	Specialty	Service	Procedure type: valve surgery
4	Specialty	Age	Service	BMI	History of cardiac surgery
5	Service	Procedure type: excise supratentorial brain tumor	BMI	No. of previous emergency encounters	Age

Abbreviations: BMI, body mass index; ICU, intensive care unit; SNF, skilled nursing facility.

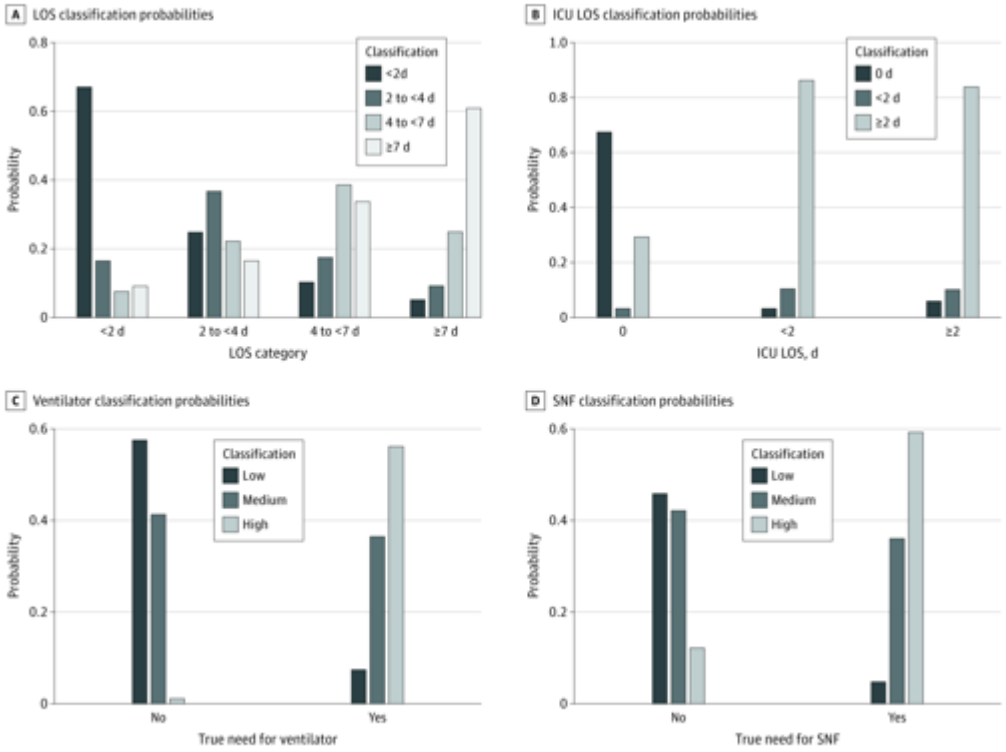


Figure 1.

Performance of Each of the 4 Classification Models. A, 786 of 1291 patients (60.9%) are categorized as having a long length of stay (LOS), while 3721 of 5561 patients (66.9%) are categorized as having a short LOS. B, 573 of 689 patients (83.2%) with a long intensive care unit (ICU) stay are correctly classified, as are 8052 of 11928 patients (67.5%) with no ICU stay. C, Of 529 patients who needed a ventilator, 503 (95.1%) are in the medium- or high-risk categories. D, Of 952 patients who will be discharged to a skilled nursing facility (SNF) 904 (94.9%) are in the medium- or high-risk categories.

PERFORMANCE OF NUCLEOCAPSID AND SPIKE-BASED SARS-COV-2 SEROLOGIC ASSAYS

Rikhtegaran Tehrani Z, Saadat S, Saleh E, Ouyang X, Constantine N, DeVico AL, Harris AD, Lewis GK, Kottilil S, Sajadi MM.. PLoS One. 2020 Nov 2;15(11):e0237828. doi: 10.1371/journal.pone.0237828. eCollection 2020.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Investigators at the University of Maryland (U.S.) examined the estimated sensitivity and specificity of several SARS-CoV-2 antibody tests, including 3 in-house ELISAs (one detecting anti-trimer IgG antibodies, one anti-trimer IgA antibodies, and another IgG anti-capsid antibodies), 4 commercial ELISAs (EDI Novel Coronavirus COVID-19 IgG and IgM, Euroimmun SARS-CoV-2 IgG and IgA), and one lateral flow immunoassay (DPP COVID-19 IgM/IgG). When analyzing 300 pre-epidemic samples (including 66 HIV infected samples) and 100 RT-PCR confirmed SARS-CoV-2 positive samples, the in-house ELISAs generally showed the greatest sensitivity and specificity (illustrated below; Tables 2 and 3). While the in-house ELISAs appear to demonstrate an improvement in antibody detection against SARS-CoV-2, the authors relate that creating testing algorithms with more than 1 assay may be needed to eliminate false positives.

SUMMARY

The sensitivities and specificities of the examined SARS-CoV-2 antibody tests are summarized below:
- in-house trimer spike IgA: 90%/100%
- in-house trimer spike IgG: 90%/99.3%
- in-house nucleocapsid IgG: 89%/98.3%
- EDI nucleocapsid IgM: 73.7%/100%
- EDI nucleocapsid IgG: 84.5%/95.1%
- Euroimmun S1 IgA: 95%/ 93.7%
- Euroimmun S1 IgG: 82.8%/99.7%
- Chembio nucleocapsid IgM: 82.0%/91.7%
- Chembio nucleocapsid IgG: 92%/93.3%

ABSTRACT

There is an urgent need for an accurate antibody test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We have developed 3 ELISA methods, trimer spike IgA, trimer spike IgG, and nucleocapsid IgG, for detecting anti-SARS-CoV-2 antibodies. We evaluated their performance along with four commercial ELISAs, EDI Novel Coronavirus COVID-19 ELISA IgG and IgM, Euroimmun Anti-SARS-CoV-2 ELISA IgG and IgA, and one lateral flow assay, DPP COVID-19 IgM/IgG System (Chembio). Both sensitivity and specificity were evaluated and the probable causes of false-positive reactions were determined. The assays were evaluated using 300 pre-epidemic samples and 100 PCR-confirmed COVID-19 samples. The sensitivities and specificities of the assays were as follows: 90%/100% (in-house trimer spike IgA), 90%/99.3% (in-house trimer spike IgG), 89%/98.3% (in-house nucleocapsid IgG), 73.7%/100% (EDI nucleocapsid IgM), 84.5%/95.1% (EDI nucleocapsid IgG), 95%/93.7% (Euroimmun S1 IgA), 82.8%/99.7% (Euroimmun S1 IgG), 82.0%/91.7% (Chembio nucleocapsid IgM), 92%/93.3% (Chembio nucleocapsid IgG). The presumed causes of false positive results from pre-epidemic samples in commercial and in-house assays were mixed. In some cases, assays lacked reproducibility. In other cases, reactivity was abrogated by competitive inhibition (spiking the sample with the same antigen that was used for coating ELISAs prior to performing the assay), suggesting positive reaction could be attributed to the presence of antibodies against these antigens. In other cases, reactivity was consistently detected but not abrogated by the spiking, suggesting positive reaction was not attributed to the presence of antibodies against these antigens. Overall, there was wide variability in assay performance using our samples, with in-house tests exhibiting the highest combined sensitivity and specificity. The causes of "false positivity" in pre-epidemic samples may be due to plasma antibodies apparently reacting with the corresponding antigen, or spurious reactivity may be directed against non-specific components in the assay system. Identification of these targets will be essential to improving assay performance.

FIGURES

Method		Trimer Spike IgA	Trimer Spike IgG	Nucleocapsid IgG
Mean Neg. OD +3 SD	Cutoff	0.12	0.19	0.20
	True Positive	91/100	90/100	89/100
	True Negative	295/300	296/300	295/300
	Indeterminate	N/A	N/A	N/A
	Sensitivity (95% CI)	91.0% (85.4–96.6)	90.0% (84.1–95.9)	89.0% (82.9–95.1)
	Specificity (95% CI)	98.3% (96.8–99.8)	98.7% (97.4–100)	98.3% (96.8–99.8)
	Accuracy (95% CI)	96.5% (94.7–98.3)	96.5% (94.7–98.3)	96.0% (94.1–97.9)
ROC Curve	Cutoff	0.15	0.28	0.19
	True Positive	90/100	90/100	89/100
	True Negative	300/300	298/300	295/300
	Indeterminate	N/A	N/A	N/A
	Sensitivity (95% CI)	90.0% (84.1–95.9)	90.0% (84.1–95.9)	89.0% (82.9–95.1)
	Specificity (95% CI)	100% (98.7–100)	99.3% (98.4–100)	98.3% (97.8–99.8)
	Maximum J index	0.900	0.893	0.873
	Accuracy (95% CI)	97.5% (96.0–99.0)	97.0% (95.3–98.7)	96.0% (94.1–97.9)
	AUC	0.975	0.966	0.976

Table 2. Performance of the in-house ELISAs using different calculated cutoff values.

	EDI IgG	EDI IgM	Euro IgA	Euroimmun IgG	ChemBio IgM	ChemBio IgG
True Positive	82/97	70/95	95/100	82/99	82/100	92/100
True Negative	274/288	299/299	266/284	297/298	275/300	280/300
Indeterminate	15/400	6/400	16/400	3/400	N/A	N/A
Sensitivity (95% CI)	84.5% (77.3–91.7)	73.7% (64.8–82.6)	95.0% (90.7–99.3)	82.8% (75.4–90.2)	82.0% (74.5–89.5)	92.0% (86.7–97.3)
Specificity (95% CI)	95.1% (92.6–97.6)	100% (98.7–100)	93.7% (90.9–96.5)	99.7% (99.1–100.0)	91.7% (88.6–94.8)	93.3% (90.5–96.1)
Accuracy (95% CI)	92.5% (89.9–95.1)	93.7% (91.3–96.1)	94.0% (91.6–96.4)	95.5% (93.5–97.5)	89.3% (86.3–92.3)	93.0% (90.5–95.5)
AUC	0.944	0.964	0.970	0.966	NA	NA

Table 3. Performance of commercial assays.

DEVELOPMENTS IN TREATMENTS

EFFECT OF DISEASE DURATION IN A RANDOMIZED PHASE III TRIAL OF RINTATOLIMOD, AN IMMUNE MODULATOR FOR MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME

Strayer DR, Young D, Mitchell WM.. PLoS One. 2020 Oct 29;15(10):e0240403. doi: 10.1371/journal.pone.0240403. eCollection 2020.

Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

A randomized Phase III trial conducted by researchers affiliated with AIM Immunotech Inc. in Philadelphia, PA investigated use of rintatolimod (a selective TLR3 agonist) in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and found a subset of patients with symptom duration of 2-8 years who received treatment (n=75) had ≥2 fold increased exercise response (Table 2) with 51.2% showing >25% increase in exercise tolerance (Figure 1). Among patients with a disease duration window of 2-8 years, this is a significant improvement when compared to 5 FDA-approved drugs, leading to clinically significant quality of life enhancement (Figure 2). Authors advocate for investigation of rintatolimod as a potential therapeutic agent in patients with COVID-19 "long-hauler" post-viral syndrome to reduce lingering brain-fog and fatigue.

ABSTRACT

BACKGROUND: Rintatolimod is a selective TLR3 agonist, which has demonstrated clinical activity for ME/CFS in Phase II and Phase III double-blind, placebo-controlled, randomized, multi-site clinical trials. METHODS AND FINDINGS: A hypothesis-based post-hoc analysis of the Intent to Treat (ITT) population diagnosed with ME/CFS from 12 independent clinical sites of a Phase III trial was performed to evaluate the effect of rintatolimod therapy based on disease duration. The clinical activity of

rintatolimod was evaluated by exercise treadmill tolerance (ETT) using a modified Bruce protocol. The ITT population (n = 208) was divided into two subsets of symptom duration. Patients with symptom duration of 2-8 years were identified as the Target Subset (n = 75); the remainder (<2 year plus >8 year) were identified as the Non-Target Subset (n = 133). Placebo-adjusted percentage improvements in exercise duration and the vertical rise for the Target Subset (n = 75) were more than twice that of the ITT population. The Non-Target Subset (n = 133) failed to show any clinically significant ETT response to rintatolimod when compared to placebo. Within the Target Subset, 51.2% of rintatolimod-treated patients improved their exercise duration by >=25% (p = 0.003) despite reduced statistical power from division of the original ITT population into two subsets. CONCLUSION/SIGNIFICANCE: Analysis of ETT from a Phase III trial has identified within the ITT population, a subset of ME/CFS patients with >=2 fold increased exercise response to rintatolimod. Substantial improvement in physical performance was seen for the majority (51.2%) of these severely debilitated patients who improved exercise duration by >=25%. This magnitude of exercise improvement was associated with clinically significant enhancements in quality of life. The data indicate that ME/CFS patients have a relatively short disease duration window (<8 years) to expect a significant response to rintatolimod under the dosing conditions utilized in this Phase III clinical trial. These results may have direct relevance to the cognitive impairment and fatigue being experienced by patients clinically recovered from COVID-19 and free of detectable SARS-CoV-2. TRIAL REGISTRATION: ClinicalTrials.gov: NCT00215800.

FIGURES

AMP-516 Cohort	Increase from baseline (in seconds) mean±SD (95% mean CI)		% Increase in intra-group means	
	Rintatolimod	Placebo	Rintatolimod	Placebo
ITT Population n = 208	95.7±251.3 (45.8, 145.5)	28.2±226.5 (-15.0, 71.5)	16.6	4.8
	Δ = 67.5 p = 0.043*		Δ = 11.8	
Target Subset n = 75	146.7±261.1 (64.3, 229.1)	24.2±262.8	27.8	4.2
	Δ = 122.5 p = 0.047*		Δ = 23.6	
Non-Target Subset n = 133	60.2±240.2 (-2.4, 122.8)	30.1±209.7 (-18.5, 78.7)	9.8	5.1
	Δ = 30.1 p = 0.44*		Δ = 4.7	

Δ = Difference between rintatolimod and placebo.
* Student's T-test (2-sided).

Table 2. Comparison of change from baseline in mean ETT duration at Week 40 for ITT population vs. target and non-target subsets.

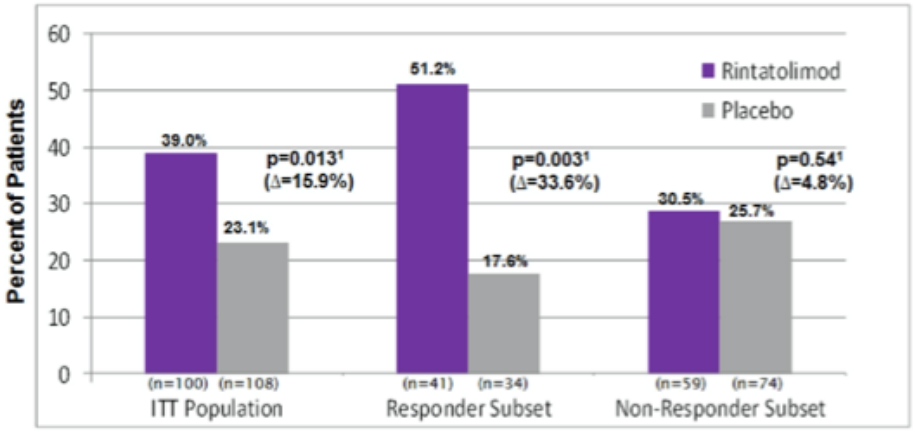


Fig 1. ME/CFS patients with a ≥25% increase in treadmill ET from baseline at Week 40.

Fig 1. ME/CFS patients with a >25% increase in treadmill ET from baseline at Week 40.

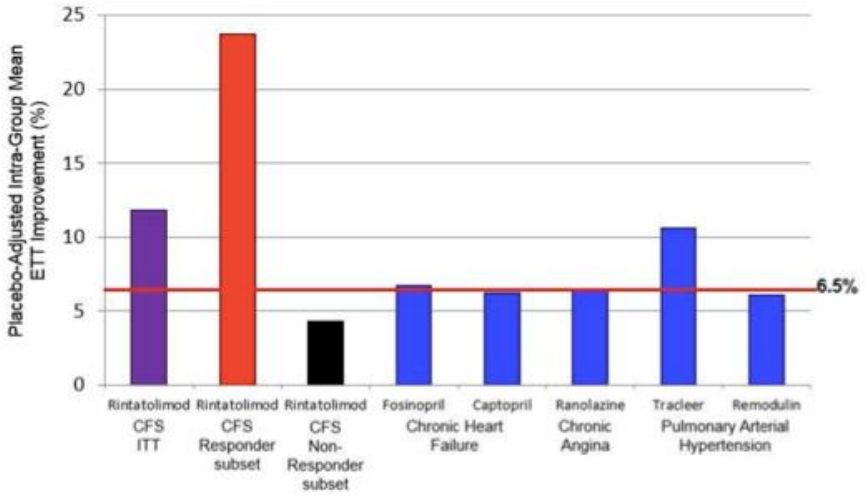


Fig 2. The Placebo-adjusted percent intra-group mean exercise improvements for rintatolimod: ITT population and the target subset comparisons to drugs approved for non-ME/CFS severe exertional fatigue.

Fig 2. The Placebo-adjusted percent intra-group mean exercise improvements for rintatolimod: ITT population and the target subset comparisons to drugs approved for non-ME/CFS severe exertional fatigue.

5-ALPHA-REDUCTASE INHIBITORS ARE ASSOCIATED WITH REDUCED FREQUENCY OF COVID-19 SYMPTOMS IN MALES WITH ANDROGENETIC ALOPECIA

McCoy J, Cadegiani FA, Wambier CG, Herrera S, Vaño-Galván S, Mesinkovska NA, Ramos PM, Shapiro J, Sinclair R, Tosti A, Goren A.. J Eur Acad Dermatol Venereol. 2020 Nov 2. doi: 10.1111/jdv.17021. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A team of biologists and dermatologists from various institutions in the United States, Spain and Brazil conducted a retrospective cohort study of SARS-CoV-2 positive male patients with androgenetic alopecia (n=113) presenting to outpatient clinics in Brazil between June 15 and July 28, 2020. They found men taking dutasteride (a 5-alpha-reductase inhibitor; n=48) had a significantly reduced frequency of 20/29 COVID-19 symptoms (P<0.05; Figure 1) compared to men not taking dutasteride (n=65; Table 1). Authors suggest androgens may play a role in COVID-19 severity and more studies are needed to investigate possible benefits of 5-alpha-reductase inhibitors.

ABSTRACT

We have previously reported that men with androgenetic alopecia (AGA) are more likely to present with severe COVID-19 symptoms, potentially implicating androgen sensitivity as a risk factor for COVID-19.1-3 As such, we hypothesized that 5-alpha-reductase inhibitors (5ARi) may reduce the severity of COVID-19 disease. To test this hypothesis we conducted a retrospective cohort analysis on male subjects with laboratory confirmed SARS-CoV-2 infection. The subjects presented at one of five outpatient clinics (Corpometria Institute Brasilia, Brazil) from June 15 to July 28, 2020. At the time of visit, 29 clinical symptoms associated with SARS-CoV-2 infection were documented. For analysis, male subjects with AGA were selected. The frequency of clinical symptoms in males with AGA using 5ARis was compared to those not using 5ARis.

FIGURES

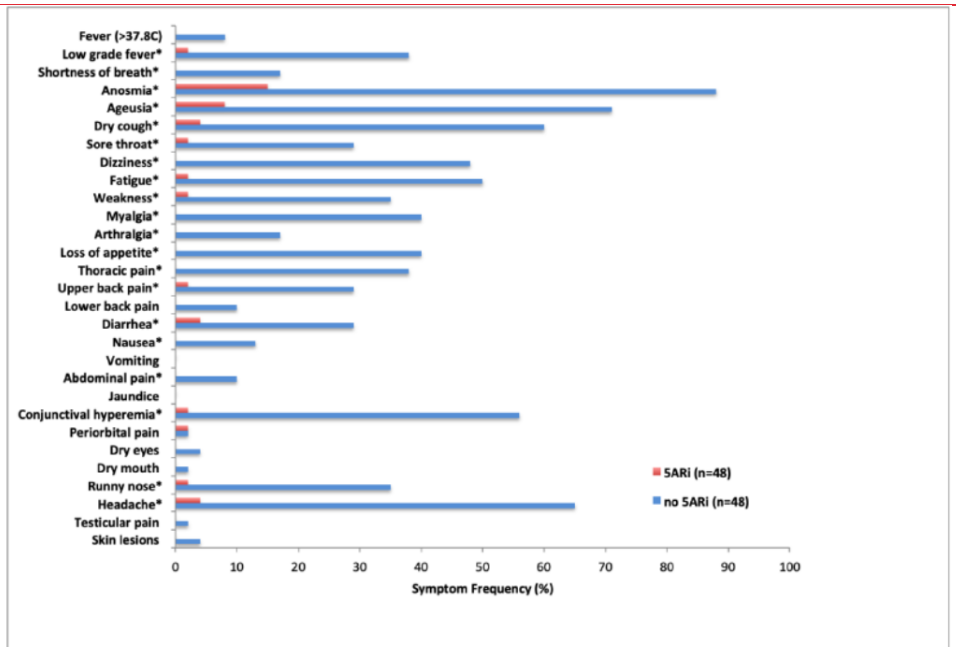
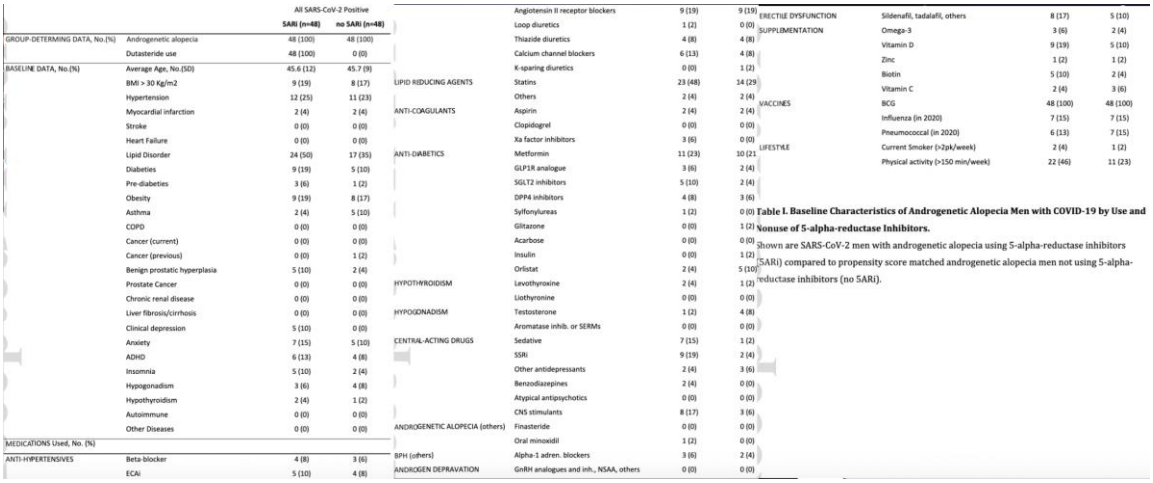


Figure 1: Frequency of 29 clinical symptoms was observed in males with androgenetic alopecia using 5-alpha-reductase inhibitors (5ARi) compared to males with AGA not using 5ARis



		All SARS-CoV-2 Positive	
		SARi (n=48)	no SARi (n=48)
GROUP-DETERMING DATA, No.(%)	Androgenetic alopecia	48 (100)	48 (100)
	Dutasteride use	48 (100)	0 (0)
BASELINE DATA, No.(%)	Average Age, No.(SD)	45.6 (12)	45.7 (9)
	BMI > 30 Kg/m2	9 (19)	8 (17)
	Hypertension	12 (25)	11 (23)
	Myocardial infarction	2 (4)	2 (4)
	Stroke	0 (0)	0 (0)
	Heart Failure	0 (0)	0 (0)
	Lipid Disorder	24 (50)	17 (35)
	Diabetes	9 (19)	5 (10)
	Pre-diabetes	3 (6)	1 (2)
	Obesity	9 (19)	8 (17)
	Asthma	2 (4)	5 (10)
	COPD	0 (0)	0 (0)
	Cancer (current)	0 (0)	0 (0)
	Cancer (previous)	0 (0)	1 (2)
	Benign prostatic hyperplasia	5 (10)	2 (4)
	Prostate Cancer	0 (0)	0 (0)
	Chronic renal disease	0 (0)	0 (0)
	Liver fibrosis/cirrhosis	0 (0)	0 (0)
	Clinical depression	5 (10)	0 (0)
	Anxiety	7 (15)	5 (10)
	ADHD	6 (13)	4 (8)
	Insomnia	5 (10)	2 (4)
	Hypogonadism	3 (6)	4 (8)
	Hypothyroidism	2 (4)	1 (2)
	Autoimmune	0 (0)	0 (0)
	Other Diseases	0 (0)	0 (0)
MEDICATIONS Used, No. (%)			
ANTI-HYPERTENSIVES	Beta-blocker	4 (8)	3 (6)
	ECAi	5 (10)	4 (8)
	Angiotensin II receptor blockers	9 (19)	9 (19)
	Loop diuretics	1 (2)	0 (0)
	Thiazide diuretics	4 (8)	4 (8)
	Calcium channel blockers	6 (13)	4 (8)
	K-sparing diuretics	0 (0)	1 (2)
LIPID REDUCING AGENTS	Statins	23 (48)	14 (29
	Others	2 (4)	2 (4)
ANTI-COAGULANTS	Aspirin	2 (4)	2 (4)
	Clopidogrel	0 (0)	0 (0)
	Xa factor inhibitors	3 (6)	0 (0)
ANTI-DIABETICS	Metformin	11 (23)	10 (21
	GLP1R analogue	3 (6)	2 (4)
	SGLT2 inhibitors	5 (10)	2 (4)
	DPP4 inhibitors	4 (8)	3 (6)
	Syffonylureas	1 (2)	0 (0)
	Glitazone	0 (0)	1 (2)
	Acarbose	0 (0)	0 (0)
	Insulin	0 (0)	1 (2)
	Orlistat	2 (4)	5 (10)
HYPOTHYROIDISM	Levothyroxine	2 (4)	1 (2)
	Liothyronine	0 (0)	0 (0)
HYPOGONADISM	Testosterone	1 (2)	4 (8)
	Aromatase inhib. or SERMs	0 (0)	0 (0)
CENTRAL-ACTING DRUGS	Sedative	7 (15)	1 (2)
	SSRi	9 (19)	2 (4)
	Other antidepressants	2 (4)	3 (6)
	Benzodiazepines	2 (4)	0 (0)
	Atypical antipsychotics	0 (0)	0 (0)
	CNS stimulants	8 (17)	3 (6)
ANDROGENETIC ALOPECIA (others)	Finasteride	0 (0)	0 (0)
	Oral minoxidil	1 (2)	0 (0)
BPH (others)	Alpha-1 adren. blockers	3 (6)	2 (4)
ANDROGEN DEPRAVATION	GnRH analogues and inh., NSAA, others	0 (0)	0 (0)
ERECTILE DYSFUNCTION	Sildenafil, tadalafil, others	8 (17)	5 (10)
SUPPLEMENTATION	Omega-3	3 (6)	2 (4)
	Vitamin D	9 (19)	5 (10)
	Zinc	1 (2)	1 (2)
	Biotin	5 (10)	2 (4)
	Vitamin C	2 (4)	3 (6)
VACCINES	BCG	48 (100)	48 (100)
	Influenza (in 2020)	7 (15)	7 (15)
	Pneumococcal (in 2020)	6 (13)	7 (15)
LIFESTYLE	Current Smoker (>2pk/week)	2 (4)	1 (2)
	Physical activity (>150 min/week)	22 (46)	11 (23)

Table I. Baseline Characteristics of Androgenetic Alopecia Men with COVID-19 by Use and Nonuse of 5-alpha-reductase Inhibitors.

Shown are SARS-CoV-2 men with androgenetic alopecia using 5-alpha-reductase inhibitors (5ARi) compared to propensity score matched androgenetic alopecia men not using 5-alpha-reductase inhibitors (no 5ARi).

SELECTION, BIOPHYSICAL AND STRUCTURAL ANALYSIS OF SYNTHETIC NANOBODIES THAT EFFECTIVELY NEUTRALIZE SARS-COV-2

Custódio TF, Das H, Sheward DJ, Hanke L, Pazicky S, Pieprzyk J, Sorgenfrei M, Schroer MA, Gruzinov AY, Jeffries CM, Graewert MA, Svergun DI, Dobrev N, Remans K, Seeger MA, McInerney GM, Murrell B, Hällberg BM, Löw C.. Nat Commun. 2020 Nov 4;11(1):5588. doi: 10.1038/s41467-020-19204-y.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

Investigators mainly from Centre for Structural Systems Biology (CSSB) in Germany detail the research efforts to rapidly isolate and characterize synthetic nanobodies (sybodies, Sb) to determine potential candidates in use for future SARS-CoV-2 therapies. Their results yielded a promising target, Sb23, which showed high affinity and effective neutralization of SARS-CoV-2 pseudovirus (Figure 3). This synthetic nanobody also exibited competitive binding capacity at the ACE2 site (Figure 6), suggesting Sb23 may be a good candidate in the development of future treatments to fight COVID-19.

ABSTRACT

The coronavirus SARS-CoV-2 is the cause of the ongoing COVID-19 pandemic. Therapeutic neutralizing antibodies constitute a key short-to-medium term approach to tackle COVID-19. However, traditional antibody production is hampered by long development times and costly production. Here, we report the rapid isolation and characterization of nanobodies from a synthetic library, known as sybodies (Sb), that target the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. Several binders with low nanomolar affinities and efficient neutralization activity were identified of which Sb23 displayed high affinity and neutralized pseudovirus with an IC50 of 0.6 microg/ml. A cryo-EM structure of the spike bound to Sb23 showed that Sb23 binds competitively in the ACE2 binding site. Furthermore, the cryo-EM reconstruction revealed an unusual conformation of the spike where two RBDs are in the 'up' ACE2-binding conformation. The combined approach represents an alternative, fast workflow to select binders with neutralizing activity against newly emerging viruses.

FIGURES

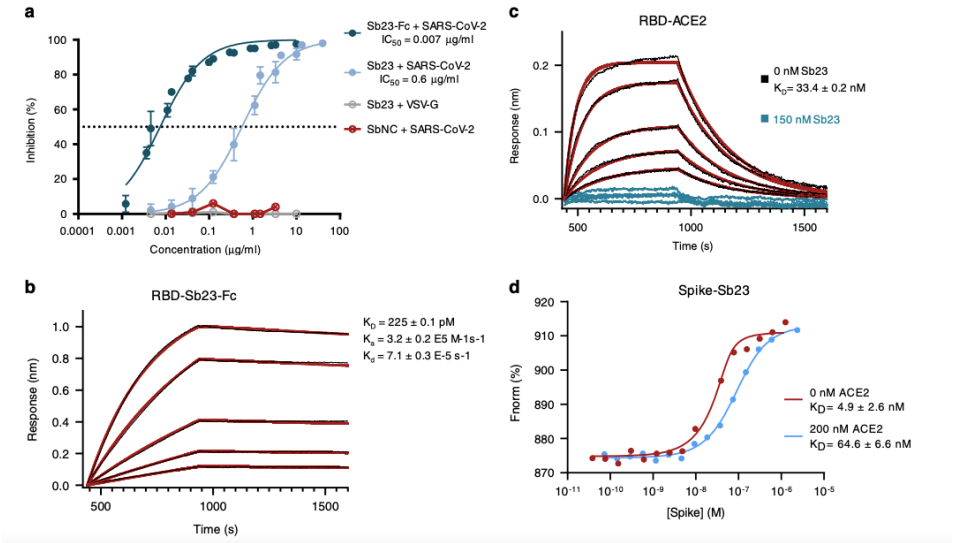


Figure 3. Sb23 neutralizes SARS-CoV-2 pseudoviruses and competes with ACE2. a SARS-CoV-2 or VSV-G spike pseudotyped lentivirus was incubated with a dilution series of Sb23, Sb23-Fc, or a control sybody (specific for hPepT2). Neutralization by Sb23 is a representative of two independent experiments. Data are mean ± SD of six replicate experiments. Neutralization by Sb23-Fc represents two independent assays, performed in duplicates. Data are mean ± SD of two or four replicate experiments. b BLI sensorgrams of immobilized SARS-CoV-2 RBD with 2-fold serial dilution of 20 nM Sb23-Fc. Binding curves are colored black and the global fit of the data to a 1:1 binding model is red. c BLI sensorgrams of immobilized SARS-CoV-2 RBD with ACE2 in the presence (blue) or absence (black) of 150 nM Sb23. The assay was performed in a concentration range of 200-12.5 nM ACE2 and fit of the data to a 1:1 binding model is shown in red. d Microscale thermophoresis (MST) binding data of spike with fluorescently labeled Sb23, in the presence or absence of 200 nM ACE2. One representative measurement is shown. Three independent measurements were performed and affinities of spike to Sb23 in the absence of ACE2 ranged from 0.6 to 10 nM, while they were significantly lower in the presence of ACE2 (KD = 58–200 nM).

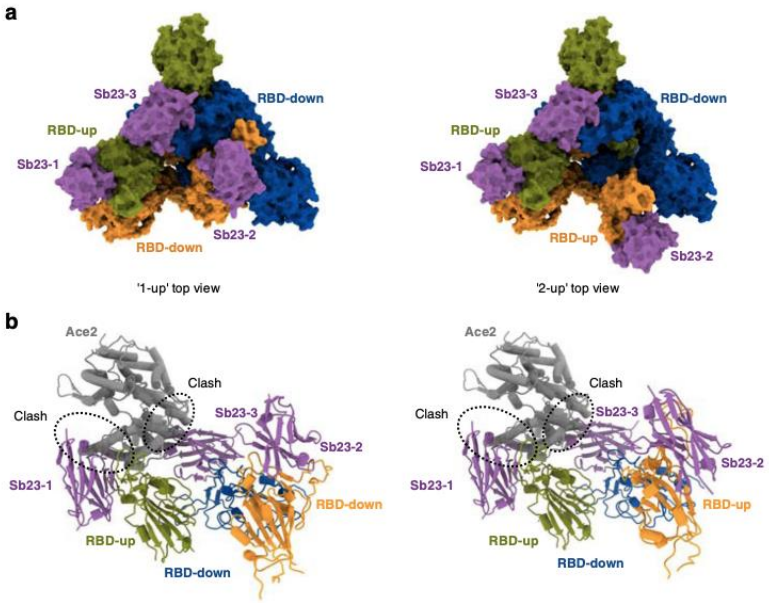


Figure 6. Top view of cryo-EM reconstruction of SARS-CoV-2 spike bound to Sb23 and modeling of the structural basis for Sb23-based blockage of SARSCoV-2 spike binding to ACE2. a Top view of locally sharpened Coulomb potential map and cartoon model of Sb23 bound to the spike protein in the "1-up"conformation b Top view of locally sharpened Coulomb potential map and cartoon model of Sb23 bound to the spike protein in the "2-up" conformation. c Cartoon model of Sb23-bound Spike in the "1-up" (left) "2-up" (right) conformation showing how ACE2 binding is blocked by Sb23 bound to the RBD in the "up" conformation as well as Sb23 bound to the neighboring RBD in the down conformation.

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