The Daily COVID-19 Literature Surveillance Summary

August 28, 2020

DISCLAIMER

This free and open source document represents a good faith effort to provide real time, distilled information for guiding best practices during the COVID-19 pandemic. This document is not intended to and cannot replace the original source documents and clinical decision making. These sources are explicitly cited for purposes of reference but do not imply endorsement, approval or validation.

This is not an official product or endorsement from the institutions affiliated with the authors, nor do the ideas and opinions described within this document represent the authors' or their affiliated institutions' values, opinions, ideas or beliefs. This is a good faith effort to share and disseminate accurate summaries of the current literature.

NOW LIVE!

Daily audio summaries of the literature in 10 minutes or less.
https://www.covid19lst.org/podcast/

COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

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

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

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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

EXECUTIVE SUMMARY

Climate

- Primary care residents at Brigham and Women's Hospital in Boston discuss the importance of community health centers (CHCs) in serving low socioeconomic status, immigrant, rural, and racial/ethnic minority patients during the COVID-19 pandemic. The authors call for Congressional action to ensure adequate funding to CHCs and universal coverage to individuals without employer-sponsored insurance, suggesting that the pandemic may provide an impetus for improving the United States healthcare system so that CHC's could serve patients more effectively.

Epidemiology

- A multicenter cross-sectional study found that among 614 patients with confirmed COVID-19, 278 had elevated troponin levels, which was associated with higher in-hospital mortality. Those with elevated troponin levels were more likely to be older, have atrial fibrillation, heart failure, hypertension, and coronary artery disease. In the hospital, patients with elevated troponins were additionally more likely to have complications including sepsis, pulmonary embolism, delirium, heart failure, acute kidney failure, and major bleeding. This study suggests that running diagnostic tests and identifying patients with elevated troponins may help earlier identify patients requiring more intensive care.

Understanding the Pathology

- A retrospective study of 191 severe COVID-19 patients looked specifically at longitudinal IgM and IgG antibody responses to the nucleocapsid, spike protein, and receptor-binding domain of SARS-CoV-2. There was no significant difference in antibody positive rates between survivors vs non-survivors nor 28-day clinically improved vs non-improved patients. Four weeks after infection, patients who ultimately died had lower spike-IgG titers than survivors, and viral clearance was strongly associated with nucleocapsid-IgG and receptor binding domain-IgG titers, suggesting the possible use of spike-IgG as a predictor of adverse outcomes and the role of IgG as an important factor against SARS-CoV-2 infection.

Transmission & Prevention

- A medical news reporter discussed the herd immunity threshold for COVID-19, stating that determining this threshold is difficult with this virus due to the many uncertainties about the level at which people can act as vectors of disease spread. This author also suggests that even if herd immunity is be achieved, there is no guarantee that it would last.

R&D: Diagnosis & Treatments

- Epidemiologists in Spain examined the avidity of antibodies to SARS-CoV-2 in 76 serum specimens from COVID-19 patients to determine whether antibody avidity corresponded with time since acquisition of the virus. They found that 39 samples tested positive for both IgG and IgM, 37 tested positive for IgG only, and IgG reactivity was lost in 28 samples after urea treatment. Serum that lost reactivity were drawn significantly sooner after onset of symptoms than serum that retained activity suggesting that serum antibody avidity corresponds to the time since onset of symptoms and thus could be useful in predicting the acquisition date of SARS-CoV-2 infection.
- An observational cohort study conducted in Wuhan, China analyzed the use of a nanomaterial-based breathalyzer system in COVID-19 pre-screening and found that their device was able to capture COVID-19-specific volatile organic compound mixtures from exhaled breath with adequate discriminations between COVID-19 positive and non-COVID-19 groups, suggesting that this technology may be useful as a rapid screening tool.

Mental Health & Resilience Needs

- A cross sectional study in Italy found that among 105 patients, 11 had abnormal depression items and 29 had abnormal anxiety items on the Hospital Anxiety and Depression Scale (HADS) 1-3 months after recovering from COVID-19 infection, whereas only 9 patients were being treated with anti-anxiety or antidepressant therapy prior to hospital admission. Additionally, those with abnormal HADS results were more likely to have mild or worse cognitive impairment on the Mini Mental State Examination (MMSE) and were significantly more likely to have persistence of physical symptoms such as dyspnea than those without abnormal HADS results. This study suggests that COVID-19 patients should recover with multidisciplinary teams, as psychological distress can persist after disease recovery.

TABLE OF CONTENTS

CLIMATE

DISPARITIES

COMMUNITY HEALTH CENTERS AND COVID-19 - TIME FOR CONGRESS TO ACT

Kishore S, Hayden M.. N Engl J Med. 2020 Aug 20;383(8):e54. doi: 10.1056/NEJMp2020576. Epub 2020 Jun 26.
Level of Evidence: Other - Expert Opinion

BLUF

Primary care residents at Brigham and Women's Hospital in Boston discuss the importance of community health centers (CHCs) in serving low socioeconomic status, immigrant, rural, and racial/ethnic minority patients during the COVID-19 pandemic. The authors call for Congressional action to ensure adequate funding to CHCs and universal coverage to individuals without employer-sponsored insurance (see summary), suggesting that the pandemic may provide an impetus for improving the United States healthcare system so that CHC's could serve patient more effectively.

SUMMARY

Specific areas of existing and proposed legislative action as follows:
1. The CARES Act and HEROES Bill include provisions for congressional funding for CHCs to support costs associated with providing healthcare, telemedicine, and various health education programs.
2. The Medicare Crisis Program Act would help to limit patient's out-of-pocket expenses. In addition, working towards Medicare for All policies would provide universal coverage while working toward a global payment program.
3. A proposed New Deal-like program hiring unemployed Americans would enable CHCs to employ individuals to help with contact tracing during the pandemic and management of chronic conditions moving forward.

RISK FACTORS FOR POSITIVE AND NEGATIVE COVID-19 TESTS: A CAUTIOUS AND IN-DEPTH ANALYSIS OF UK BIOBANK DATA

Chadeau-Hyam M, Bodinier B, Elliott J, Whitaker MD, Tzoulaki I, Vermeulen R, Kelly-Irving M, Delpierre C, Elliott P.. Int J Epidemiol. 2020 Aug 20:dyaa134. doi: 10.1093/ije/dyaa134. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

Epidemiologists in Europe triangulated the test data on SARS-CoV-2 infection from Public Health England (n= 4,509, including 1,325 positive and 3,184 negative tests) with the UK Biobank study (n = 488,083; Figure 1). After accounting for selection bias and multiple potential confounders, they found that male sex, non-white ethnicity, and lower education attainment were independently correlated with positive COVID-19 results (Figure 3). Health risk factors such as smoking, alcohol drinking, and high BMI and co-morbidities such as cancer, cardiovascular disease, hypertension, diabetes, respiratory disease were not linked to the risk of testing positive (Figure 2). Further, greater exposure to environmental pollutants (measured by particulate matter 2.5 absorbance) was independently linked with risk of being tested for SARS-CoV-2, although the association between pollutant exposure and risk of testing positive is not clear. The authors suggest that these findings may help clarify the natural history of COVID-19 and highlights avenues for further study into diagnosis, prevention and treatment.

ABSTRACT

BACKGROUND: The recent COVID-19 outbreak has generated an unprecedented public health crisis, with millions of infections and hundreds of thousands of deaths worldwide. Using hospital-based or mortality data, several COVID-19 risk factors have been identified, but these may be confounded or biased. METHODS: Using SARS-CoV-2 infection test data (n = 4509 tests; 1325 positive) from Public Health England, linked to the UK Biobank study, we explored the contribution of demographic, social, health risk, medical and environmental factors to COVID-19 risk. We used multivariable and penalized logistic regression models for the risk of (i) being tested, (ii) testing positive/negative in the study population and, adopting a test negative design, (iii) the risk of testing positive within the tested population. RESULTS: In the fully adjusted model, variables independently associated with the risk of being tested for COVID-19 with odds ratio >1.05 were: male sex; Black ethnicity; social disadvantage (as measured by education, housing and income); occupation (healthcare worker, retired, unemployed); ever smoker; severely obese; comorbidities; and greater exposure to particulate matter (PM) 2.5 absorbance. Of these, only male sex, non-White ethnicity and lower educational attainment, and none of the comorbidities or health risk factors, were associated with testing positive among tested individuals. CONCLUSIONS: We adopted a careful and exhaustive approach within a large population-based cohort, which enabled us to triangulate evidence linking male sex, lower educational attainment and non-White ethnicity with the risk of COVID-19. The elucidation of the joint and independent effects of these factors is a high-priority area for further research to inform on the natural history of COVID-19.

FIGURES

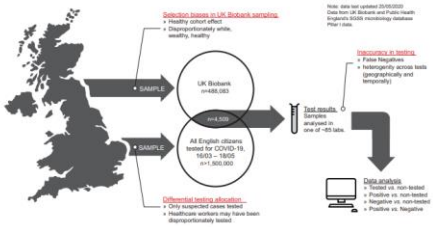

Figure 1 Overview of the data workflow, depicting the synthesis of data from the UK Biobank for COVID-19 testing data. Key biases that are innate to the data gathering processes and test allocation are annotated, as these impact the statistical inferences that can be made from the data.

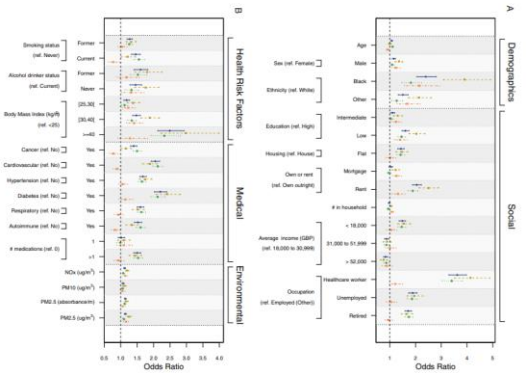

Figure 2 Results from the univariate logistic models predicting from each covariate separately the risk of (i) being tested for COVID-19 (outcome: tested vs non-tested, in blue, plain line), (ii) being tested positive for COVID-19 (outcome: tested positive vs non-tested, in beige dashed line), (iii) being tested negative for COVID-19 (outcome: tested negative vs non-tested, in green, dotted line), and (iv) being tested positive conditional on being tested (outcome: tested positive vs tested negative, in orange dashed/dotted line). Effect size estimates are expressed as odds ratios and are represented for demographic covariates and social factors (A), health risk, medical and environmental factors (B).

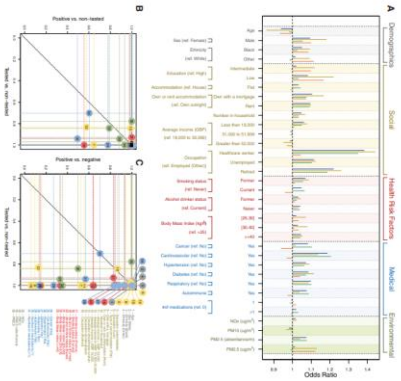

Figure 3 Penalized odds ratios from logistic-LASSO models regressing jointly all predictors against the risk of (i) being tested for COVID-19 (outcome: tested vs non-tested, in blue), (ii) being tested positive for COVID-19 (outcome: tested positive vs non-tested, in beige), (iii) being tested negative for COVID-19 (outcome: tested negative vs non-tested, in green), and (iv) being tested positive conditionally on being tested (outcome: tested positive vs tested negative, in orange) (A). Selection proportion from stability analysis of the LASSO for (i) the risk of testing positive in the full population (B), and (ii) the risk of testing positive for COVID-19 conditionally on being tested (y-axis) (C) against the selection proportion for the model of the probability of being tested (x-axis). Selection proportions were inferred from 1000 models based on an 80% subsample of the population and are reported for each of the demographics (in grey, n = 4), social (brown, n = 12), health risk (red, n= 7), medical (blue, n = 8), and environmental (green, n = 4) factors

ASSOCIATION OF TROPONIN LEVELS WITH MORTALITY IN ITALIAN PATIENTS HOSPITALIZED WITH CORONAVIRUS DISEASE 2019: RESULTS OF A MULTICENTER STUDY

Lombardi CM, Carubelli V, Iorio A, Inciardi RM, Bellasi A, Canale C, Camporotondo R, Catagnano F, Dalla Vecchia LA, Giovinazzo S, Maccagni G, Mapelli M, Margonato D, Monzo L, Nuzzi V, Oriecuia C, Peveri G, Pozzi A, Provenzale G, Sarullo F, Tomasoni D, Ameri P, Gnecchi M, Leonardi S, Merlo M, Agostoni P, Carugo S, Danzi GB, Guazzi M, La Rovere MT, Mortara A, Piepoli M, Porto I, Sinagra G, Volterrani M, Specchia C, Metra M, Senni M.. JAMA Cardiol. 2020 Aug 26. doi: 10.1001/jamacardio.2020.3538. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A multicenter cross-sectional study conducted by Italian cardiologists from March 1 to April 19, 2020 found that among 614 patients (eTable 4) with confirmed COVID-19 across 13 cardiology units, 278 had elevated troponin levels, which was associated with higher in hospital mortality (37% vs 13%; HR, 1.71 [95% CI, 1.13-2.59]; P = 0.01; Figure 1). Those with elevated troponin levels were more likely to be older, have atrial fibrillation, heart failure, hypertension, and coronary artery disease (all p<0.001; Table). In the hospital, patients with elevated troponins were additionally more likely to have complications including sepsis, pulmonary embolism, delirium, heart failure, acute kidney failure, and major bleeding (all p<0.04). This study suggests that running diagnostic tests and identifying patients with elevated troponins may help earlier identify patients requiring more intensive care.

ABSTRACT

Importance: Myocardial injury, detected by elevated plasma troponin levels, has been associated with mortality in patients hospitalized with coronavirus disease 2019 (COVID-19). However, the initial data were reported from single-center or 2-center studies in Chinese populations. Compared with these patients, European and US patients are older, with more comorbidities and higher mortality rates. Objective: To evaluate the prevalence and prognostic value of myocardial injury, detected by elevated plasma troponin levels, in a large population of White Italian patients with COVID-19. Design, Setting, and Participants: This is a multicenter, cross-sectional study enrolling consecutive patients with laboratory-confirmed COVID-19 who were hospitalized in 13 Italian cardiology units from March 1 to April 9, 2020. Patients admitted for acute coronary syndrome were excluded. Elevated troponin levels were defined as values greater than the 99th percentile of normal values. Main Outcomes and Measures: Clinical characteristics and outcomes stratified as elevated or normal cardiac troponin levels at admission, defined as troponin T or troponin I at a level greater than the 99th percentile of normal values. Results: A total of 614 patients with COVID-19 were included in this study (mean age [SD], 67 [13] years; 70.8% male), of whom 148 patients (24.1%) died during the hospitalization. Elevated troponin levels were found in 278 patients (45.3%). These patients were older (mean [SD] age, 64.0 [13.6] years vs 71.3 [12.0] years; P < .001) and had higher prevalence of hypertension (168 patients [50.5%] vs 182 patients [65.9%]; P < .001), heart failure (24 [7.2%]; 63 [22.8%]; P < .001), coronary artery disease (50 [15.0%] vs 87 [31.5%]; P < .001), and atrial fibrillation (33 [9.9%] vs 67 [24.3%]; P < .001). Elevated troponin levels were associated with an increased in-hospital mortality (37% vs 13%; HR, 1.71 [95% CI, 1.13-2.59]; P = .01 via multivariable Cox regression analysis), and this was independent from concomitant cardiac disease. Elevated troponin levels were also associated with a higher risk of in-hospital complications: heart failure (44 patients [19.2%] vs 7 patients [2.9%]; P < .001), sepsis (31 [11.7%] vs 21 [6.4%]; P = .03), acute kidney failure (41 [20.8%] vs 13 [6.2%]; P < .001), multiorgan failure (21 [10.9%] vs 6 [2.9%]; P = .003), pulmonary embolism (27 [9.9%] vs 17 [5.2%]; P = .04), delirium (13 [6.8%] vs 3 [1.5%]; P = .02), and major bleeding (16 [7.0%] vs 4 [1.6%]; P = .008). Conclusions and Relevance: In this multicenter, cross-sectional study of Italian patients with COVID-19, elevated troponin was an independent variable associated with in-hospital mortality and a greater risk of cardiovascular and noncardiovascular complications during a hospitalization for COVID-19.

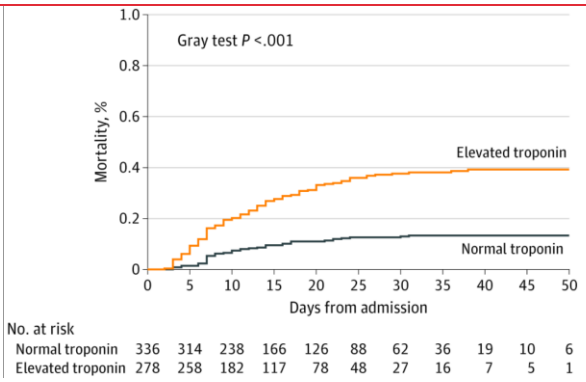

Figure 1. Cumulative Incidence of Death During Hospitalization Stratified by Baseline Troponin Level (N = 614)

Table. Demographic and Clinical Characteristics of the Study Population at Admission Stratified by Baseline Troponin Level (N = 614)

Characteristic	Troponin				
	Normal (n = 336)		Elevated (n = 278)		
	No. Assessed	No. Affected (%)	No. Assessed	No. Affected (%)	*P* value
Age, mean (SD), y	336	64.0 (13.6)	278	71.3 (12.0)	<.001
Male	336	234 (69.6)	278	201 (72.3)	.53
BMI ≥30	262	51 (19.5)	213	46 (21.6)	.65
Smoker (ever)	292	78 (26.7)	224	73 (32.6)	.18
Hypertension	333	168 (50.5)	276	182 (65.9)	<.001
Dyslipidemia	333	71 (21.3)	275	106 (38.5)	<.001
Diabetes	333	66 (19.8)	276	82 (29.7)	.006
Heart failure	333	24 (7.2)	276	63 (22.8)	<.001
Atrial fibrillation	333	33 (9.9)	276	67 (24.3)	<.001
Coronary artery disease	333	50 (15.0)	276	87 (31.5)	<.001
Prior cardiac surgery or percutaneous valve treatment	333	27 (8.1)	276	39 (14.1)	.03
Prior heart transplant/LVAD	333	0 (0.0)	276	4 (1.4)	.09
COPD	333	27 (8.1)	276	31 (11.2)	.24
Chronic kidney disease with eGFR <60 mL/min/m^2	333	34 (10.2)	276	76 (27.5)	<.001
Prior ACEi or ARB therapy	312	110 (35.3)	259	114 (44.0)	.04
Prior anticoagulant therapy	309	29 (9.4)	254	55 (21.7)	<.001
Prior statin therapy	313	68 (21.7)	258	101 (39.1)	<.001
Temperature, mean (SD), °C	332	37.3 (1.0)	269	37.2 (1.0)	.40
Temperature ≥37.5 °C	332	151 (45.5)	269	111 (41.3)	.34
Respiratory rate ≥22 breaths/min	277	141 (50.9)	176	107 (60.8)	.049
Blood pressure, mean (SD), mm Hg					
Systolic	330	129 (20)	271	129 (24)	.97
Diastolic	330	75 (12)	271	73 (15)	.06
Heart rate, mean (SD), beats/min	328	86 (16)	272	87 (20)	.60
Oxygen saturation, ambient air, median (IQR), %	329	93 (88-96)	271	92 (87-96)	.03
Pao_2/FiO_2, median (IQR), mm Hg/%	298	246 (127-319)	238	233 (120-310)	.29
Pao_2/FiO_2 <300 mm Hg/%	298	207 (69.5)	238	170 (71.4)	.69
SOFA score					
Median (IQR)	194	2 (1-3)	188	3 (2-4)	<.001
≥3	194	70 (36.1)	188	103 (54.8)	<.001
≥6	194	9 (4.6)	188	24 (12.8)	.008
COVID-19 score peak, median (IQR)	64	4.5 (1.0-10.3)	104	10.0 (3.8-14.0)	<.001
LV ejection fraction, median (IQR), %	104	58.0 (53.8-61.0)	131	55.0 (40.0-58.0)	<.001

eTable 4. Univariable and multivariable Cox regression model for death.

		Univariable		*Multivariable N=510**	
	Level/Units	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Age	+5 years	1.33 (1.24-1.44)	*<0.001*	1.29 (1.16-1.44)	*<0.001*
Sex	M vs F	1.44 (0.97-2.14)	*0.073*	1.58 (0.99-2.51)	*0.054*
Respiratory rate	≥22 vs <22	1.69 (1.12-2.55)	*0.012*		
Body mass index	+1 kg/m^2	1.01 (0.97-1.04)	*0.687*		
SBP	+10 mmHg	0.95 (0.88-1.03)	*0.186*		
Oxygen saturation	+5 %	0.83 (0.77-0.90)	*<0.001*	0.87 (0.78-0.97)	*0.013*
RBC	+0.5 x10^6/µL	0.84 (0.75-0.95)	*0.004*		
WBC	+1000 U/µL	1.03 (1.00-1.06)	*0.053*		
Lymphocytes	+100 U/µL	0.93 (0.89-0.96)	*<0.001*		
CRP	+10 mg/L	1.03 (1.01-1.04)	*<0.001*	1.03 (1.01-1.05)	*0.006*
Troponin	Elevated vs Normal	3.22 (2.26-4.59)	*<0.001*	1.71 (1.13-2.59)	*0.012*
NT-proBNP	+1000 ng/L	1.03 (1.00-1.05)	*0.026*		
LDH	+1000 mg/dL	1.11 (1.04-1.18)	*0.001*		
Bilirubin	+0.3 mg/dL	1.07 (0.96-1.19)	*0.249*		
D-dimer	+1000 ng/mL	1.02 (0.99-1.05)	*0.271*		
Creatinine	+1 mg/dL	1.12 (1.05-1.20)	*<0.001*		
eGFR (CKD-EPI)	+10 mg/L	0.83 (0.78-0.87)	*<0.001*	0.95 (0.86-1.04)	*0.263*
INR	+1	1.18 (0.98-1.41)	*0.075*		
ABG test lactate	+1 mmol/L	1.20 (1.12-1.29)	*<0.001*		
PaO_2/FiO_2	+50 mmHg/%	0.89 (0.82-0.96)	*0.003*	0.89 (0.80-0.99)	*0.030*
Interleukin-6	+10 pg/mL	1.00 (1.00-1.01)	*0.216*		
SOFA	+1 point	1.36 (1.26-1.47)	*<0.001*		
SOFA	3-4-5 vs 0-1-2	3.37 (2.00-5.68)	*<0.001*		
SOFA	≥6 vs 0-1-2	6.75 (3.65-12.48)	*<0.001*		
Heart failure	Yes vs No	2.54 (1.75-3.68)	*<0.001*	2.15 (1.28-3.63)	*0.004*
Coronary artery disease	Yes vs No	2.16 (1.54-3.04)	*<0.001*	1.12 (0.71-1.76)	*0.629*
Atrial fibrillation	Yes vs No	2.34 (1.62-3.38)	*<0.001*	1.14 (0.69-1.86)	*0.615*
Chronic obstructive pulmonary disease	Yes vs No	1.88 (1.20-2.97)	*0.006*	1.34 (0.78-2.32)	*0.286*
Diabetes	Yes vs No	1.41 (0.99-2.02)	*0.057*		
Obesity	Yes vs No	1.26 (0.85-1.85)	*0.25*		
Hypertension	Yes vs No	1.95 (1.37-2.78)	*<0.001*	1.26 (0.81-1.96)	*0.312*
Chronic kidney disease	Yes vs No	2.68 (1.90-3.79)	*<0.001*	1.03 (0.60-1.78)	*0.908*
Smoking	Ever vs Never smoker	1.33 (1.24-1.44)	*<0.001*		
Prior ACEi/ARB therapy	Yes vs No	1.62 (1.16-2.25)	*0.005*		
Prior statin therapy	Yes vs No	1.73 (1.23-2.43)	*0.002*		

*number of patients with complete data

Legend: ABG: arterial blood gas, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, , CKD-EPI: chronic kidney disease epidemiology collaboration formula, CRP: C-reactive protein, eGFR:

ANTIBODY RESPONSES AND CLINICAL OUTCOMES IN ADULTS HOSPITALIZED WITH SEVERE COVID-19: A POST HOC ANALYSIS OF LOTUS CHINA TRIAL

Ren L, Fan G, Wu W, Guo L, Wang Y, Li X, Wang C, Gu X, Li C, Wang Y, Wang G, Zhou F, Liu Z, Ge Q, Zhang Y, Li H, Zhang L, Xu J, Wang C, Wang J, Cao B.. Clin Infect Dis. 2020 Aug 25:ciaa1247. doi: 10.1093/cid/ciaa1247. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

Researchers at several institutions in Beijing and Wuhan, China collaborated on a retrospective cohort study of 191 severe COVID-19 patients from the January 2020 LOTUS China Trial, looking specifically at longitudinal IgM and IgG antibody responses to the nucleocapsid (N), spike protein (S), and receptor-binding domain (RBD) of SARS-CoV-2. There was no significant difference in antibody positive rates in survivors vs non-survivors nor 28-day clinically improved vs non-improved patients (Figure 1). IgG titers were significantly higher than IgM titers (RBD-IgG > S-IgG > N-IgG > RBD-IgM > S-IgM > N-IgM) (Figure 1). Four weeks after infection, non-survivors had lower S-IgG titers than survivors (P=0.020), and viral clearance was strongly associated with N-IgG and RBD-IgG titers (P<0.0001), suggesting the possible use of S-IgG as a predictor of adverse outcomes and the role of IgG as an important factor against SARS-CoV-2 infection.

ABSTRACT

BACKGROUND: The characteristics of neutralizing antibodies (NAbs) and antibody against major antigen proteins related to clinical outcomes in severe COVID-19 patients were still less known. METHODS: The neutralizing antibodies (NAbs) and antibodies targeting nucleocapsid (N), spike protein (S), and the receptor-binding domain (RBD) in longitudinal plasma samples from the LOTUS China trial were measured by microneutralization assay and ELISA. Viral load was determined by real-time RT-PCR. A total of 576 plasma and 576 throat swabs were collected from 191 COVID-19 patients. Antibody titers related to adverse outcome and clinical improvement were analysed. Multivariable adjusted generalized linear mixed model for random effects were developed. RESULTS: After day 28 post symptoms onset, the rate of antibody positivity reached 100% for RBD-IgM, 97.8% for S-IgM, 100% for N-IgG, 100% for RBD-IgG, 91.1% for N-IgM and 91.1% for NAbs. The NAbs titers increased over time in both survivors and non-survivors and correlated to IgG antibodies against N, S and RBD, while its presence showed no statistical correlation with death. N-IgG (slope -2.11, 95% CI -3.04 to -1.18, p&0.0001), S-IgG (slope -2.44, 95% CI -3.35 to -1.54, p&0.0001) and RBD-IgG (slope -1.43, 95% CI -1.98 to -0.88, p&0.0001) were negatively correlated with viral load. S-IgG titers were lower in non-survivors than survivors (p=0.020) at week 4 after symptoms onset. CONCLUSIONS: IgM, IgG against N, S and RBD and NAbs developed in most severe COVID-19 patients, and do not correlate clearly with clinical outcomes. The levels of IgG antibodies against N, S and RBD were related to viral clearance.

FIGURES

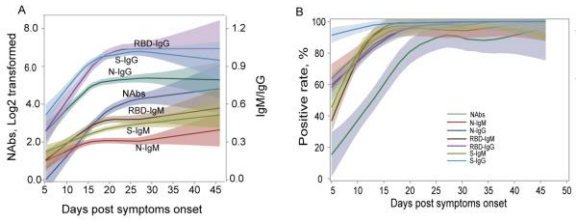

Figure 1: Temporal changes of antibody positive rates against SARS-CoV-2 and titers by locally weighted scatterplot smoothing method. Panel A. The positive rates of each antibody. The x-axis indicated the days after symptoms onset. The y-axis indicated the positive rate. Panel B. The titers of each antibody. The x-axis indicated the days after symptoms onset. The y-axis indicated the neutralizing antibody titers showed as genomic median titers (left) and immunoglobin (Ig) levels showed as mean optical density. N, nucleocapsid; S, spike; RBD, receptor-binding domain.

DIFFICULT TO DETERMINE HERD IMMUNITY THRESHOLD FOR COVID-19

Rubin R.. JAMA. 2020 Aug 25;324(8):732. doi: 10.1001/jama.2020.14778.
Level of Evidence: Other - Opinion

BLUF

A medical news reporter penned an opinion piece on the difficulty of determining the herd immunity threshold for COVID-19, stating that determining this threshold is difficult with this virus as there still are many uncertainties about it including how contagious it possibly is and the level at which people can act as vectors of disease spread. This piece suggests that even if herd immunity would be achieved, there is no guarantee for how long immunity will persist which will impact the severity of spread of COVID-19 infection.

SUMMARY

Herd immunity is achieved when 70-90% of the population is immune to an infectious disease, whether through means of natural immunity or vaccinations. To determine the threshold, that is, the percent of the population needed to be immune to induce said herd immunity is determined by many factors including: amount of infectious ability one person has to infect another, the parameters of how contagious it is, and the length of time immunity will last.

The author states that "the average number of people that a contagious person can infect range from 1 to 7. By comparison, a person with measles infects an average of 11 to 16 people."

Furthermore the author states that even if immunity were to be achieved, there is no current idea for how long immunity will be imparted. The author asserts that "analyses of other viruses related to the severe acute respiratory syndrome coronavirus 2 have shown that infection provides some immunity, but it doesn't appear to last more than a year."

CRITICAL CARE

ARGATROBAN FOR THERAPEUTIC ANTICOAGULATION FOR HEPARIN RESISTANCE ASSOCIATED WITH COVID-19 INFECTION

McGlynn F, McGrath J, Varghese C, Ryan B, McHugh J, Fahy A, Enright H.. J Thromb Thrombolysis. 2020 Aug 24. doi: 10.1007/s11239-020-02251-z. Online ahead of print.
Level of Evidence: 5 - Case-series, case-control studies, or historically controlled studies

BLUF

In this case series, physicians at Tallaght University Hospital in Ireland describe two critically ill COVID-19 patients who suffered complications from coagulopathy events without a response to conventional heparin therapy. Both patients were subsequently switched to argatroban (a factor Xa inhibitor) and had no further complications after therapeutic anti-coagulation levels were met (see summary). Authors suggest alternative anticoagulants may have a role in treating COVID-19 coagulopathy with heparin resistance.

SUMMARY

Two cases of SARS-CoV-2 positive patients are presented to highlight the potential efficacy of substituting factor Xa inhibitor over conventional heparin therapy in the setting of apparent heparin resistance:
1. A 33-year-old man with no significant past medical history was admitted to the ICU and intubated, with subsequent arterial line clotting, catheter associated venous thromboses, and segmental pulmonary embolism with pulmonary infarction. He was subsequently started on unfractionated heparin. When partial thromboplastin time (aPTT) did not become prolonged, he was switched to argatroban. He maintained adequate anti-coagulation on argatroban for nine days without further thrombotic complications and was eventually discharged.
2. A 47-year-old man was admitted to the ICU, intubated, placed on dialysis, and empirically started on intravenous heparin due to elevated d-dimer of 5.25 µg/L. He continued to have clotting of his dialysis catheter, with aPTT not responding to increased heparin dosage, and was subsequently switched to argatroban. There were no further complications, and the patient was extubated after 25 days of mechanical ventilation.
Although argatroban was successful in the two patients presented, the authors acknowledge a need for additional evidence based research for treatment of heparin resistant patients in the setting of COVID-19.

QUALITATIVE ASSESSMENT OF SARS-COV-2-SPECIFIC ANTIBODY AVIDITY BY LATERAL FLOW IMMUNOCHROMATOGRAPHIC IGG/IGM ANTIBODY ASSAY

Valdivia A, Torres I, Huntley D, Alcaraz MJ, Albert E, Colomina J, Ferrer J, CarratalÃ¡ A, Navarro D.. J Med Virol. 2020 Jul 24. doi: 10.1002/jmv.26344. Online ahead of print.
Level of Evidence: 3 - Mechanism-based reasoning

BLUF

Authors in Spain examined the avidity of antibodies to SARS-CoV-2 in 76 serum specimens from 57 COVID-19 patients using a urea dissociation test on a lateral flow immunochromatographic (LFIC) IgG/IgM device to determine whether antibody avidity corresponded with time since acquisition of the virus. They found:
- 39 samples tested positive for both IgG and IgM; 37 tested positive for IgG only (Table 2).
- IgG reactivity was lost in 28 samples after urea treatment. Serum that lost reactivity were drawn significantly sooner after onset of symptoms than serum that retained activity (p=0.04; Table 1).
- IgM reactivity was lost in 17 of the 39 samples after urea treatment, although the time since symptom onset did not differ between groups (median 24 days; range 1-45 days vs 14.5 days; range 2-48 days, respectively; p = 0.14)

This data suggests that LFIC with urea dissociation effectively measures serum antibody avidity and thus could be useful in predicting the acquisition date of SARS-CoV-2 infection.

ABSTRACT

Knowledge of the precise timing of SARS-CoV-2 infection may be of clinical and epidemiological relevance. The presence of low-avidity IgGs has conventionally been considered an indicator of recent infection. Here, we carried out qualitative assessment of SARS-CoV-2-specific antibody avidity using an urea (6M) dissociation test performed on a lateral flow immunochromatographic IgG/IgM device. We included a total of 76 serum specimens collected from 57 COVID-19 patients, of which 39 tested positive for both IgG and IgM and 37 only for IgG. Sera losing IgG reactivity after urea treatment (n=28) were drawn significantly earlier (P=0.04) after onset of symptoms than those which preserved it (n=48). This assay may be helpful to estimate the time of acquisition of infection in patients with mild to severe COVID-19. This article is protected by copyright. All rights reserved.

FIGURES

TABLE 1 Qualitative assessment of SARS-CoV-2-specific IgG antibody avidity in sera from patients with COVID-19 according to the time of specimen collection since the onset of symptoms

Time of serum collection, d	Number of sera tested/number of reactive sera after urea dissociation
1-7	5/1
8-14	20/10
15-21	10/9
22-28	19/11
>29	22/17

Abbreviations: COVID-19, corona virus 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 2 Qualitative assessment of SARS-CoV-2-specific antibody avidity in serial serum samples from patients with COVID-19

Patient	Time since symptoms onset, d	Antibody reactivity			
		IgG	IgG after urea treatment	IgM	IgM after urea treatment
1	27	+	−	−	−
	39	+	+	−	−
2	22	+	−	−	−
	34	+	−	−	−
3	25	+	−	+	−
	35	+	+	−	−
4	20	+	+	−	−
	24	+	+	−	−
5	10	+	−	+	+
	16	+	+	+	+
6	23	+	−	+	−
	24	+	−	+	−
7	30	+	+	−	−
	31	+	+	−	−
	51	+	+	−	−
	59	+	+	−	−
8	11	+	−	−	−
	23	+	+	−	−
9	30	+	+	+	−
	40	+	+	−	−
	47	+	+	−	−
10	7	+	−	+	+
	15	+	−	+	+
11	28	+	+	+	−
	40	+	+	+	−
12	21	+	−	−	−
	26	+	+	−	−
	38	+	+	−	−
13	21	+	+	+	+
	48	+	+	+	+
14	6	+	−	−	−
	14	+	−	−	−
15	14	+	+	+	−
	18	+	+	−	−

Abbreviations: COVID-19, corona virus 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

MULTIPLEXED NANOMATERIAL-BASED SENSOR ARRAY FOR DETECTION OF COVID-19 IN EXHALED BREATH

Shan B, Broza YY, Li W, Wang Y, Wu S, Liu Z, Wang J, Gui S, Wang L, Zhang Z, Liu W, Zhou S, Jin W, Zhang Q, Hu D, Lin L, Zhang Q, Li W, Wang J, Liu H, Pan Y, Haick H.. ACS Nano. 2020 Aug 18. doi: 10.1021/acsnano.0c05657. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

This observational cohort study conducted in Wuhan, China by authors affiliated with University of Science and Technology of China analyzed use of a nanomaterial-based breathalyzer system in COVID-19 pre-screening and found capturing COVID-19-specific volatile organic compound (VOC) mixtures from exhaled breath obtained signals from the nanomaterial-based sensors with adequate discriminations between COVID-19 positive and non-COVID-19 groups (see summary), suggesting that this technology may be useful as a rapid screening tool.

SUMMARY

This study included 130 participants from March 9th, 2020 to March 27th, 2020. Three binary comparisons were made: COVID-19 versus healthy control, COVID-19 versus other lung infections, and COVID-19 first sample versus COVID-19 second sample (Table 1). The groups were randomly assigned to training sets (70% of samples) and test sets (30% of samples) (Figure 2). Results are summarized below:
- On receiver operating curve, training set area under the curve (AUC) for COVID-19 versus control was 0.81 (95% CI, 0.70 to 0.89), 0.97 for COVID-19 versus other lung infections (95% CI, 0.92 to 0.99), and 0.87 for COVID-19 first sample versus COVID-19 second sample (95% CI, 0.67 to 1.00), (Figure 3)
- Accuracy values: 90%-94% for the "training set" and 76%-95% for the "test set"
- Sensitivity values: 90%-100% for the "training set" and 83%-100% for the "testing set"
- Specificity values: 69%-90% for the "training set" and 61% to 100% for the "testing set"
- Coexisting conditions, smoking status, age, and sex did not have a significant influence on outcomes

ABSTRACT

This article reports on a non-invasive approach in detecting and following-up individuals who are at-risk or have an existing COVID-19 infection, with a potential ability to serve as an epidemic control tool. The proposed method uses a developed breath device comprised of a nanomaterial-based hybrid sensors array with multiplexed detection capabilities that can detect disease-specific biomarkers from exhaled breath, thus enabling rapid and accurate diagnosis. An exploratory clinical study with this approach was examined in Wuhan, China during March 2020. The study cohort included 49 confirmed COVID-19 patients, 58 healthy controls and 33 non-COVID lung infection controls. When applicable, positive COVID-19 patients were sampled twice: during the active disease, and after recovery. Discriminant analysis of the obtained signals from the nanomaterial-based sensors achieved very good test discriminations between the different groups. The training and test set data exhibited, respectively, 94% and 76% accuracy in differentiating patients from controls as well as 90% and 95% accuracy in differentiating between patients with COVID-19 and patients with other lung infections. While further validation studies are needed, the results may serve as a base for technology that would lead to a reduction in number of unneeded confirmatory tests and lower the burden on the hospitals, while allowing individuals a screening solution that can be performed in PoC facilities. The proposed method can be considered as a platform that could be applied for any other disease infection with proper modifications to the artificial intelligence and would therefore be available to serve as a diagnostic tool in case of a new disease outbreak.

FIGURES

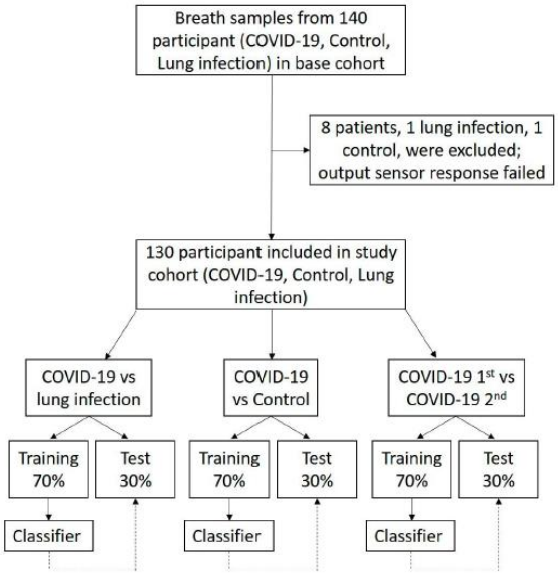

Figure 2. Patient enrollment and observational design

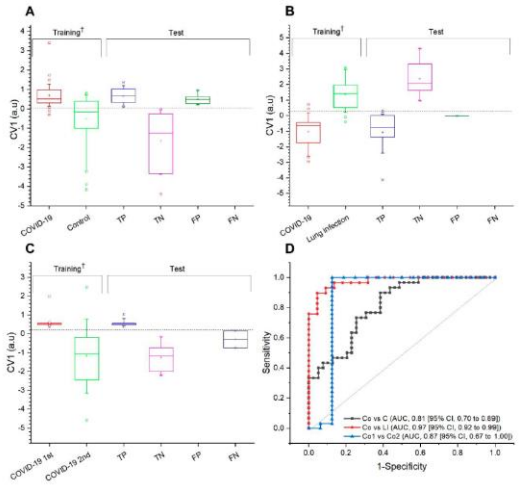

Figure 3. Diagnosis of COVID-19 patients based on cumulative breath sample response.
Panels A, B and C show data classification from cumulative sensor responses to breath samples as represented by the canonical variable of the discriminant analysis. Box plots of the first canonical score of the training-set (70% of samples) and test-set (30% of samples). The horizontal dashed line in the box plots represents the cut-off value of the model. True positive (TP), True negative (TN), False positive (FP), False negative (FN). Panel A: COVID-19 patients (n=41) and healthy controls (n=57). Panel B: COVID-19 patients (n=41) and other lung infection\condition controls (n=32). Panel C: COVID-19 patients at first (n=41) and second sampling (n=21). P-values are for the comparisons of the training-set for each of two binary classifications. The horizontal line in the boxes represents the median, the cross represents the mean, and the bottom and top of the boxes represent the 25th and 75th percentiles, respectively. Bars represent the upper 90 and lower 10 percentile, and the square-dots outliers. All P-values were adjusted for multiple comparisons using the Tukey–Kramer method. For Panel C, the P-value is also adjusted for paired analysis. Panel D shows ROC curves for the cumulative breath-sensor response in patients with COVID-19 (Co) infection compared with controls (C), (black); in COVID-19 infection compared with other lung infection\conditions (LI), (red); and in COVID-19 infection first sample (Co1) compared to COVID-19 infection second sample (Co2), (blue). †P less than 0.0001.

Statistics	Training set			Testing set‡		
	COVID-19 *vs.* Control†	COVID-19 *vs.* Lung Infection§	COVID-19 1st *vs.* COVID-19 2st,§	COVID-19 *vs.* Control	COVID-19 *vs.* Lung Infection	COVID-19 1st *vs.* COVID-19 2st
Accuracy (%)	94	90	90	76	95	88
Sensitivity (%)	100	90	100	100	100	83
Specificity (%)	90	91	69	61	90	100
PPV (%)	88	93	86	61	92	100
NPV (%)	100	87	100	100	100	71
TP (cases)	30	26	32	11	12	10
TN (cases)	35	20	11	11	9	5
FP (cases)	4	2	5	7	1	0
FN (cases)	0	3	0	0	0	2

Table 1. Breath test outcomes for the study population. † Classification based on QDA, § Classification based on LDA, ‡ Classification based on the
ROC cut-off

ANXIETY AND DEPRESSION SYMPTOMS AFTER VIROLOGICAL CLEARANCE OF COVID-19: A CROSS-SECTIONAL STUDY IN MILAN, ITALY

Tomasoni D, Bai F, Castoldi R, Barbanotti D, Falcinella C, Mulè G, Mondatore D, Tavelli A, Vegni E, Marchetti G, d'Arminio Monforte A.. J Med Virol. 2020 Aug 25. doi: 10.1002/jmv.26459. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A cross sectional study conducted by infectious disease specialists at the University of Milan in Italy found that among 105 patients (Table 1) at S. Paolo and S. Carlo Hospitals, 11 had abnormal depression items and 29 had abnormal anxiety items on the Hospital Anxiety and Depression Scale (HADS) 1-3 months after recovering from COVID-19 infection, whereas only 9 patients were being treated with anti-anxiety or antidepressant therapy prior to hospital admission. Additionally, those with abnormal HADS results were more likely (36.7% vs 10%) to have mild or worse cognitive impairment on the Mini Mental State Examination (MMSE) and were significantly more likely to have persistence of physical symptoms such as dyspnea (CI 95%: 1.56-13.05, p=0.006) than those without abnormal HADS results. This study suggests that COVID-19 patients should recover with multidisciplinary teams, as psychological distress can persist after disease recovery.

ABSTRACT

Prevalence of anxiety/depression was investigated in 105 COVID-19 patients at 1-3 months from virological clearance by Hospital Anxiety and Depression Scale (HADS-A/D). 30% of patients displayed pathological HADS-A/D, 52.4% showed persistent symptoms. Pathological HADS-A/D patients more commonly reported symptom persistence, even after adjustment for age, gender, disease severity. Psychological assessments should be encouraged in COVID-19 patients' follow-up. This article is protected by copyright. All rights reserved.

FIGURES

Table I

Demographic and clinical characteristics of the study population

Demographic parameters	Study population (N=105)	Normal HADS-A/D[a] (N=70)	Pathological HADS-A/D[a] (N=30)	*p* values
Age, years	55 (43-65)	55 (42-64)	55 (45,5-66)	0,976
Gender, males	77 (73,3%)	55 (78,6%)	19 (63,3%)	0,111
Charlson Comorbidity Score	1 (0-2,5)	1 (0-3)	1 (0-2)	0,798
In-hospital parameters				
Oxygen therapy: None, low flow oxygen therapy CPAP, NIV, OTI	 76 (72.4%) 24 (22.9%)	 52 (76,5%) 16 (23,5%)	 20 (74,1%) 7 (25,9%)	 0,806
Length of hospital days (LOS)	8 (6-11)	8 (6-12)	8 (5,75-10)	0,831
Follow-up visit				
Time since virological clearance, days	46 (43-48)	46 (43-48)	46 (44-49)	0,317
Symptoms at follow-up visit:				
Symptoms' persistence[b]	55 (52,4%)	30 (42,9%)	23 (76,7%)	**0,002**

Table I. Demographic and clinical characteristics of the study population

LEGEND. Quantitative variables are presented as median, (Interquartile Range); categorical variables are presented as absolute numbers, (percentages). Abbreviations: CPAP, Continuous Positive Airway Pressure; OTI, orotracheal intubation; NIV,

non-invasive ventilation. aHADS-(A) and in the scale for depression (D) was considered altered (borderline/pathological). b. Symptoms' persistence: persistence of at least one symptom among those investigated including fever, gastro-intestinal symptoms, at rest and exertional dyspnea, asthenia, anosmia/dysgeusia, pain, cognitive deficits defined as memory disorders, other. c. Other symptoms included: chest pain, headache, constipation, tinnitus, insomnia, palpitations, NSTEMI, cough, sore throat. dMMSE, Mini Mental State Examination (adjusted for age and education years).

Anosmia:				
No, ever	44 (41,9%)	30 (42,9%)	13 (43,3%)	
Ongoing	**6 (5,7%)**	4 (5,7%)	2 (6,7%)	0,826
Resolved	51 (48,6%)	34 (48,6%)	15 (50%)	
Unknown	4 (3,8%)	2 (2,9%)	0	
Dysgeusia:				
No, ever	39 (37,1%)	25 (35,7%)	13 (43,3%)	
Ongoing	**6 (5,7%)**	4 (5,7%)	1 (3,3%)	0,697
Resolved	57 (54,3%)	39 (55,7%)	16 (53,3%)	
Unknown	3 (2,9%)	2 (2,9%)	0	
Gastro-intestinal symptoms:				
No, ever	62 (59%)	49 (70%)	13 (43,3%)	
Ongoing	**1 (1%)**	0	1 (3,3%)	**0,02**
Resolved	37 (35,2%)	21 (30%)	16 (53,3%)	
Unknown	5 (4,8%)	0	0	
Fever:				
No, ever	8 (7,6%)	7 (10%)	1 (3,3%)	
Ongoing	**0**	0	0	0,26
Resolved	92 (87,6%)	63 (90%)	29 (96,7%)	
Unknown	5 (4,8%)	0	0	
Burning pain:				
No, ever	69 (65,7%)	52 (74,3%)	17 (56,7%)	
Ongoing	**11 (10,5%)**	5 (7,1%)	6 (20%)	0,091
Resolved	19 (18,1%)	13 (18,6%)	6 (20%)	
Unknown	6 (5,7%)	0	1 (3,3%)	

Table I. Continued.

Dyspnea:				
No, ever	30 (28,6%)	19 (27,1%)	6 (20%)	
Ongoing	**7 (6,7%)**	13 (18,6%)	14 (46,7%)	**0,034**
Resolved	62 (59%)	37 (52,9%)	10 (33,3%)	
Unknown	6 (5,7%)	1 (1,4%)	0	
Asthenia:				
No, ever	29 (27,6%)	24 (34,3%)	5 (16,7%)	
Ongoing	**33 (31,4%)**	18 (25,7%)	15 (50%)	**0,044**
Resolved	38 (36,2%)	28 (40%)	10 (33,3%)	
Unknown	5 (4,8%)	0	0	
Cognitive deficits (memory disorder):				
No, ever	75 (71,4%)	60 (87,5%)	15 (50%)	
Ongoing	**18 (17,1%)**	7 (10%)	11 (36,7%)	**0,002**
Resolved	4 (3,8%)	2 (2,9%)	2 (6,7%)	
Unknown	8 (7,6%)	1 (1,4%)	2 (6,7%)	
Other[c]:				
No, ever	34 (32,4%)	56 (80%)	19 (63,3%)	0,122
Ongoing	18 (17,1%)	9 (12,9%)	9 (30%)	
Resolved	7 (6,7%)	5 (7,1%)	2 (6,7%)	
MMSE[d] (N=25):				
Normal (26-30)	11/25 (44%)	7/16 (43,8%)	4/9 (44,4%)	
Mild cognitive deficits (18-25)	9/25 (36%)	6/16 (37,5%)	3/9 (33,3%)	0,818
Pathological (<18)	1/25 (4%)	1/16 (6,3%)	0	
Unknown	4/25 (16%)	2/16 (12,5%)	2/9 (22,2%)	

Table I. Continued.

ACKNOWLEDGEMENTS

CONTRIBUTORS

Alisa Malyavko
Ashley Kern
Brad Mott
Julia Ghering
Sara Rutz
Shayan Ebrahimian
Tasha Ramparas
Veronica Graham

EDITORS

Alvin Rafou
Julie Tran
Maggie Donovan
Michelle Arnold
Nour Bundogji

SENIOR EDITORS

Allison Hansen
Ann Staudinger Knoll
Avery Forrow
Cameron Richards

CHIEF EDITOR

Brennan Enright

ADVISOR

Will Smith