The Daily COVID-19 Literature Surveillance Summary

February 08, 2021

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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

Epidemiology

- Thrombosis and bleeding in COVID-19 VV ECMO patients continues to be present. Intensivists and a hematologist from Cambridge evaluated the incidence of thrombotic and bleeding events in 30 patients with COVID-19 who had received a full body computed tomography (CT) scan prior to initiation of veno-venous extracorporeal oxygenation (VV-ECMO). The authors report their data inconsistently, but their figures suggest that whole body computed tomography scanner (CT) on admission showed 12 patients had isolated thrombosis, 1 patient had an isolated bleed, and 5 had both. There was no association between a thrombotic or bleeding event and aPTT range. The authors conclude bleeding and thrombotic events are common in COVID-19 patients despite anticoagulation.

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CLIMATE

SLEEP AND MENTAL HEALTH IN ATHLETES DURING COVID-19 LOCKDOWN

Facer-Childs ER, Hoffman D, Tran JN, Drummond SPA, Rajaratnam SMW.. Sleep. 2021 Feb 4:zsaa261. doi: 10.1093/sleep/zsaa261. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A team from the Turner Institute for Brain and Mental Health in Victoria, Australia surveyed 375 self-identified athletes recruited via social media and sports team contacts from May 1 to June 1, 2020. They found athletes trained less frequently, in shorter durations, and earlier in the day while reporting increased sleep time and sleep latency, later mid-sleep times and decreased social jet lag. These changes correlated with a reported increase in depression, anxiety and stress (Figure 2). Authors suggest the observed differences in sleep and training patterns should help guide management of all athletes in the COVID-19 pandemic and beyond.

ABSTRACT

The global coronavirus 19 (COVID-19) pandemic and associated lockdown restrictions resulted in the majority of sports competitions around the world being put on hold. This includes the National Basketball Association, the UEFA Champions League, Australian Football League, the Tokyo 2020 Olympic Games, and regional competitions. The mitigation strategies in place to control the pandemic have caused disruption to daily schedules, working environments, and lifestyle factors. Athletes rely on regular access to training facilities, practitioners, and coaches to maintain physical and mental health to achieve maximal performance and optimal recovery. Furthermore, participation in sport at any level increases social engagement and promotes better mental health. It is, therefore, critical to understanding how the COVID-19 pandemic and associated lockdown measures have affected the lives of athletes. We surveyed elite and sub-elite athletes (n = 565) across multiple sports. Significant disruptions were reported for all lifestyle factors including social interactions, physical activity, sleep patterns, and mental health. We found a significant increase in total sleep time and sleep latency, as well as a delay in mid-sleep times and a decrease in social jetlag. Training frequency and duration significantly decreased. Importantly, the changes to training and sleep-related factors were associated with mental health outcomes. With spikes in COVID-19 cases rising around the world and governments reinstituting lockdowns (e.g. United Kingdom; Melbourne, Australia; California, USA) these results will inform messaging and strategies to better manage sleep and mental health in a population for whom optimal performance is critical.

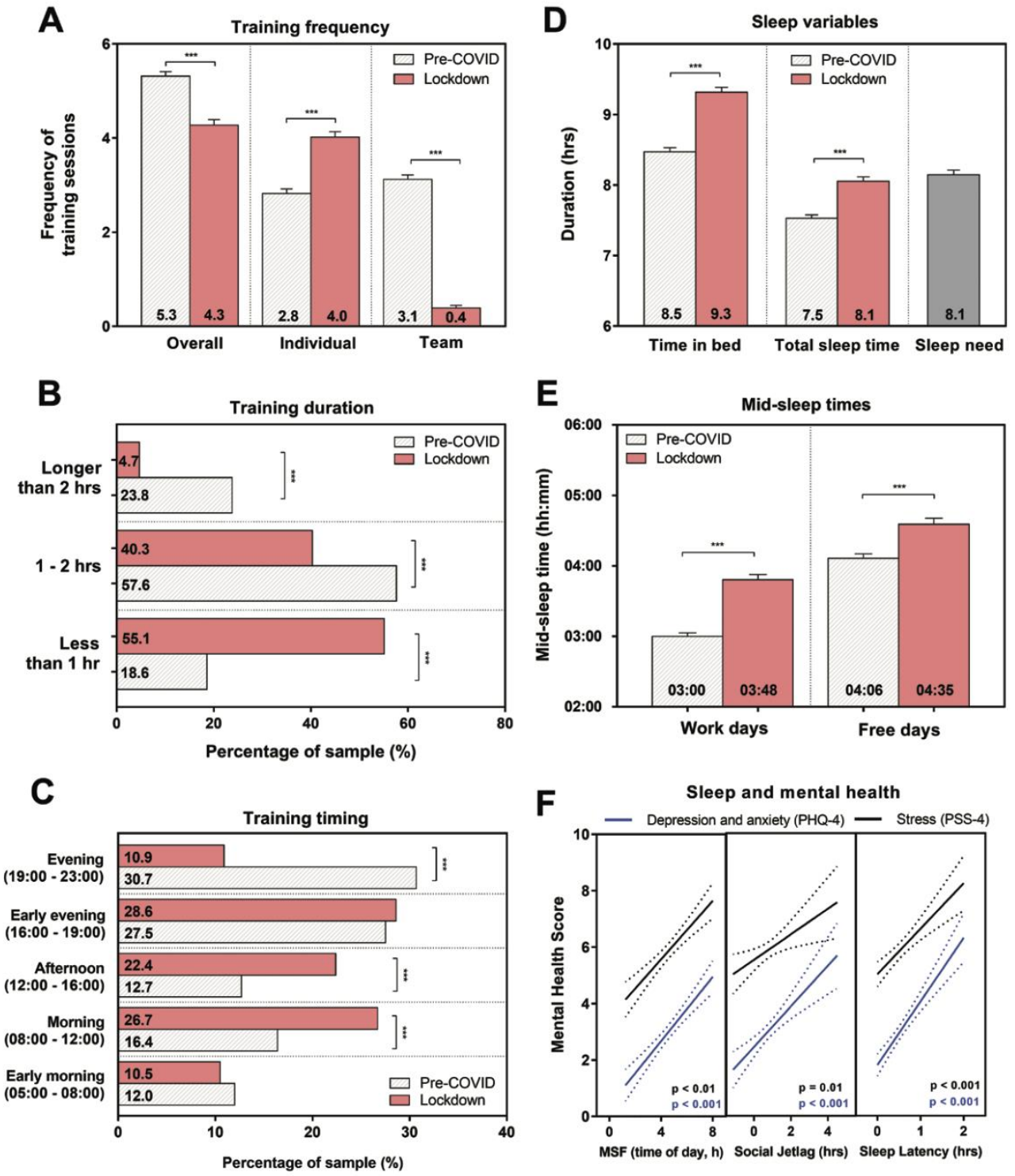

Figure 2. Changes to training, sleep and mid-sleep times during lockdown and the relationship with mental health. Frequency of training sessions is shown in panel A, duration in panel B, and timing in panel C. Sleep patterns are shown in panel D, chronotype measured using mid-sleep times in panel E. Statistical significance is shown as $p < 0.001$***. The relationship between mental health (PHQ-4; red line, PSS-4; black line) and mid-sleep on free days (MSF), social jetlag and sleep latency are shown in panel F. Dotted lines show 95% confidence bands of the best fit line.

THE COVID-19 PANDEMIC DRAMATICALLY REDUCED ADMISSIONS OF CHILDREN WITH AND WITHOUT CHRONIC CONDITIONS TO GENERAL PAEDIATRIC WARDS

Gavish R, Levinsky Y, Dizitzer Y, Bilavsky E, Livni G, Pirogovsky A, Scheuerman O, Krause I.. Acta Paediatr. 2021 Feb 4. doi: 10.1111/apa.15792. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Pediatricians from Schneider Children's Medical Center in Israel examined pediatric hospital admissions during the COVID-19 lockdown from March 20 to April 18, 2020 (Figure 2). They found mean daily hospitalizations decreased by 59% (IRR: 0.41, p<0.001) compared to immediately before the pandemic and same periods in 2018 and 2019 (Figure 1). Compared to the same period in 2019, 74% fewer patients were admitted with infectious etiologies and 44% fewer with non-infectious etiologies (Figure 2, 3). Authors suggest pediatric hospitalizations decreased during the lockdown period and urge additional investigation to determine whether factors negatively impacting the health of the pediatric population (late presentations or referrals) drove the observed reduction.

ABSTRACT

AIM: We examined the impact of the COVID-19 pandemic on how many children were admitted to Israel's largest tertiary paediatric hospital and why they were admitted. METHODS: Israel declared COVID-19 a national emergency on 19 March 2020. This study examined daily hospital admissions to our three general paediatric wards during the COVID-19 lockdown period from 20 March to 18 April 2020. These 258 admissions were compared with the 4,217 admissions from the period immediately before this, 1 February to 19 March 2020, plus 1 February to 18 April in 2018 and 2019. We also compared why patients were admitted during the study period, and any pre-existing conditions, with 638 children hospitalised during the same period in 2019. RESULTS: The mean number of daily hospitalisations during the COVID-19 lockdown period was 8.6, which was 59% lower than the 20.9 recorded during the other three periods before COVID-19. There was a significant decrease in the number of patients admitted with infectious (74%) and non-infectious (44%) aetiologies from 2019 to 2020 and these occurred among patients with (58%), and without (55%), pre-existing medical conditions. CONCLUSION: The Israeli COVID-19 lockdown had a dramatic effect on admissions to the paediatric wards of a tertiary hospital.

FIGURES

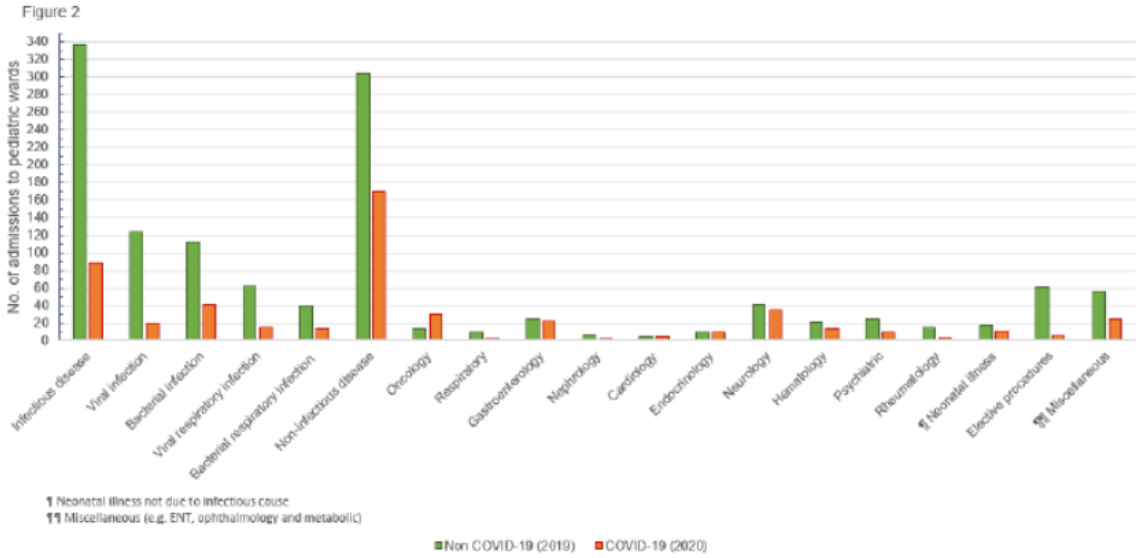

Figure 2. Number of hospitalisations by admission during the COVID-19 study period and the corresponding period in 2019

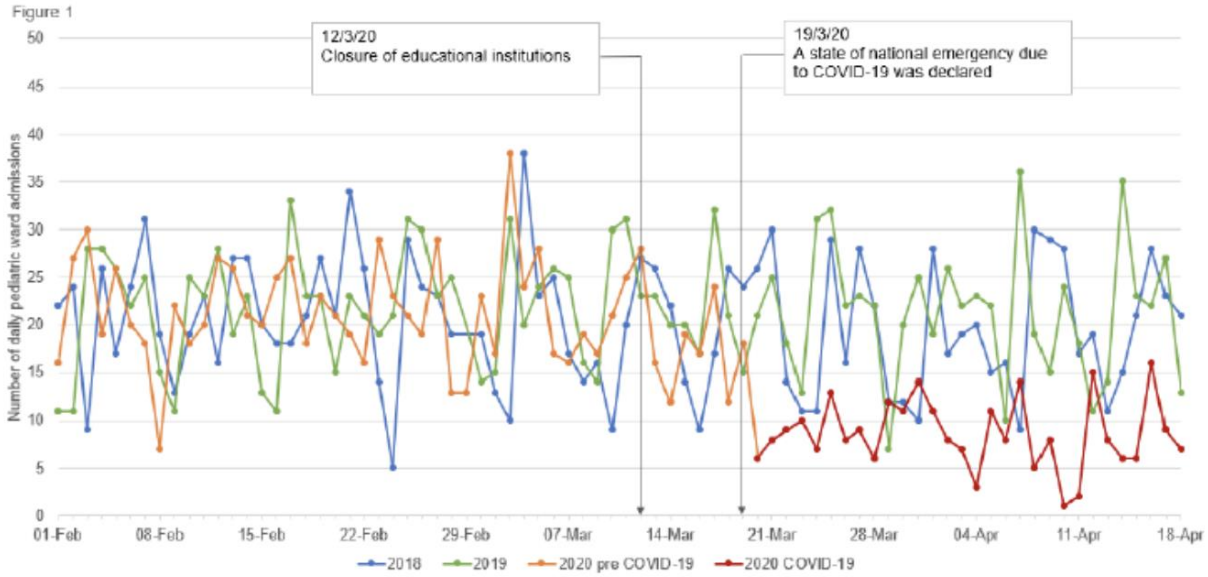

Figure 1. Number of hospitalisations in paediatric wards before and during the first four weeks of the pandemic relative to the same period in 2018 and 2019.

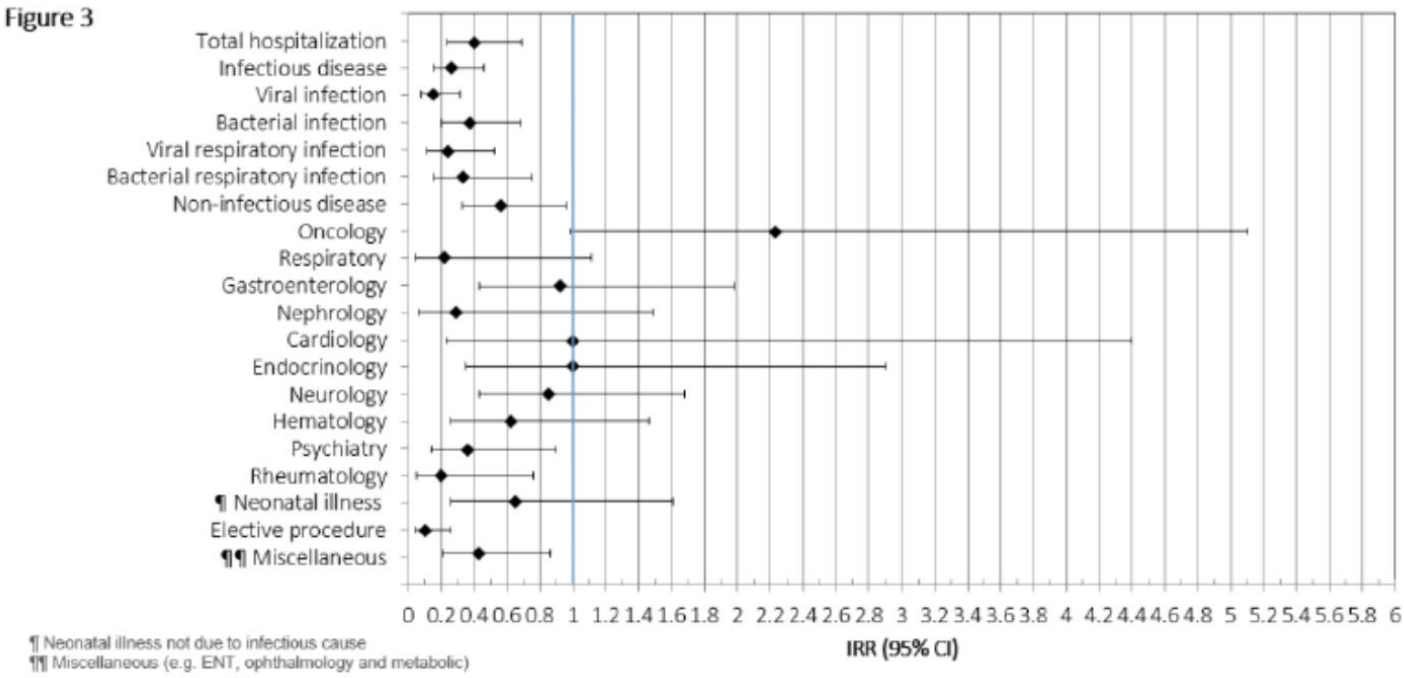

Figure 3. Forest plot showing the incidence rate ratios of the different reasons for hospitalisations between the COVID-19 study period and the corresponding period in 2019

PATIENT-REPORTED OLFACTORY RECOVERY AFTER SARS-COV-2 INFECTION: A 6-MONTH FOLLOW-UP STUDY

Lucidi D, Molinari G, Silvestri M, De Corso E, Guaraldi G, Mussini C, Presutti L, Fernandez IJ.. Int Forum Allergy Rhinol. 2021 Feb 4. doi: 10.1002/alr.22775. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Otolaryngologists and infectious disease physicians from Italy surveyed a cohort of patients infected with SARS-CoV-2 who reported olfactory dysfunction (n=126) between February and September 2020 (Table 1). Of 110 respondents, 63% (n=70) reported complete recovery of olfactory function and 22% (n=24) partial recovery, with multivariable analysis showing cigarette smoking as the only factor significantly associated with recovery (Table 2). Authors suggest many, but not all, patients with olfactory dysfunction associated with SARS-CoV-2 infection recover their ability to smell, but that their results are limited by lack of an objective olfactory assessment.

FIGURES

TABLE 1 Evaluation of the role of the different variables associated with anosmia/hyposmia recovery*

Variable	Complete recovery	Incomplete/No recovery	*p* value
Age, years (mean ± SD)	**40 ± 12.9**	**42.9 ± 11.2**	**0.34**
Duration of anosmia/hyposmia			<0.0001†
<7 days	14 (19.7)	0 (0)	
7-14 days	29 (40.3)	1 (4.2)	
15-30 days	17 (23.9)	1 (4.2)	
1-3 months	10 (14.1)	18 (75.0)	
>3 months	1 (1.4)	4 (16.6)	
Gender			0.21
Male	23 (57.5)	17 (42.5)	
Female	47 (42.5)	23 (67.1)	
Risk factors			
Cigarette smoking	5 (7.1)	10 (25.0)	0.011†
Cranial trauma	0 (0)	1 (2.5)	0.36
CRS	4 (5.7)	10 (25.0)	0.005†
Respiratory pathologies	4 (5.7)	8 (20.0)	0.025†
CV pathologies	4 (5.7)	8 (20.0)	0.025†
Neurologic pathologies	1 (1.4)	0 (0)	0.64
Symptoms before anosmia/hyposmia			
Fever	44 (62.9)	18 (45.0)	0.054
Chills	23 (32.9)	11 (27.5)	0.36
Malaise	49 (70.0)	22 (55.0)	0.085
Headache	32 (45.7)	15 (37.5)	0.26
Cough	32 (45.7)	15 (37.5)	0.26
Nasal congestion	19 (27.1)	16 (40.0)	0.12
Rhinorrhea	16 (22.9)	10 (25.0)	0.48
GE symptoms	19 (27.1)	9 (22.5)	0.38
Symptoms after anosmia/hyposmia			
Fever	34 (48.6)	11 (27.5)	0.043†
Chills	16 (22.9)	10 (25.0)	0.81
Malaise	44 (62.9)	20 (50.0)	0.23
Headache	31 (44.3)	9 (22.5)	0.025†
Cough	28 (40.0)	18 (45.0)	0.68
Nasal congestion	19 (27.1)	14 (35.0)	0.39
Rhinorrhea	12 (17.1)	9 (22.5)	0.62
GE symptoms	19 (27.1)	8 (20.0)	0.49
Pharmacologic treatment			
Hydroxychloroquine	10 (14.3)	1 (2.5)	0.042†
Azithromycin	7 (10.0)	1 (2.5)	0.14
Heparin	4 (5.7)	3 (7.5)	0.50
Steroids	2 (2.9)	2 (5.0)	0.46

*Data expressed as number (%), unless noted otherwise.
†Statistically significant ($p < 0.05$).
CRS = chronic rhinosinusitis; CV = cardiovascular; GE = gastroenteric; SD = standard deviation.

TABLE 2 Evaluation of role of different variables associated with anosmia/hyposmia recovery by multivariate analysis

Variable	B	Standard error	Wald test	*df*	*p* value	OR	OR 95% CI Inferior	OR 95% CI Superior
Smoking	3257	1.617	4.055	1	0.044[a]	25.96	1.11	61.8
CRS	21.288	28420.721	0.000	1	0.999	E	—	—
Respiratory pathologies	−22.820	28420.721	0.000	1	0.999	E	—	—
CV pathologies	−0.904	0.486	3.453	1	0.063	0.41	0.156	1.051
Headache	−0.964	0.512	3.550	1	0.060	0.38	0.140	1.039
Fever	−0.904	0.486	3.453	1	0.063	0.38	0.156	1.051
Hydroxychloroquine	−2.117	1.170	3.272	1	0.070	0.12	0.012	1.193
Intercept	−0.085	0.309	0.075	1	0.784	0.91	—	—

[a]statistically significant ($p < 0.05$).

B = Beta coefficient; CI = confidence interval; CRS = chronic rhinosinusitis; CV = cardiovascular; *df* = degree of freedom of the variable; E = nonreliable OR value, considering the high SE for coefficient B and Wald test = 0; OR = odds ratio; SE = standard error.

OBSERVATIONAL STUDY OF THROMBOSIS AND BLEEDING IN COVID-19 VV ECMO PATIENTS

Ripoll B, Rubino A, Besser M, Patvardhan C, Thomas W, Sheares K, Shanahan H, Agrawal B, Webb S, Vuylsteke A.. Int J Artif Organs. 2021 Jan 28:391398821989065. doi: 10.1177/0391398821989065. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Intensivists and a hematologist from Cambridge evaluated the incidence of thrombotic and bleeding events in 30 patients with COVID-19 who had received a full body computed tomography (CT) scan prior to initiation of veno-venous extracorporeal oxygenation (VV-ECMO) (Table 1). The authors report their data inconsistently, but their figures suggest that whole body computed tomography scanner (CT) on admission showed 12 patients had isolated thrombosis, 1 patients had an isolated bleed, and 5 had both. There was no association between a thrombotic or bleeding event and aPTT range (Figures 1, 2). The authors conclude bleeding and thrombotic events are common in COVID-19 patients despite anticoagulation.

ABSTRACT

INTRODUCTION: COVID-19 has been associated with increased risk of thrombosis, heparin resistance and coagulopathy in critically ill patients admitted to intensive care. We report the incidence of thrombotic and bleeding events in a single center cohort of 30 consecutive patients with COVID-19 supported by veno-venous extracorporeal oxygenation (ECMO) and who had a whole body Computed Tomography Scanner (CT) on admission. METHODOLOGY: All patients were initially admitted to other hospitals and later assessed and retrieved by our ECMO team. ECMO was initiated in the referral center and all patients admitted through our CT scan before settling in our intensive care unit. Clinical management was guided by our institutional ECMO guidelines, established since 2011 and applied to at least 40 patients every year. RESULTS: We diagnosed a thrombotic event in 13 patients on the initial CT scan. Two of these 13 patients subsequently developed further thrombotic complications. Five of those 13 patients had a subsequent clinically significant major bleeding. In addition, two patients presented with isolated intracranial bleeds. Of the 11 patients who did not have baseline thrombotic events, one had a subsequent oropharyngeal hemorrhage. When analyzed by ROC analysis, the area under the curve for % time in intended anticoagulation range did not predict thrombosis or bleeding during the ECMO run (0.36 (95% CI 0.10-0.62); and 0.51 (95% CI 0.25-0.78); respectively). CONCLUSION: We observed a high prevalence of VTE and a significant number of hemorrhages in these severely ill patients with COVID-19 requiring veno-venous ECMO support.

Table 1. Demographic data of patients admitted under the ECMO service during the study period.

Median age in years (IQR)	45 (39, 56)	
Sex No. (%)	24 males (80 %) and 6 (20 %) females	
Median weight in kg (IQR)	94 (78, 110)	
BMI	*n* (%)	
<25	1 (3.3%)	
25–29.9	10 (33.3%)	
30–39.9	17 (56.6%)	
40+	2 (6.6%)	
Ethnicity	*n* (%)	
African black	4 (13%)	
White	11 (36.7%)	
Asian	9 (30%)	
Other	4 (13%)	
Mixed	2 (6.7%)	
Medical conditions	*n* (%)	
Obesity (BMI>30)	19 (63.3%)	
Type 2 diabetes mellitus	9 (30%)	
Hypertension	5 (16%)	
Metabolic syndrome	4 (13%)	
Asthma	3 (10%)	
Hypothyroidism	3 (10%)	
Pre ECMO anticoagulation in %	*n* (%)	
Standard prophylactic LMWH	22 (73%)	
Intermediate LMWH BD	3 (10%)	
Therapeutic dose for CVVH or PE	3 (10%)	
UFH for CVVH	2 (6%)	
Length of staying at referring hospital prior to ECMO in days (IQR)	7 (3, 10)	
Days intubated before ECMO median (IQR)	4 (1, 5)	
Mean laboratory results on admission findings (IQR)		Reference range
Hb (g/L)	95 (85, 101)	120–156
Platelets (10*9/L)	312 (243, 396)	150–370
Lymphocytes (10*9/L)	0.65 (0.81, 0.14)	1.10–4.50
CRP (mg/L)	250 (190, 360)	0–6
Ferritin (ug/L)	1583 (846, 2615)	33–490
Fibrinogen (g/L)	5.99 (4.9, 7.54)	1.46–3.33
D-Dimer ng/mL	3206 (1574, 4541)	0–230
PT (sec)	14.7 (13.7, 15.9)	10.8–13.3
APTT (sec)	34.4 (29, 37.1)	28.2–36.6
Antithrombin (%)	97.1 (78.9, 114.3)	82–117
Creatinine (umol/L)	66 (41, 126)	44–127
Urea (mmol/L)	9.4 (6.8, 14)	2.5–7.8
PCR COVID19 Nasal Swab	Positive 100%	

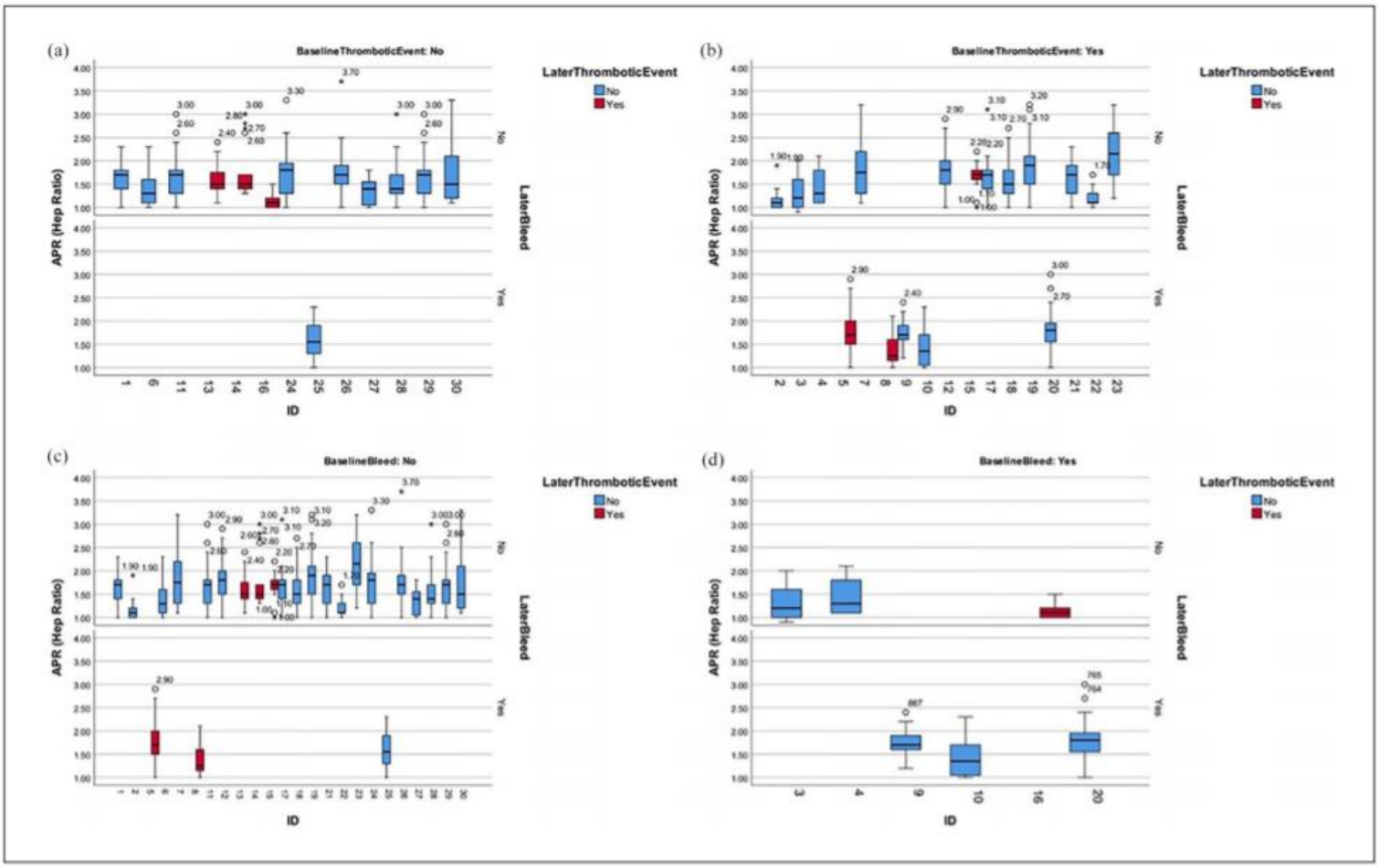

Figure 1. (a–d) Y-axis depicts aPTT range (APR) as a box plot. Midline indicates Median and Whiskers of box plot indicate 25th and 75th percentile. (a) and (b) depict patients without (a) and with (b) baseline thrombotic events. Horizontally all panels (a–d) are split by whether a bleeding complication during ECMO therapy or not. Red and blue color indicates whether a thrombotic complication occurred (red) or not (blue) during ECMO therapy. Patient 3, 9 14, 15.16 were switched to Argatroban due to heparin resistance. Patient 9 suffered a ICH 2 days after switching to Argatroban. Patient 18 was switched to Apixaban due to heparin resistance.

*Marks patients who are deceased, bold horizontal lines show target APR range for VVECMO by our institutional guidelines (1.5–2.0).

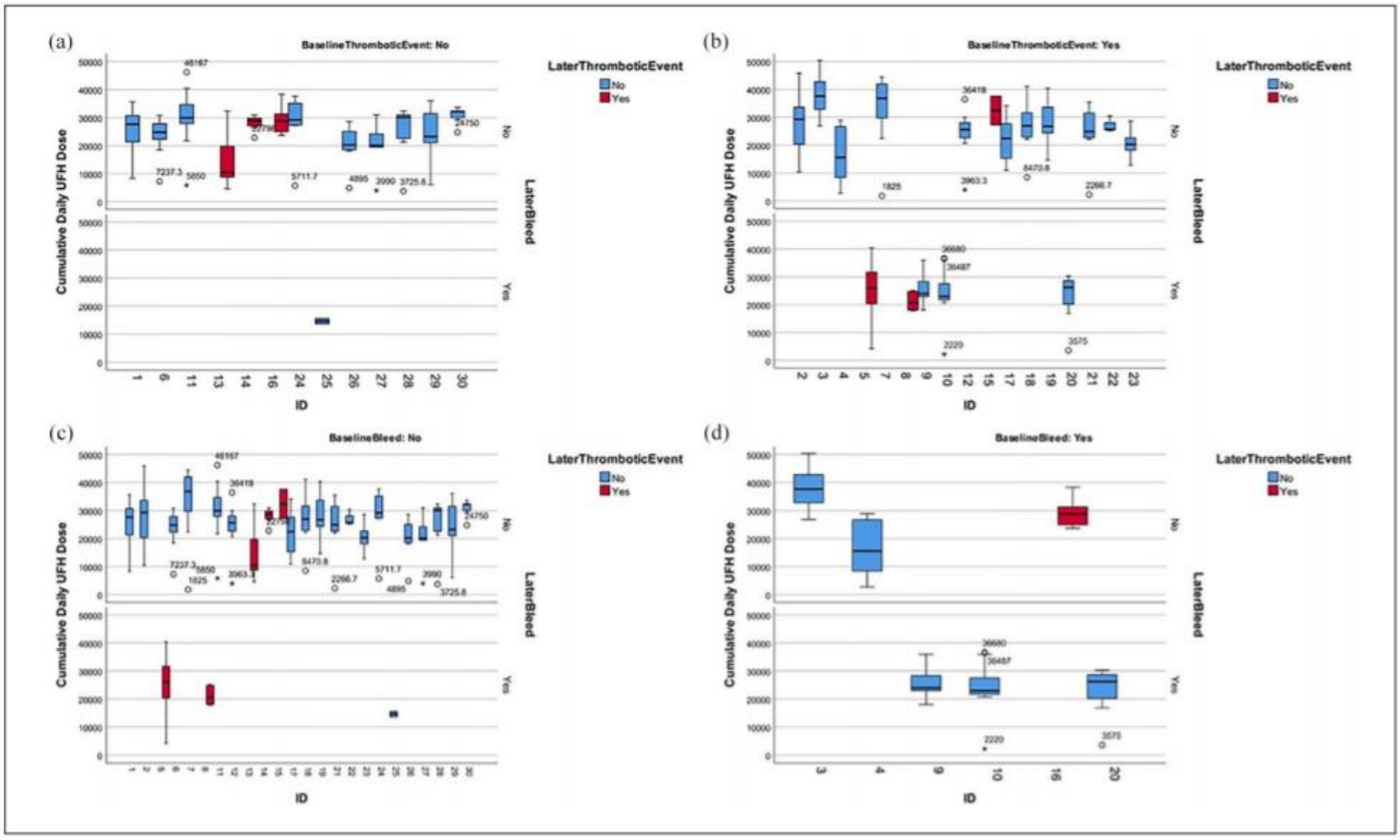

Figure 2. (a–d) Y-axis depicts cumulative Heparin dose (in units per 24 h) as a box plot. Midline indicates Median and Whiskers of box plot indicate 25th and 75th percentile. (a) and (b) depict patients without (a) and with (b) baseline thrombotic events. (c) and (d) depict patients without (c) and with (d) baseline bleeding events. Horizontally all panels (A-D) are split by whether a bleeding complication during ECMO therapy or not. Red and blue color indicates whether a thrombotic complication occurred (red) or not (blue) during ECMO therapy. Patient 3, 9 14, 15.16 were switched to Argatroban due to heparin resistance. Patient 9 suffered a ICH 2 days after switching to Argatroban. Patient 18 was switched to Apixaban due to heparin resistance.
*Marks patients who are deceased.

POST CONVALESCENT SARS-COV-2 IGG AND NEUTRALIZING ANTIBODIES ARE ELEVATED IN INDIVIDUALS WITH POOR METABOLIC HEALTH

Racine-Brzostek SE, Yang HS, Jack GA, Chen Z, Chadburn A, Ketas TJ, Francomano E, Klasse PJ, Moore JP, McDonough KA, Girardin RC, Dupuis Ii AP, Payne AF, Ma L, Sweeney J, Zhong E, Yee J, Cushing MM, Zhao Z.. J Clin Endocrinol Metab. 2021 Feb 1:dgab004. doi: 10.1210/clinem/dgab004. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Lab medicine experts, endocrinologists, and microbiologists from Weill Cornell Medicine in New York City analyzed the relationship between SARS-CoV-2 antibody levels and metabolic syndrome comorbidities in 1055 outpatients who had not been hospitalized for COVID-19 and tested positive for SARS-CoV-2 IgG between April 17 and June 21, 2020 (Table 1). SARS-CoV-2 IgG levels were higher in patients with hemoglobin A1c (HbA1c) ≥6.5% compared to HbA1c <5.7% (p=0.0197) and there was a positive correlation between antibody levels and BMI (p<0.0001) (Figure 1). Authors suggest serum immunoglobulin levels may be higher in patients with metabolic syndrome comorbidities and recommend further study to better characterize this finding and understand its implications.

ABSTRACT

PURPOSE: Comorbidities making up metabolic syndrome (MetS), such as obesity, type 2 diabetes and chronic cardiovascular disease can lead to increased risk of coronavirus disease-2019 (COVID-19) with a higher morbidity and mortality. SARS-CoV-2 antibodies are higher in severely or critically ill COVID-19 patients, but studies have not focused on levels in convalescent patients with MetS, which this study aimed to assess. METHODS: This retrospective study focused on adult convalescent outpatients with SARS-CoV-2 positive serology during the COVID-19 pandemic at NewYork Presbyterian/Weill Cornell. Data collected for descriptive and correlative analysis included SARS-COV-2 IgG levels and history of MetS comorbidities during 4/17/2020-5/20/2020. Additional data, including SARS-CoV-2 IgG levels, Body Mass Index, HbA1c and lipid levels were collected and analyzed for a second cohort during 5/21/2020-6/21/2020. SARS-CoV-2 neutralizing antibodies were measured in a subset of the study cohort. RESULTS: SARS-CoV-2 IgG levels were significantly higher in convalescent individuals with MetS comorbidities. When adjusted for age, sex, race, and time duration from symptom onset to testing, increased SARS-CoV-2 IgG levels remained significantly associated with obesity (p<0.0001). SARS-CoV-2 IgG levels were significantly higher in patients with HbA1c >=6.5% compared to those with HbA1c <5.7% (p=0.0197) and remained significant on multivariable analysis (p=0.0104). A positive correlation was noted between Body Mass Index (BMI) and antibody levels (95% CI: 0.37 [0.20-0.52] p<0.0001). Neutralizing antibody titers were higher in COVID-19 individuals with BMI >= 30 (p=0.0055). CONCLUSION: Post-convalescent SARS-CoV-2 IgG and neutralizing antibodies are elevated in obese patients and a positive correlation exists between BMI and antibody levels.

FIGURES

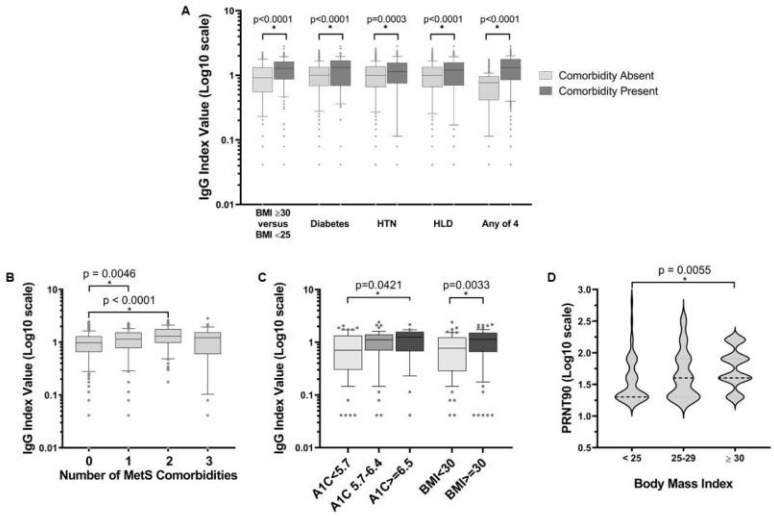

Figure 1 Study results of correlation between SARS-CoV-2 IgG antibody levels and known metabolic syndrome comorbidities

Table 1.
Patient characteristics by diabetes status

Characteristics	Total (n = 1055)	No type 2 diabetes (n = 963)	Type 2 diabetes (n = 92)
Age			
Mean (SD)	40.89 (12.44)	39.87 (11.95)	51.64 (12.48)
Median (IQR)	37.00 (31.00–49.00)	36.00 (30.00–47.00)	51.00 (42.00–61.00)
Sex, n (%)			
Female	705 (66.8)	648 (67.3)	57 (62.0)
Male	350 (33.2)	315 (32.7)	35 (38.0)
Race, n (%)			
Asian	129 (12.8)	120 (13.0)	9 (10.0)
Black/African American	91 (9.0)	75 (8.2)	16 (17.8)
Declined	196 (19.4)	184 (20.0)	12 (13.3)
Other	193 (19.1)	174 (18.9)	19 (21.1)
White	401 (39.7)	367 (39.9)	34 (37.8)
BMI (kg/m^2), n (%)			
<25	198 (46.7)	193 (52.0)	5 (9.4)
≥25 and <30	116 (27.4)	101 (27.2)	15 (28.3)
≥30	110 (25.9)	77 (20.8)	33 (62.3)
Median (IQR)	25.44 (22.79–30.00)	24.87 (22.50–29.05)	31.53 (27.76–36.33)
Hypertension, n (%)	113 (10.7)	73 (7.6)	40 (43.5)
Hyperlipidemia, n (%)	110 (10.4)	67 (7.0)	43 (47.3)
Days from symptom onset to testing, median (IQR)	39.67 (31.76–49.63)	38.94 (31.70–48.94)	43.76 (34.58–53.19)

Abbreviations: BMI, body mass index; diabetes, type 2 diabetes; IQR, interquartile range.

SARS-COV-2 SPECIFIC ANTIBODY AND NEUTRALIZATION ASSAYS REVEAL THE WIDE RANGE OF THE HUMORAL IMMUNE RESPONSE TO VIRUS

Dogan M, Kozhaya L, Placek L, Gunter C, Yigit M, Hardy R, Plassmeyer M, Coatney P, Lillard K, Bukhari Z, Kleinberg M, Hayes C, Arditi M, Klapper E, Merin N, Liang BT, Gupta R, Alpan O, Unutmaz D.. Commun Biol. 2021 Jan 29;4(1):129. doi: 10.1038/s42003-021-01649-6.
Level of Evidence: 3 - Local non-random sample

BLUF

American experts in immunology and genomics assessed in-vitro dynamic humoral immunity in 115 patients with SARS-CoV-2 via PCR from across the United States (Table 1) using in-house SARS-CoV-2-specific antibody and neutralization assays. They found SARS-CoV-2 anti-spike (S) and nucleocapsid (N) IgG in all patients, with 3000-fold higher antibody and neutralization titers in hospitalized and deceased patients compared to outpatients and convalescent plasma donors (Figure 5). Antibody levels positively correlated with neutralization titers, age, and NAbs (Figure 6). Authors suggest understanding these humoral immune responds will inform development of vaccines and antibody based therapies.

ABSTRACT

Development of antibody protection during SARS-CoV-2 infection is a pressing question for public health and for vaccine development. We developed highly sensitive SARS-CoV-2-specific antibody and neutralization assays. SARS-CoV-2 Spike

protein or Nucleocapsid protein specific IgG antibodies at titers more than 1:100,000 were detectable in all PCR+ subjects (n = 115) and were absent in the negative controls. Other isotype antibodies (IgA, IgG1-4) were also detected. SARS-CoV-2 neutralization was determined in COVID-19 and convalescent plasma at up to 10,000-fold dilution, using Spike protein pseudotyped lentiviruses, which were also blocked by neutralizing antibodies (NAbs). Hospitalized patients had up to 3000-fold higher antibody and neutralization titers compared to outpatients or convalescent plasma donors. Interestingly, some COVID-19 patients also possessed NAbs against SARS-CoV Spike protein pseudovirus. Together these results demonstrate the high specificity and sensitivity of our assays, which may impact understanding the quality or duration of the antibody response during COVID-19 and in determining the effectiveness of potential vaccines.

FIGURES

Table 1 Characteristics of SARS-CoV-2 infected and control subjects.

From: SARS-CoV-2 specific antibody and neutralization assays reveal the wide range of the humoral immune response to virus

Demographics		Healthy controls (*n* = 56)	Negative (*n* = 94)	Outpatient (*n* = 39)	Hospitalized (*n* = 19)	ICU/deceased (*n* = 24)	Plasma donors (*n* = 33)
Sex	Male	14	33	11	7	10	18
	Female	42	61	28	12	14	15
Age	Mean (±SEM)	45.5 (±1.78)	54.1 (±1.97)	46.0 (±2.20)	62.2 (±3.41)	68.0 (±1.87)	45.5 (±1.99)
	Median	47.0	59.0	47.0	63.0	70.0	48.0
Days between PCR/blood	Mean (±SEM)	N/A	N/A	40.7 (±2.79)	21.0 (±3.28)	25.8 (±3.17)	65.4 (±1.68)
	Median	N/A	N/A	43.0	28.0	24.5	66.0

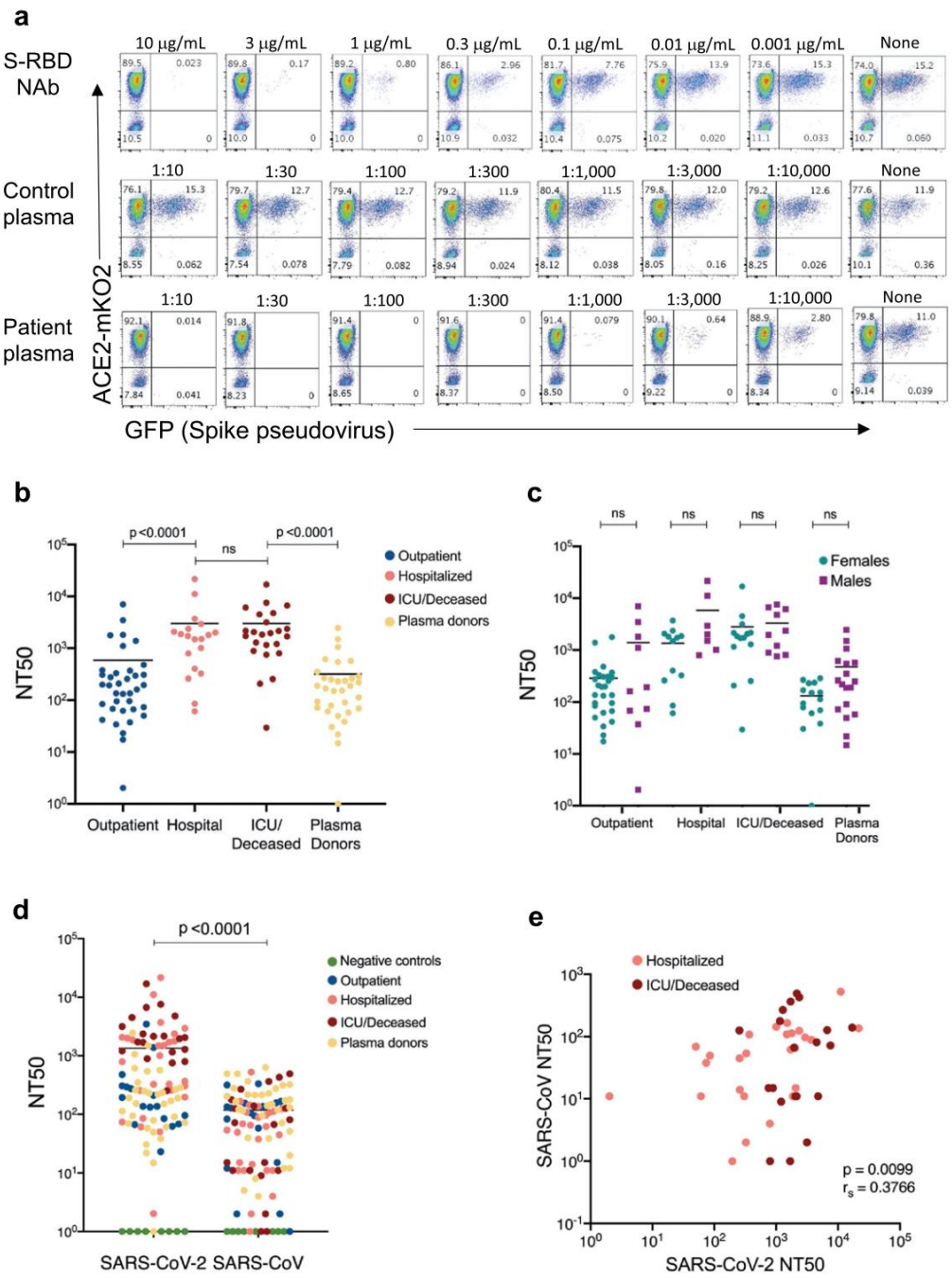

Fig. 5 Neutralizing titers for SARS-CoV-2 and SARS-CoV in COVID-19 subject plasma. a Neutralization assay with S-RBD-specific NAb, healthy control plasma, and a COVID-19 patient plasma. Threefold serial dilutions of NAb from 10 μg/ml to 1 ng/ml or the plasma from 1:10 to 1:10,000 were pre- incubated with spike protein pseudovirus and added to 293-ACE2 cells. GFP expression was analyzed by flow cytometry 3 days post infection. b SARS- CoV-2 neutralization titers (NT50) of COVID-19 plasma grouped as an outpatient, hospitalized, ICU or deceased and convalescent plasma donor groups (n = 113). c NT50 of COVID-19 patient and plasma donor groups subdivided into males and females (n = 113). d Comparison of NT50 of COVID-19 plasma for SARS-CoV-2 and SARS-CoV neutralization. SARS-CoV-2 or SARS-CoV pseudoviruses were pre-incubated with COVID-19 plasma from all severity groups (n = 104), 293-ACE2 cells were infected and RFP expression was determined at day 3 using flow cytometry. e Graph of SARS-CoV-2 NT50 values from hospitalized subjects plotted against SARS-CoV (n = 46). Two-tailed Mann–Whitney U test was used to determine the statistical significances in figures (b), (c) and (d) and two-tailed Spearman’s was used for figure (e). Horizontal bars in (b), (c) and (d) indicate mean values.

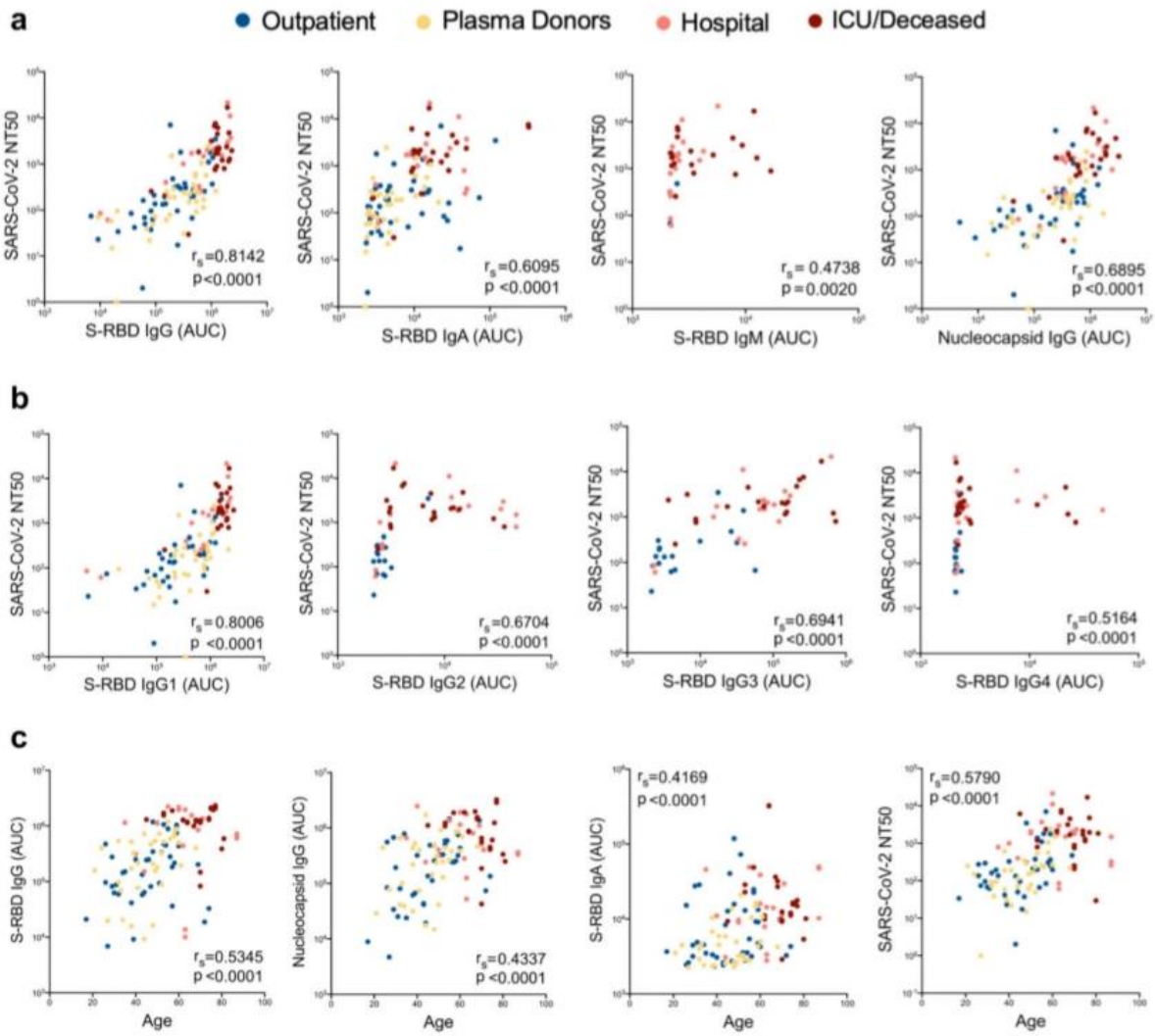

Figure 6: "a Neutralization (NT50) of COVID-19 plasma correlated with S-RBD IgG (n = 113), S-RBD IgA (n = 113), S-RBD IgM (n = 40), and nucleocapsid IgG (n = 113). b Correlation of NT50 with S-RBD-specific IgG subclasses; IgG1 (n = 113), IgG2 (n = 74), IgG3 (n = 74), and IgG4 (n = 74). c Correlation of S-RBD IgG (n = 115), nucleocapsid IgG (n = 115), S-RBD IgA (n = 115), and NT50 (n = 113) with age. Two-tailed Spearman’s was used to determine statistical significance".

THE IMPACT OF FACE MASKS ON CHILDREN - A MINI REVIEW

Martin E, Stefan O, Reinhold K.. Acta Paediatr. 2021 Feb 3. doi: 10.1111/apa.15784. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A review of literature through November 7, 2020 conducted by physicians in the Department of Paediatrics and Adolescent Medicine in Leoben, Austria found two studies discussing the impact of face masks on children and eight studies on adults (Table 1). The two pediatric studies (Goh et al, 2019 & Smart et al, 2020) found that N95 masks had no significant negative impacts on breathing; however, these studies were limited as children only wore masks for activities lasting five minutes or less. This review suggests that more studies are needed to understand the long term impacts of children wearing masks.

ABSTRACT

AIM: Face masks are essential during the COVID-19 pandemic and the United Nations Children's Fund and the World Health Organization, recommend that they are used for children aged six years and older. However, parents are increasingly expressing concerns about whether these might be physically harmful. This mini review assessed the evidence. METHOD: We conducted a narrative review on the effects of mask wearing on physiological variables in children, using PubMed, the Cochrane Library and the World Health Organization COVID-19 Database up to 7 November 2020. The lack of paediatric studies prompted a second search for adult studies. RESULTS: We only found two paediatric studies, published in 2019 and 2020. The 2020 study was not related to COVID-19. Only one study, performed with N95 respirators, collected medical parameters and this did not suggest any harmful effects of gas exchange. The eight adult studies, including four prompted by the pandemic and one on surgeons, reported that face masks commonly used during the pandemic did not impair gas exchange during rest or mild exercise. CONCLUSION: International guidelines recommend face masks for children aged six years and older, but further studies are needed to provide evidence-based recommendations for different age groups.

FIGURES

Table 1: Characteristics of included studies (12, 13, 15-17, 19) including four studies prompted by the COVID-19 pandemic (14, 18, 20, 21)

Study	Study design	Population, recruiting	Exposure duration	Control group	Mask or respirator	Outcomes measured	Findings
Goh et al Singapore Published 2019 (14)	Randomised, crossover study	106 children (7-14 years)	Five minutes rest and five minutes walking	Yes, crossover design	N95	$ETCO_2$, $FICO_2$, SpO_2, HR, RR, comfort	No differences in RR, HR, SpO_2. Marginal increase of $ETCO_2$and $FICO_2$. 7% reported discomfort.
Smart et al UK Published 2020 (15)	Randomised, crossover study	24 children (8–11 years)	Three minutes walking and three minutes running	No	N95	Comfort, breathability, hotness, fit	Main complaint hotness. One- third had negative subjective perception of breathing.
Samannan et al USA Published 2020 (16)	Clinical observation	15 adults from medical house staff and 15 COPD patients	30 minutes rest and six minutes walking	No	surgical	$ETCO_2$, SpO_2, HR, RR; COPD patients: pCO_2 and pO_2	No differences in RR, HR, SpO_2 and $ETCO_2$. Decrease in oxygenation after walking in COPD patients.
Roberge et al USA Published 2012 (17)	Nonrandomised ,crossover study	20 adults from public	1 hour walking	Yes, crossover design	surgical	$P_{tc}CO_2$, SpO_2, HR, RR, temperature, comfort	Mild increases of HR, RR and $P_{tc}CO_2$ without clinical significance.

Butz Germany Published 2005 (18)	Randomised crossover study	15 adults from medical staff	30 minutes rest	Yes, crossover design	surgical	$P_{tc}CO_2$, SpO_2, HR, RR, CO_2 concentration under mask, comfort	Significant increase of $P_{tc}CO_2$. No change in SpO_2, HR and RR. CO_2 accumulation under mask.
Beder et al Turkey Published 2008 (19)	Clinical observation	53 surgeons	Operations between one and four hours	No	surgical	SpO_2, HR	Decrease in SpO_2. Slight increase in HR compared to preoperative values.
Dattel et al USA Published 2020 (20)	Clinical observation	32 pilots from Aeronautical University	90 minutes flight simulator (altitude of 5,000 feet)	No	surgical, cloth	$ETCO_2$and, SpO_2, HR, RR	No significant changes or differences between mask types. $ETCO_2$and SpO_2within acceptable range.
Person et al France Published 2018 (21)	Randomized cross over study	44 adults from public	Six minutes walking	Yes, crossover design	surgical	Distance, HR, SpO_2, dyspnea	No differences in distance, HR or SpO_2. Significantly more dyspnea.
Fikenzer et al Germany Published 2020 (22)	Randomized cross over study	12 adults rom medical staff	Ergo-spirometry (incremental exertion test)	Yes, crossover design	surgical, N95	HR, RR, pCO_2, pO2, VE, VT, Pmax, VO_2max/kg	No significant changes with surgical masks. Pulmonary parameters and maximum power decreased significantly with N95 respirators.

Epstein et al Israel Published 2020 (23)	Randomized cross over study	16 adults, from public	Cycle ergometry (incremental exertion test)	Yes, crossover design	surgical, N95	$ETCO_2$, SpO_2, HR, RR, time to exhaustion	Significant increase of $ETCO_2$ with N95 respirators. No significant changes in SpO_2, HR, RR and time to exhaustion.

COPD, chronic obstructive pulmonary disease; $ETCO_2$, end-tidal carbon dioxide; $FICO_2$, fractional concentration of inspired carbon dioxide; $P_{tc}CO_2$, transcutaneous carbon dioxide; RR, respiratory rate; SpO_2 = oxygen saturation; HR, Heart rate; P, power; VO_2, oxygen uptake; VE, minute ventilation; VT, tidal volume; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; VO_2max/kg, maximal oxygen consumption per kilogram bodyweight.

Table 1 Continued

ENDOCRINOLOGY

GLYCEMIC CONTROL IN TYPE 1 DIABETES CHILDREN AND TEENAGERS AROUND LOCKDOWN FOR COVID-19: A CONTINUOUS GLUCOSE MONITORING BASED OBSERVATIONAL STUDY

Wu X, Luo S, Zheng X, Ding Y, Wang S, Ling P, Yue T, Xu W, Yan J, Weng J.. J Diabetes Investig. 2021 Feb 4. doi: 10.1111/jdi.13519. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Chinese endocrinologists assessed glycemic control in 43 children and teenagers with type 1 diabetes (T1D) during the COVID-19 pandemic using cloud based continuous glucose monitoring data and questionnaires. They found median time below target glucose range and number of hypoglycemic events decreased during and increased after lockdown (Figure 2, Table 2), with participants reporting more time spent on diabetes management, decreased physical activity, and longer sleep times during lockdown (Table 3). Authors suggest despite lifestyle changes during pandemic lockdowns, there was no deterioration in glycemic control.

ABSTRACT

OBJECTIVE: COVID-19 pandemic has urged the authorities to impose rigorous quarantines and brought considerable changes to lifestyles. The impact of these changes on glycemic control has remained unclear, especially the long-term effect. We aimed to investigate the impact of lockdown on glycemic control in type 1 diabetes (T1D) children and adolescents. METHODS: This observational study enrolled T1D children using continuous glucose monitoring(CGM). CGM data were extracted from the cloud-based platform before, during, and after lockdown. Demographics and lifestyle change-related information were collected from database or questionnaires. We compared these data before, during, and after lockdown. RESULTS: 43 T1D children were recruited (20 female; mean age, 7.45 years; median diabetes duration, 1.05 years). We collected 41,784 hours of CGM data. Although time in range(3.9 - 10.0 mmol/L) was similar before, during, and after lockdown, the median time below range(TBR)<3.9mmol/l decreased from 3.70%(IQR 2.25%,9.53%) before lockdown to 2.91%(IQR 1.43%,5.95%) during lockdown, but reversed to 4.95%(IQR 2.11%,9.42%) after lockdown,(p=0.004). TBR<3.0mmol/l was 0.59%(IQR 0.14%,2.21%), 0.38%(IQR 0.05%,1.35%) and 0.82%(IQR 0.22%,1.69%), respectively(p=0.008). The amelioration in hypoglycemia during lockdown was more prominent among those who had less time spent<3.9mmol/L at baseline. During lockdown, individuals reduced their physical activity, received longer sleep duration, and spent more time on diabetes management. Besides, they attended outpatient clinics less and turned to telemedicine more frequently. CONCLUSION: Glycemic control did not deteriorate in T1D children and teenagers around the COVID-19 pandemics. Hypoglycemia declined during lockdown but reversed after lockdown, and the changes related to lifestyle might not provide a long-term effect.

	Before lockdown	During lockdown	After lockdown	*P* value†
Time in range (3.9-7.8 mmol/L) (%)	52.57 ± 14.42	52.18 ± 15.40	51.16 ± 15.29	*0.614*
Time in range (3.9-10.0 mmol/L) (%)	74.28 ± 12.13	75.35 ± 12.66	73.60 ± 12.83	*0.081*

Mean glucose (mmol/L)	7.74 ± 1.19	7.85 ± 1.14	7.70 ± 1.20	*0.368*
Estimated HbA1c (%)	6.47 ± 0.75	6.54 ± 0.72	6.54 ± 0.72	*0.368*
Hyperglycemia				
Time>13.9 mmol/L (%)	2.95 (0.42, 5.91)	1.58 (0.69, 7.29)	1.80 (0.71, 3.86)	*0.862*
Time>10.0 mmol/L (%)	18.68 (12.05, 27.92)	15.39 (12.16, 27.67)	15.84 (11.78, 26.71)	*0.404*
High blood glucose index	41.54 (31.27, 54.69)	41.20 (33.49, 57.78)	40.74 (31.23, 52.61)	*0.298*
Hypoglycemia				
Time<3.9 mmol/L (%)	3.70 (2.25, 9.53)	2.91 (1.43, 5.95)	4.95 (2.11, 9.42)	*0.004*
Time<3.0 mmol/L (%)	0.59 (0.14, 2.21)	0.38 (0.05, 1.35)	0.82 (0.22, 1.69)	*0.008*
Low blood glucose index	1.15 (0.73, 2.60)	1.03 (0.58, 1.68)	1.40 (0.81, 2.36)	*0.020*
Hypoglycemic events (per week)	1.50 (0, 3.50)	0.50 (0, 2.00)	1.27 (0.50, 4.00)	*0.020*
Prolong hypoglycemia (per week)	0 (0, 0.50)	0 (0, 0)	0 (0, 0.50)	*0.039*
Glucose variability				
CV (%)	35.48 ± 7.17	34.06 ± 6.51	35.20 ± 6.38	*0.242*
SD (mmol/L)	2.77 ± 0.81	2.70 ± 0.75	2.72 ± 0.69	*0.911*
MAGE (mmol/L)	7.17 ± 2.04	7.01 ± 1.85	6.99 ± 1.76	*0.975*
MODD (mmol/L)	3.02 ± 1.00	2.89 ± 0.87	2.87 ± 0.99	*0.086*

Data are expressed as mean ± SD or median (IQR). †ANOVA of repeated measuring or Friedman rank test.

CV, coefficient of variation. SD, standard deviation. MAGE, mean amplitude of glucose excursion. MODD, mean of daily differences.

Table 2: "Continuous Glucose Monitoring Metrics (n=43)."

Lifestyle changes compared with	During lockdown			After lockdown			
pre-lockdown (n=34)	more	same	less	more	same	less	*P* value†
Total physical activity#	4 (11.8%)	15 (44.1%)	15 (44.1%)	4 (11.8%)	28 (82.4%)	2 (5.9%)	*0.004*
Food amount	6 (17.6%)	25 (73.5%)	3 (8.8%)	1 (2.9%)	31 (91.2%)	2 (5.9%)	*0.142*
Regularity of mealtimes	0	26 (76.5%)	8 (23.5%)	3 (8.8%)	31 (91.2%)	0	*0.029*
Number of snacks	11 (32.4%)	22 (64.7%)	1 (2.9%)	3 (8.8%)	30 (88.2%)	1 (2.9%)	*0.018*
Number of midnight snacks	3 (8.8%)	31 (91.2%)	0	0	34 (100.0%)	0	*0.317*
Sleep duration	14 (41.2%)	19 (55.9%)	1 (2.3%)	4 (11.8%)	27 (79.4%)	3 (8.8%)	*0.024*
Bedtime‡	19 (55.9%)	13 (38.2%)	2 (5.9%)	5 (14.7%)	26 (76.5%)	3 (8.8%)	*0.003*
Waking time§	20 (58.8%)	13 (38.2%)	1 (2.9%)	3 (8.8%)	28 (82.4%)	3 (8.8%)	*<0.001*
Study time	5 (14.7%)	11 (32.4%)	18 (52.9%)	6 (17.6%)	26 (76.5%)	2 (5.9%)	*<0.001*
Stress	1 (2.9%)	33 (97.1%)	0	2 (5.9%)	32 (94.1%)	0	*0.317*
Anxiety	1 (2.9%)	33 (97.1%)	0	2 (5.9%)	32 (94.1%)	0	*0.317*
Self-perceived hypoglycemia	1 (2.9%)	9 (26.5%)	24 (70.6%)	5 (14.7%)	29 (85.3%)	0	*<0.001*
Time in glycemic management	23 (67.6%)	11 (32.4%)	0	0	34 (100.0%)	0	*<0.001*
Access to outpatient clinics	0	12 (35.3%)	22 (64.7%)	1 (2.9%)	22 (64.7%)	11 (32.4%)	*0.002*
Use of online Medical Service	10 (29.4%)	23 (67.6%)	1 (2.9%)	1 (2.9%)	30 (88.2%)	3 (8.8%)	*0.011*
Insulin purchase	2 (6.1%)	26 (78.8%)	5 (15.2%)	3 (9.1%)	29 (87.9%)	1 (3%)	*0.172*
	Yes	No		Yes	No		
Hyperglycemia coma	0	34 (100.0%)		0	34 (100.0%)		*>1.000*
Hypoglycemia coma	0	34 (100.0%)		0	34 (100.0%)		*>1.000*
Shortage of insulin	3 (8.8%)	31 (91.2%)		0	34 (100.0%)		*0.002*
Online shopping for insulin	5 (14.7%)	29 (85.3%)		5 (14.7%)	29 (85.3%)		*1.000*

Data are expressed as the number of participants (%). †McNemar's $\chi 2$ test.

#Based on the frequency and duration of physical activity.

‡, § In bedtime and waking time, "more" and "less" referred to "later" and "earlier".

Table 3: "Questionnaire-derived lifestyle and medical data around lockdown in the study participants".

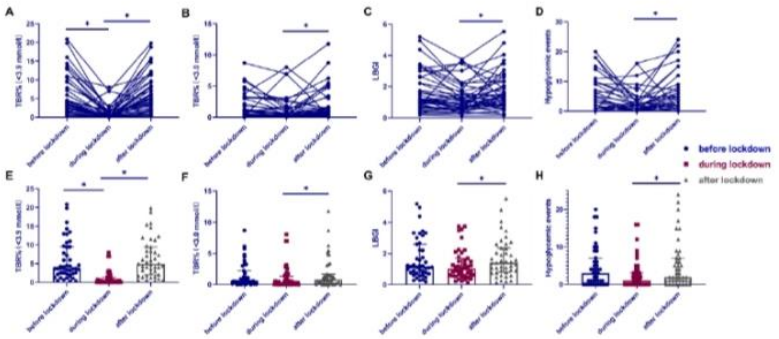

Figure 2: "Changes in hypoglycemia among children and teenagers (n=43). Panels a-d show trend line of changes of individual patients. Panels e-h show box-scatterplots based on the median value. a, e TBR<3.9 mmol/l significantly decreased during lockdown (p=0.011) and reversed after lockdown (p=0.011). b, f TBR<3.0mmol/l trended downward during lockdown (p=0.093) and elevated after lockdown (p=0.008). c, e LBGI declined during lockdown (p=0.053) and rose again after lockdown (p=0.039). d,h The number of hypoglycemic events decreased during lockdown and reversed after lockdown (p=0.039). TBR, time below range. LBGI, low blood glucose index".

DETECTION OF SARS-COV-2 IN OUTPATIENTS: A MULTI-CENTRE COMPARISON OF SELF-COLLECTED SALINE GARGLE, ORAL SWAB AND COMBINED ORAL-ANTERIOR NASAL SWAB TO A PROVIDER COLLECTED NASOPHARYNGEAL SWAB

Kandel CE, Young M, Serbanescu MA, Powis JE, Bulir D, Callahan J, Katz K, McCready J, Racher H, Sheldrake E, Quon D, Vojdani OK, McGeer A, Goneau LW, Vermeiren C.. Infect Control Hosp Epidemiol. 2021 Jan 13:1-20. doi: 10.1017/ice.2021.2. Online ahead of print.
Level of Evidence: 2 - Individual cross sectional studies with consistently applied reference standard and blinding

BLUF

A cross-sectional study conducted at three COVID-19 testing centers in Toronto, Canada between August 28 - October 17, 2020 found that of the three alternative COVID-19 swabbing methods tested (oral swab, saline gargle, and combined oral-anterior nasal swab), the saline gargle and combined oral-anterior nasal swab had similar sensitivity to the nasopharyngeal swab, suggesting these methods may be more desired than the oral swab alone (Table 1, 2).

ABSTRACT

BACKGROUND: Widespread testing for SARS-CoV-2 is necessary to curb the spread of COVID-19, but is undermined when the only option is a nasopharyngeal swab. Self-collected swab techniques can overcome many of the disadvantages of a nasopharyngeal swab, but require evaluation. METHODS: Three self-collected non-nasopharyngeal swab techniques (saline gargle, oral swab and combined oral-anterior nasal swab) were compared to a nasopharyngeal swab for SARS-CoV-2 detection at multiple COVID-19 assessment centers in Toronto, Canada. The performance characteristics of each test were assessed. RESULTS: The adjusted sensitivity of the saline gargle was 0.90 (95% CI 0.86-0.94), the oral swab was 0.82 (95% CI 0.72-0.89) and the combined oral-anterior nasal swab was 0.87 (95% CI 0.77-0.93) as compared to a nasopharyngeal swab, which demonstrated a sensitivity of around 90% when all positive tests were the reference standard. The median cycle threshold values for the SARS-CoV-2 E-gene for concordant and discordant saline gargle specimens were 17 and 31 ($p<0.001$), for the oral swabs were 17 and 28 ($p<0.001$) and oral-anterior nasal swabs were 18 and 31 ($p=0.007$). CONCLUSIONS: Self-collected saline gargle and an oral-anterior nasal swab have a similar sensitivity to a nasopharyngeal swab for the detection of SARS-CoV-2. These alternative collection techniques are cheap and can eliminate barriers to testing, particularly in underserved populations.

FIGURES

		Nasopharyngeal Swab	
Non-Nasopharyngeal Swab	**Non-Nasopharyngeal Swab Result**	Positive	Negative
Saline Gargle	Positive	57	1
	Negative	7	543
Oral Swab	Positive	44	1
	Negative	11	549
Oral-Anterior Nasal Swab	Positive	34	2
	Negative	6	352

Table 1: Results of SARS-CoV-2 detection in paired nasopharyngeal swab and the nonnasopharyngeal swab specimens from individuals who presented to an outpatient COVID-19 testing center.

Swab	Reference Standard	Sensitivity[b]	Adjusted Sensitivity[b]	Specificity[b]	NPV[b]	Adjusted NPV[b]	PPV[b]
NP	Gargle + NP	0.98 (0.92–1.00)	0.88 (0.83–0.92)		1.00 (0.99–1.00)	1.00 (0.98–1.00)	
Gargle	Gargle + NP	0.89 (0.79–0.96)	0.90 (0.86–0.94)		0.99 (0.97–0.99)	1.00 (0.98–1.00)	
Gargle	NP	0.89 (0.79–0.96)	0.89 (0.79–0.95)	1.00 (0.99–1.00)	0.99 (0.97–0.99)	1.00 (1.00–1.00)	1.00 (0.94–1.00)
NP	Oral + NP	0.98 (0.90–1.00)	0.92 (0.84–0.97)		1.00 (0.99–1.00)	1.00 (0.95–1.00)	
Oral	Oral + NP	0.80 (0.68–0.90)	0.82 (0.72–0.89)		0.98 (0.97–0.99)	1.00 (0.95–1.00)	
Oral	NP	0.80 (0.67–0.90)	0.80 (0.67–0.89)	1.00 (0.99–1.00)	0.98 (0.97–0.99)	1.00 (1.00–1.00)	0.98 (0.88–1.00)
NP	Oral–Anterior Nasal + NP	0.95 (0.84–0.99)	0.89 (0.80–0.95)		0.99 (0.98–1.00)	1.00 (0.95–1.00)	
Oral–Anterior Nasal	Oral–Anterior Nasal + NP	0.86 (0.71–0.95)	0.87 (0.77–0.93)		0.98 (0.96–0.99)	1.00 (0.95–1.00)	
Oral–Anterior Nasal	NP	0.85 (0.70–0.94)	0.85 (0.70–0.93)	0.99 (0.98–1.00)	0.98 (0.96–0.99)	0.99 (0.99–1.00)	0.94 (0.81–0.99)

Note. NP, nasopharyngeal; NPV, negative predictive value; PPV, positive predictive value.
[a]Unadjusted and adjusted (by inverse probability weighting) for the testing subsample were calculated.
[b]Data shown with 95% confidence intervals.

Table 2. Performance Characteristics of Nasopharyngeal and Non-nasopharyngeal Swab Detection Methods for SARS-CoV-2 by Various Reference Standards

DEVELOPMENTS IN TREATMENTS

METHYLPREDNISOLONE IN ADULTS HOSPITALIZED WITH COVID-19 PNEUMONIA : AN OPEN-LABEL RANDOMIZED TRIAL (GLUCOCOVID)

Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C, Mora V, Cerezo-Hernández A, Hernández JL, López-Muñíz G, Hernández-Blanco F, Cifrián JM, Olmos JM, Carrascosa M, Nieto L, Fariñas MC, Riancho JA; GLUCOCOVID investigators.. Wien Klin Wochenschr. 2021 Feb 3. doi: 10.1007/s00508-020-01805-8. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

Spanish internists, pulmonogists, and infectious disease physicians conducted a randomized open-label trial comparing outcomes (definition in summary) of 64 patients with COVID-19 (Table 1) who received standard of care (SOC, see summary) versus SOC plus 6-days of methylprednisone (MP) at 5 hospitals in Spain. Intention-to-treat analysis showed no difference in outcomes between the two groups (RR: 0.68; 95%CI 0.37–1.26; p = 0.250), while the MP group had a decreased risk of poor outcomes in the per protocol (PP) analysis (RR: 0.42; 95%CI 0.20–0.89; p = 0.043) (Table 2). Authors suggest their PP data is consistent with data from other trials demonstrating that MP has a beneficial effect on patient outcomes, but note the lack of significance in ITT and study limitations (inadequate sample size, premature cancellation of the trial) prohibit broad generalizability of their results.

SUMMARY

The authors define their primary outcome as a composite of in-hospital all-cause mortality, ICU admissions, and noninvasive ventilation requirement.

Standard of care (SOC) included symptomatic treatment with acetaminophen, oxygen therapy, low-molecular weight heparin, and antibiotics for co-infections. Azithromycin, hydroxychloroquine, and lopinavir plus ritonavir were frequently prescribed.

ABSTRACT

PURPOSE: To determine whether a 6-day course of methylprednisolone (MP) improves outcome in patients with severe SARS-CoV-2 (Corona Virus Disease 2019 [COVID-19]). METHODS: The study was a multicentric open-label trial of COVID-19 patients who were aged >= 18 years, receiving oxygen without mechanical ventilation, and with evidence of systemic inflammatory response who were assigned to standard of care (SOC) or SOC plus intravenous MP (40 mg bid for 3 days followed by 20 mg bid for 3 days). The primary outcome was a composite of death, admission to the intensive care unit, or requirement for noninvasive ventilation. Both intention-to-treat (ITT) and per protocol (PP) analyses were performed. RESULTS: A total of 91

patients were screened, and 64 were randomized (mean age70 +- 12 years). In the ITT analysis, 14 of 29 patients (48%) in the SOC group and 14 of 35 (40%) in the MP group suffered the composite endpoint (40% versus 20% in patients under 72 years and 67% versus 48% in those over 72 years; p = 0.25). In the PP analysis, patients on MP had a significantly lower risk of experiencing the composite endpoint (age-adjusted risk ratio 0.42; 95% confidence interval, CI 0.20-0.89; p = 0.043). CONCLUSION: The planned sample size was not achieved, and our results should therefore be interpreted with caution. The use of MP had no significant effect on the primary endpoint in ITT analysis; however, the PP analysis showed a beneficial effect due to MP, which consistent with other published trials support the use of glucocorticoids in severe cases of COVID-19.

FIGURES

Table 1 Baseline characteristics of the study groups at randomization

From: Methylprednisolone in adults hospitalized with COVID-19 pneumonia

	Total (*n* = 64)	SOC (*n* = 29)	MP (*n* = 35)	Mean differences SOC vs. MP (95% CI)
Age, years, mean ± SD	70 ± 12	66 ± 12	73 ± 11	−7 (−13 to −2)
Sex (male, %)	39 (61)	16 (55)	23 (66)	−11% (−33 to 13)
Days from symptom onset to inclusion, mean ± SD	12 ± 6	12 ± 7	12 ± 5	0.3 (−2.6 to 3.2)
COVID-19 characteristics				
SAFI (SaO2/FI O2), median (IQR)	262 (179–350)	319 (169–406)	254 (180–337)	18 (−38 to 74)
Creatinine, mg/dl, median (IQR)	0.9 (0.7–1.1)	0.9 (0.7–1.1)	0.9 (0.8–1.1)	−0.1 (−0.3 to 0.2)
Lymphocytes 10^9/L, median (IQR)	0.8 (0.6–10)	0.8 (0.6–10)	0.8 (0.6–10)	−0.2 (−0.6 to 0.3)
Platelets 10^9/L, median (IQR)	232 (180–335)	244 (215–359)	216 (159–338)	19 (−41 to 80)
CRP, mg/dl, median (IQR)	16 (12–24)	16 (11–24)	16 (12–24)	0.1 (−4 to 4)
D-dimer, ng/ml, median (IQR)	1240 (681–2093)	980 (557–1856)	1340 (712–2152)	−1912 (−4879 to 1054)
Ferritin, mg/dl, median (IQR)	1052 (517–1504)	976 (449–1355)	1100 (627–1574)	−182 (−661 to 297)
qSOFA (points), median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	−0.06 (−0.3 to 0.2)
Comorbidities				
Hypertension, *n* (%)	30 (47)	12 (41)	18 (51)	−10% (−32 to 14)
Cardiac disease, *n* (%)	8 (13)	4 (14)	4 (11)	3% (−14 to 20)
Respiratory disease, *n* (%)	5 (8)	1 (3)	4 (11)	−8% (−22 to 7)
Diabetes, *n* (%)	11 (17)	4 (14)	7 (20)	−6% (−24 to 13)
Therapy				
Azithromycin, *n* (%)	58 (91)	29 (100)	29 (83)	17% (−2 to 33)
Hydroxychloroquine, *n* (%)	61 (95)	29 (100)	32 (91)	9% (−4 to 22)
Lopinavir/ritonavir, *n* (%)	53 (83)	28 (97)	25 (71)	26% (7 to 42)
LMWH (prophylactic dose), *n* (%) LMWH (anticoagulant dose), *n* (%)	49 (77) 9 (14)	22 (76) 4 (14)	27 (77) 5 (14)	1% (−22 to 18) 0.5 (−17 to 18)

CI confidence interval, *CRP* C-reactive protein, *IQR* interquartile range, *LMWH* low molecular weight heparin, *MP* methylprednisolone, *qSOFA* Quick Sequential Organ Failure Assessment, *SAFI* hemoglobin O2 saturation/fraction of inspired oxygen, *SD* standard deviation, *SOC* standard of care, *SOFA* sequential organ failure assessment

Table 1. CI confidence interval, CRP C-reactive protein, IQR interquartile range, LMWH low molecular weight heparin, MP methylprednisolone, qSOFA Quick Sequential Organ Failure Assessment, SAFI hemoglobin O2 saturation/fraction of inspired oxygen, SD standard deviation, SOC standard of care, SOFA sequential organ failure assessment

Table 2 Comparison of patients in the control and methylprednisolone (MP) arms. Age-stratified analyses

From: Methylprednisolone in adults hospitalized with COVID-19 pneumonia

Outcome	Methylprednisolone	Standard of care	Relative risk (95% CI)	*p*
Intention-to-treat				
<72 years	2/10 (20%)	8/20 (40%)	0.50 (0.13–1.93)	0.273
≥72 years	12/25 (48%)	6/9 (67%)	0.72 (0.39–1.33)	0.336
Total	14/35 (40%)	14/29 (48%)	0.68 (0.37–1.26)[a]	0.250
Per protocol				
<72 years	1/9 (11%)	8/20 (40%)	0.28 (0.04–1.90)	0.120
≥72 years	8/21 (38%)	6/8 (75%)	0.51 (0.26–1.00)	0.074
Total	9/30 (30%)	14/28 (50%)	**0.42 (0.20–0.89)[a]**	**0.043**

[a]Mantel-Haenszel, age-stratified risk

Table 2 Comparison of patients in the control and methylprednisolone (MP) arms. Age-stratified analyses

EFFICACY OF CANAKINUMAB IN MILD OR SEVERE COVID-19 PNEUMONIA

Katia F, Myriam DP, Ucciferri C, Auricchio A, Di Nicola M, Marchioni M, Eleonora C, Emanuela S, Cipollone F, Vecchiet J..
Immun Inflamm Dis. 2021 Jan 19. doi: 10.1002/iid3.400. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A cohort study from the Clinic of Infectious Disease at D'Annunzio University of Chieti-Pescara in Italy examined the efficacy of canakinumab, an anti-interleukin-1beta, in mild or severe COVID-19 patients. Among the 34 patients enrolled in the study, 17 received standard therapy and 17 were treated with a single dose of 300 mg canakinumab; their inflammation indices were recorded at several different points before and after the intervention. The canakinumab group saw a reduction in inflammation indices, a significant and rapid increase in P/F ratio, and a reduction in supply of high oxygen flows, suggesting canakinumab as a valid therapeutic option for hospitalized non-ICU COVID-19 patients with a mild or severe case (Table 2).

ABSTRACT

BACKGROUND: Clinicians all around the world are currently experiencing a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Several therapeutic strategies have been used until now but, to date, there is no specific therapy to treat SARS-CoV-2 infection. In this study, we used canakinumab, a human monoclonal antibody targeting interleukin-1 beta to improve respiratory function and laboratory parameters compared with standard therapy (hydroxycloroquine plus lopinavir/ritonavir). METHODS: We enrolled 34 patients with mild or severe non intensive care unit (ICU) coronavirus disease 2019 (COVID-19): 17 patients treated with standard therapy and 17 patients treated with a subcutaneous single dose of canakinumab 300 mg. We collected data about oxygen supports and laboratory parameters such as inflammation indices and hemogasanalysis. We compared the data collected before the administration of canakinumab (T0), 3 days after T0 (T1) and 7 days after T0 (T2) with the same data from patients taking the standard therapy. RESULTS: We observed a reduction in inflammation indices and a significant and rapid increase in P/F ratio in canakinumab group, with improvement of 60.3% after the administration. We reported a significant reduction in oxygen flow in patients treated with canakinumab (-28.6% at T1 vs. T0 and -40.0% at T2 vs. T1). Conversely, the standard group increased the supply of high oxygen at T1 versus T0 (+66.7%), but reduced oxygen flows at T2 versus T1 (-40.0%). CONCLUSION: In hospitalized adult patients with mild or severe non ICU COVID-19, canakinumab could be a valid therapeutic option. Canakinumab therapy causes rapid and long-lasting improvement in oxygenation levels in the absence of any severe adverse events.

FIGURES

	Baseline (T0)		Third day (T1)		Seventh day (T2)		*p* Value		
Variable	Standard group	Canakinumab group	Standard group	Canakinumab group	Standard group	Canakinumab group	Group[a]	Time[b]	Interaction[c]
Hb (g/dl)	13.4 (13.0, 14.2)	14.6 (13.0, 15.5)	13.0 (12.2, 13.5)	13.0 (12.2, 13.5)	12.3 (11.4, 13.4)	13.5 (12.2, 14.3)	.710	**.004**	.615
WBC (cells/mcl)	7.8 (4.7, 9.0)	6.3 (4.8, 10.0)	6.4 (4.5, 7.7)	7.5 (5.3, 8.5)	6.4 (5.6, 8.0)	7.0 (5.0, 8.9)	.286	.730	.469
Neutrophils (cells/mcl)	5.8 (3.1, 7.6)	5.3 (3.7, 9.0)	4.8 (2.8, 6.0)	5.2 (4.0, 6.2)	4.5 (3.1, 5.6)	4.3 (3.6, 5.4)	.127	.230	.173
Lymphocytes (cells/mcl)	1.1 (0.8, 1.2)	0.7 (0.6, 0.9)	1.1 (0.9, 1.3)	1.1 (0.8, 1.9)	1.4 (1.1, 1.7)	1.4 (1.2, 2.0)	.146	**.005**	.074
PLT (x 10^3cells/mcl)	213.0 (151.0, 245.0)	194.0 (174.0, 226.0)	243.0 (192.0, 326.0)	265.0 (224.0, 347.0)	299.0 (258.0, 386.0)	244.0 (208.0, 289.0)	.708	**<.001**	.065
Fibrinogen (mg/dl)	542.0 (479.0, 622.0)	639.0 (550.0, 700.0)	500.0 (450.0, 551.0)	450.0 (321.0, 530.0)	400.0 (308.5, 514.0)	360.0 (329.0, 400.0)	.869	**.029**	.166
D-dimer (ng/ml)	0.7 (0.6, 0.9)	0.8 (0.6, 1.4)	1.0 (0.9, 1.5)	0.9 (0.6, 1.1)	1.0 (0.8, 2.4)	0.5 (0.4, 0.8)	.659	**.034**	**.003**
Creatinin (mg/dl)	0.8 (0.7, 1.0)	0.9 (0.8, 1.1)	0.8 (0.7, 0.8)	0.9 (0.7, 1.0)	0.8 (0.6, 0.8)	0.8 (0.7, 0.8)	.110	.412	.241
Blood Urea (mg/dl)	35.0 (29.0, 37.0)	32.0 (24.0, 42.0)	33.0 (25.0, 38.0)	27.0 (23.0, 38.0)	28.0 (25.0, 37.0)	29.0 (23.0, 34.0)	.308	.393	.356
CRP (mg/dl)	136.3 (69.8, 197.0)	181.0 (125.3, 201.8)	140.0 (50.8, 194.7)	17.1 (2.8, 78.0)	38.0 (16.5, 76.4)	4.2 (1.5, 5.9)	.545	**.001**	.507
PCT (ng/ml)	0.1 (0.0, 0.2)	0.2 (0.1, 1.0)	0.0 (0.0, 0.1)	0.1 (0.0, 0.2)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	**.014**	.862	.067
LDH (U/L)	300.0 (291.8, 334.0)	287.0 (245.0, 374.0)	410.0 (254.0, 490.0)	279.0 (221.0, 313.0)	226.0 (187.5, 267.0)	199.0 (184.0, 250.0)	.233	**.003**	.745
AST (U/L)	40.0 (28.0, 52.0)	29.0 (24.0, 37.0)	48.0 (23.2, 55.0)	50.0 (30.0, 109.0)	61.0 (28.5, 85.5)	58.0 (45.0, 104.0)	.233	**.003**	.745

Table 2. Clinical characteristics between standard group and canakinumab group at three times (T0, T1, T2)

REAL-WORLD EVIDENCE FOR ASSESSING PHARMACEUTICAL TREATMENTS IN THE CONTEXT OF COVID-19

Franklin JM, Lin KJ, Gatto N, Rassen J, Glynn RJ, Schneeweiss S.. Clin Pharmacol Ther. 2021 Feb 2. doi: 10.1002/cpt.2185. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

This article from Brigham and Women's Hospital and Harvard Medical School evaluates the utility of nonrandomized real-world evidence (RWE) as a means for assessing the pharmacological efficacy of emerging COVID-19 treatments and vaccine outcomes during the pandemic. The authors highlight the examples of open and closed claims in ambulatory settings, Premier Healthcare Database and electronic health records in the inpatient setting, and the Vaccine Adverse Event Reporting System (VAERS) for monitoring vaccines as examples of potentially useful sources of nonrandomized real world-evidence. They conclude that journals should consider including one reviewer with a history of publications regarding healthcare databases when evaluating RWE regarding COVID-19 interventions.

ABSTRACT

The emergence and global spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in an urgent need for evidence on medical interventions and outcomes of the resulting disease, COVID-19. While many randomized controlled trials (RCTs) evaluating treatments and vaccines for COVID-19 are already in-progress, the number of clinical questions of interest greatly outpaces the available resources to conduct RCTs. Therefore, there is growing interest in whether nonrandomized real-world evidence (RWE) can be used to supplement RCT evidence and aid in clinical decision-making, but concerns about nonrandomized RWE have been highlighted by a proliferation of RWE studies on medications and COVID-19 outcomes with widely varying conclusions. The objective of this paper is to review some clinical questions of interest, potential data types, challenges, and merits of RWE in COVID-19, resulting in recommendations for nonrandomized RWE designs and analyses based on established RWE principles.

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