The Daily COVID-19 Literature Surveillance Summary

December 29, 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

Understanding the Pathology

- SARS-CoV-2 Infection likely triggers an autoimmune response. A case control study from Northern Italy found elevated inflammatory markers and autoantibodies (ANA, ASCA, IgG and anti-Cardiolipin) in 40 hospitalized COVID-19 patients compared to healthy controls. These results add to the growing body of evidence suggesting the association of COVID-19 with autoimmune disease and inflammatory dysfunction. The authors suggest utilizing these antibodies as prognostic indicators, especially when considering treatment with plasma therapy.

Management

- Is there an effect of artificial liver blood purification treatment on the survival of critically ill COVID-19 patients? A prospective study by multiple infectious disease centers in China to investigated the efficacy of liver blood purification treatment on the survival of severe/critical COVID-19 patients with serum inflammatory factors greater than or equal to five times the upper limit. A total of 101 critical COVID-19 patients were enrolled in the study and divided into either the treatment group or the control group. The authors demonstrated that artificial liver therapy clears inflammatory mediators through blocking the cytokine storm thus preventing theses cases from worsening any further and improving the survival rate.

Mental Health & Resilience Needs

- Mental health continues to take a toll approximately 35 days after hospitalization for COVID-19 infection. Investigators from Hackensack Meridian School of Medicine and Hospital in New Jersey conducted a single center prospective cohort study of 183 COVID-19 patients admitted to Hackensack Meridian Hospital in order to identify persistent physical symptoms, psychological health, social relationships, and activities of daily living all pertaining to their self-reported quality of life 35 ± 5 days after hospital discharge. The results revealed 16.9% of participants reported their mental health as poor or fair, impairing their daily living, physical and mental health, and quality of life, suggesting the importance of early intervention for both physical and mental symptoms, along with social support, as an essential part of full recovery from COVID-19.

TABLE OF CONTENTS

DISCLAIMER **2**

NOW LIVE! 2

LEVEL OF EVIDENCE **3**

EXECUTIVE SUMMARY **4**

TABLE OF CONTENTS **5**

CLIMATE **6**

COVID-19 vaccine trial ethics once we have efficacious vaccines 6

EPIDEMIOLOGY **7**

MODELING 7

Genomic epidemiology of superspreading events in Austria reveals mutational dynamics and transmission properties of SARS-CoV-2 7

SYMPTOMS AND CLINICAL PRESENTATION 9

Adults *9*

A 61-Year-Old Man with SARS-CoV-2 Infection and Venous Thrombosis Presenting with Painful Swelling and Gangrene of the Lower Limb Consistent with Phlegmasia Cerulea Dolens 9

UNDERSTANDING THE PATHOLOGY **11**

SARS-CoV-2 Infection as a trigger of autoimmune response 11

IN VITRO 12

Defining the features and duration of antibody responses to SARS-CoV-2 infection associated with disease severity and outcome 12

MANAGEMENT **16**

The Advisory Committee on Immunization Practices' Interim Recommendation for Allocating Initial Supplies of COVID-19 Vaccine - United States, 2020 16

ACUTE CARE 16

Critical Care *16*

Effect of Artificial Liver Blood Purification Treatment on the Survival of Critical Ill COVID-19 Patients 16

Noninvasive Mechanical ventilation in COVID-19 era: Proposal for a continuous positive airway pressure closed-loop circuit minimizing air contamination, oxygen consumption and noise 18

R&D: DIAGNOSIS & TREATMENTS **20**

DEVELOPMENTS IN TREATMENTS 20

Oxford-AstraZeneca COVID-19 vaccine efficacy 20

Endothelial pulsatile shear stress is a backstop for COVID-19 20

MENTAL HEALTH & RESILIENCE NEEDS **22**

Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection 22

COVID-19'S IMPACT ON HEALTHCARE WORKFORCE 24

Burnout, depersonalization, and anxiety contribute to post-traumatic stress in frontline health workers at COVID-19 patient care, a follow-up study 24

ACKNOWLEDGEMENTS **26**

CLIMATE

COVID-19 VACCINE TRIAL ETHICS ONCE WE HAVE EFFICACIOUS VACCINES

Wendler D, Ochoa J, Millum J, Grady C, Taylor HA.. Science. 2020 Dec 11;370(6522):1277-1279. doi: 10.1126/science.abf5084. Epub 2020 Dec 3.
Level of Evidence: 5 - Expert Opinion

BLUF

Bioethicists from the National Institute of Health discuss the ethical dilemmas of continuing clinical trials for novel vaccines now that we have efficacious vaccines (Pfizer and Moderna) that are approved and widely available. The authors discuss the important balance between the theoretical risk to the placebo groups of new trials vs the social value of competition and possibly discovering a superior vaccine candidate. Ultimately, they conclude that it is ethical to continue current and future trials as long as participants are properly informed and consented of the potential risks and benefits. They also comment on the need for more cost-effective vaccine options, especially for less developed countries, citing Pfizer's complicated storage and distribution process.

ABSTRACT

Some placebo-controlled trials can continue ethically after a candidate vaccine is found to be safe and efficacious.

EPIDEMIOLOGY

MODELING

GENOMIC EPIDEMIOLOGY OF SUPERSPREADING EVENTS IN AUSTRIA REVEALS MUTATIONAL DYNAMICS AND TRANSMISSION PROPERTIES OF SARS-COV-2

Popa A, Genger JW, Nicholson MD, Penz T, Schmid D, Aberle SW, Agerer B, Lercher A, Endler L, Colaço H, Smyth M, Schuster M, Grau ML, Martínez-Jiménez F, Pich O, Borena W, Pawelka E, Keszei Z, Senekowitsch M, Laine J, Aberle JH, Redlberger-Fritz M, Karolyi M, Zoufaly A, Maritschnik S, Borkovec M, Hufnagl P, Nairz M, Weiss G, Wolfinger MT, von Laer D, Superti-Furga G, Lopez-Bigas N, Puchhammer-Stöckl E, Allerberger F, Michor F, Bock C, Bergthaler A.. Sci Transl Med. 2020 Dec 9;12(573):eabe2555. doi: 10.1126/scitranslmed.abe2555. Epub 2020 Nov 23.
Level of Evidence: 3 - Local and current random sample surveys (or censuses)

BLUF

Researchers in Austria, Massachusetts, and Spain performed a national-scale analysis of SARS-CoV-2 superspreading using deep whole-genome sequencing of more than 500 virus samples from Austria to quantify SARS-CoV-2 mutations. They found that mutations spread via clusters throughout the world (Figure 1), and the number of virus particles to begin infection and reproduce were ~1000 particles, illustrating that protective measures like social distancing, mask-wearing, and avoiding large gatherings are effective despite being unable to prevent the spread of all viral particles.

ABSTRACT

Superspreading events shaped the Coronavirus Disease 2019 (COVID-19) pandemic, and their rapid identification and containment are essential for disease control. Here we provide a national-scale analysis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) superspreading during the first wave of infections in Austria, a country that played a major role in initial virus transmissions in Europe. Capitalizing on Austria's well-developed epidemiological surveillance system, we identified major SARS-CoV-2 clusters during the first wave of infections and performed deep whole-genome sequencing of more than 500 virus samples. Phylogenetic-epidemiological analysis enabled the reconstruction of superspreading events and charts a map of tourism-related viral spread originating from Austria in spring 2020. Moreover, we exploited epidemiologically well-defined clusters to quantify SARS-CoV-2 mutational dynamics, including the observation of a low-frequency mutation that progressed to fixation within the infection chain. Time-resolved virus sequencing unveiled viral mutation dynamics within individuals with COVID-19, and epidemiologically validated infector-infectee pairs enabled us to determine an average transmission bottleneck size of 103 SARS-CoV-2 particles. In conclusion, this study illustrates the power of combining epidemiological analysis with deep viral genome sequencing to unravel the spread of SARS-CoV-2, and to gain fundamental insights into mutational dynamics and transmission properties.

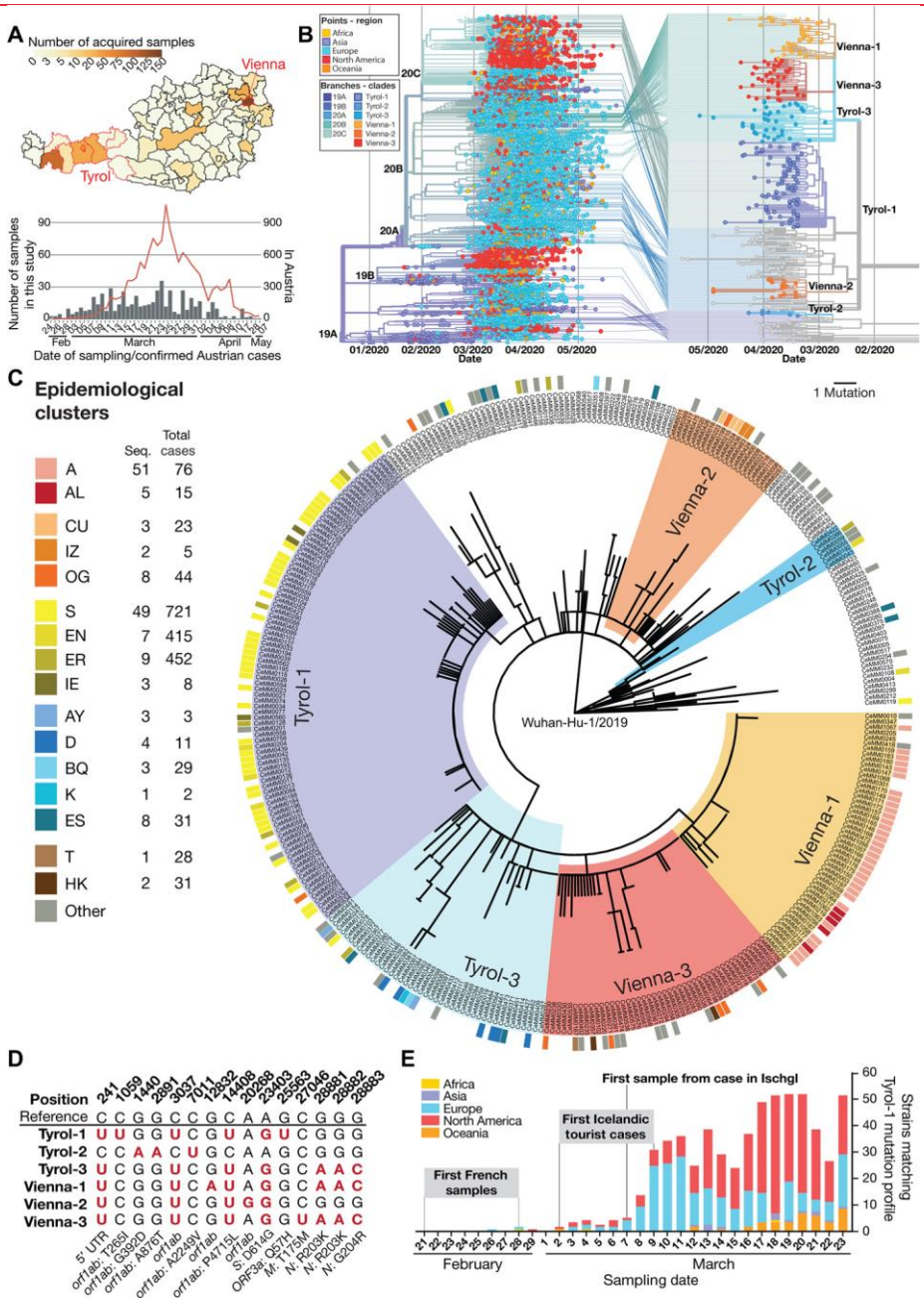


Figure 1. Phylogenetic-epidemiological reconstruction of SARS-CoV-2 infection clusters in Austria. (A) Number of acquired samples per district in Austria (top) and sampling dates of samples that underwent viral genome sequencing in this study (bottom), plotted in the context of all confirmed cases (red line) in Austria. (B) Connection of Austrian strains to global clades of SARS-CoV-2. Points indicate the regional origin of a strain in the time-resolved phylogenetic tree from 7666 randomly subsampled sequences obtained from GISAID including 345 Austrian strains sequenced in this study (left). Lines from global phylogenetic tree (left) to phylogenetic tree of all Austrian strains obtained in this study (right) indicate the phylogenetic relation and Nextstrain clade assignment of Austrian strains. Color schemes of branches represent Nextstrain clade assignment (left) or phylogenetic clusters of Austrian strains (right). (C) Phylogenetic tree of SARS-CoV-2 strains from Austrian patients with COVID-19 sequenced in this study. Phylogenetic clusters were identified on the basis of characteristic mutation profiles in viral genome sequences of SARS-CoV-2–positive cases in Austria. Cluster names indicate the most abundant location of patients based on epidemiological data. The circular color code indicates the epidemiological cluster assigned to patients based on contact tracing. (D) Mutation profiles of phylogenetic clusters identified in this study. Positions with characteristic mutations compared to reference sequence "Wuhan-Hu-1" (GenBank: MN908947.3) are highlighted in red. Details regarding the affected genes or genomic regions and the respective codon and amino acid change are given below the table. (E) Timeline of the emergence of strains matching the mutation profile of the Tyrol-1 cluster in the global phylogenetic analysis by geographical distribution with additional information from European phylogenetic reconstruction.

ADULTS

A 61-YEAR-OLD MAN WITH SARS-COV-2 INFECTION AND VENOUS THROMBOSIS PRESENTING WITH PAINFUL SWELLING AND GANGRENE OF THE LOWER LIMB CONSISTENT WITH PHLEGMASIA CERULEA DOLENS

Bamgboje A, Hong J, Mushiyev S, Pekler G.. Am J Case Rep. 2020 Dec 16;21:e928342. doi: 10.12659/AJCR.928342.
Level of Evidence: 5 - Case Report

BLUF

A case report by New York physicians describes a 61-year-old male with COVID-19 who was diagnosed with phlegmasia cerulean dolens (literally "painful blue inflammation"), which is a gangrenous foot ulcer that results from extensive deep vein thrombotic (DVT) occlusion of the lower extremities. A venous doppler ultrasound revealed evidence of acute, bilateral DVTs (Figure 2), and lab results demonstrated coagulopathy and elevated inflammatory markers (Table 1). While this patient was effectively managed with supportive care, anticoagulation, and antibiotics, this rare condition highlights the severity of COVID-19 coagulopathy.

ABSTRACT

BACKGROUND Coronavirus disease 2019 (COVID-19) is a novel infectious disease with an evolving understanding of its clinical manifestations, complications, and therapeutic implications. Thromboembolic disease and coagulopathy are common and have been seen in COVID-19 patients. Phlegmasia cerulea dolens had been reported in previous cases associated with malignancy which is a known cause of a procoagulable state. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may also induce a procoagulable state and be associated with PCD. CASE REPORT A 61-year-old man presented with a painful, swollen limb and gangrene, findings consistent with a diagnosis of PCD due to venous thrombosis. The patient tested positive for SARS-CoV-2 infection after a nasopharyngeal swab sample using the XPRSARS-COV2-10 reverse transcription polymerase chain reaction kit. He had bilateral leg swelling with a gangrenous left fourth digit in the presence of a palpable peripheral pulse. His venous duplex showed bilateral acute deep venous thrombosis, whereas his arterial Doppler scan was normal and his skin biopsy was negative for vasculitis. One of our screening blood tests was suggestive of an antiphospholipid-like syndrome. These clinical and radiologic findings were consistent with PCD. This patient was promptly anticoagulated; other supportive treatments were also initiated. He had a significant resolution of his pedal swelling with the associated revitalization of his previously gangrenous toe. CONCLUSIONS This case report shows the importance of testing for SARS-CoV-2 infection in patients who present with unusual thrombotic symptoms and signs and highlights the potential severity of these thrombotic complications.

FIGURES

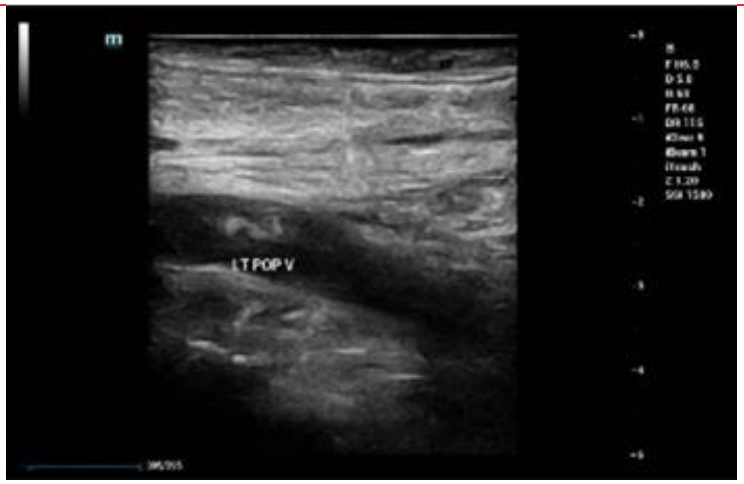


Figure 2. Longitudinal venous duplex during acute phase showing thrombus in the left popliteal vein.

Markers of coagulopathy	Result
D-Dimer	3,612 ng/dL (0–230 ng/dl) high
Cardiolipin antibodies	Positive
Cardiolipin immunoglobulin (Ig)G	60.5 GPL (0.0–12.5) GPL high
Cardiolipin IgM	44.5 MPL (0.0–12.5 MPL) high
Cardiolipin IgA	8.8 APL (0.0–12.5 APL) normal
Beta-2 glycoprotein	Positive
Beta-2 glycoprotein IgM	61.9 SMU (≤20.0 SMU) high
Beta-2 glycoprotein IgG and IgA	5 SGU and 5.9 SAU respectively (normal)
Homocysteine	6.8 µmol/l (≤15.0 µmol/L) normal
Factor V Leiden mutation	Negative
Prothrombin mutation analysis	Negative for prothrombin G20210A mutation
International normalized ratio	1.1
Activated partial thromboplastin time	31.6 (25.1–36.5) normal
Fibrinogen	283 (200–393 mg/dL) normal
Markers of infection/inflammation	**Result**
Procalcitonin	0.28 ng/mL (0.02–0.08 ng/mL) high
C-reactive protein	6.11 mg/dL (0.00–0.40 mg/dL) high
Ferritin	444 ng/mL (30–400 ng/mL) high
Blood culture	Negative
Blood biochemistry	**Result**
Creatinine	1.4 mg/dL (0.7–1.2mg/dl) high
Blood urea nitrogen	35 mg/dL (6.0–20.0 mg/dl) high
Lactic acid	3.1 mmol/L (0.5–2.0 mmol/L) high
Probrain natriuretic peptide	1,716 pg/mL (1.0–125.0 pg/mL) high
Arterial blood gas	pH 7.30 low
Lactase dehydrogenase	758 U/L (135–225 U/L) high
Albumin	3.5 mg/dL (3.5–5.2 mg/dL) normal
Total protein	8.0 g/dL (6.6–8.7 g/dL) normal
Alkaline phosphatase	352 U/L (40–129 U/L) high
Aspartate transaminase	74 U/L (0–40 U/L) high
Alanine transaminase	61 U/L (0–41 U/L) high
Total bilirubin	1.3 mg/dL (0.0–1.2 mg/dL) high
Blood count	**Result**
White blood cell count	19,530 cell/mm³ (4.30–11.00 cell/mm³)
Hemoglobin	11.1 g/dL (14.0–18.0 g/dL)
Platelet	148×10³/µL (150–450×10³/µL)

Table 1. Blood results.

SARS-COV-2 INFECTION AS A TRIGGER OF AUTOIMMUNE RESPONSE

Sacchi MC, Tamiazzo S, Stobbione P, Agatea L, De Gaspari P, Stecca A, Lauritano EC, Roveta A, Tozzoli R, Guaschino R, Bonometti R.. Clin Transl Sci. 2020 Dec 11. doi: 10.1111/cts.12953. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A case control study from Northern Italy found elevated inflammatory markers and autoantibodies (ANA, ASCA, IgG and anti-Cardiolipin) in 40 hospitalized COVID-19 patients (N=40) compared to healthy controls (Table 1). These results add to the growing body of evidence suggesting the association of COVID-19 with autoimmune disease and inflammatory dysfunction (Table 2; Table 3). The authors suggest utilizing these antibodies as prognostic indicators, especially when considering treatment with plasma therapy.

ABSTRACT

Nowadays, few evidences have shown the possible involvement of autoimmunity in patients affected by Coronavirus disease 2019 (COVID-19). In this study, we elucidate whether severe acute respiratory syndrome (SARS-CoV-2) stimulates autoantibody production and contributes to autoimmunity activation. We enrolled 40 adult patients (66.8 years mean age) admitted to Alessandria hospital between March and April 2020. All the patients had a confirmed COVID-19 diagnosis and no previously clinical record of autoimmune disease. 40 blood donors were analyzed for the same markers and considered as healthy controls. Our patients had high levels of common inflammatory markers, such as C Reactive Protein, Lactate Dehydrogenase, ferritin and creatinine. Interleukin-6 concentrations were also increased, supporting the major role of this interleukin during COVID-19 infection. Lymphocytes number were generally lower compared to healthy individuals. All the patients were also screened for the most common autoantibodies. We found a significant prevalence of ANA, ANCA and ASCA IgA antibodies. We observed that patients having a de novo autoimmune response had the worst acute viral disease prognosis and outcome. Our results sustain the hypothesis that COVID-19 infection correlates with the autoimmunity markers. Our study might help clinicians to: a) better understand the heterogeneity of this pathology and b) correctly evaluate COVID-19 clinical manifestations. Our data explained why drugs used to treat autoimmune diseases may also be useful for SARS-CoV-2 infection. In addition, we highly recommend checking COVID-19 patients for autoimmunity markers, mainly when deciding on whether to treat them with plasma transfer therapy.

FIGURES

Inflammatory markers	Reference range	All paents	<60ys	≥60 ys
LDH	230-500 U/L	30/40 (75%)	64.28%	80.77%
Ferritin	10-291ng/ml	32/40 (80%)	7.86%	80.77%
Lymphocytes number	0.9-5,2 x1000/mcl	23/40 (57.50%)	35.71%	73.08%
Creatinin	0.4-1 mg/dl	16/40 (40%)	7.14%	57.69%
PCR	0-0.8 mg/dl	37/40 (92.50%)	8.57%	96.15%
C3	82-160 mg/dl	12/40 (30%)	42.86%	23.07%
C4	12-36 mg/dl	21/40 (52.50%)	50%	53.85%
IL-6	0-5.9 mg/dl	34/40 (85%)	71.43%	92.31%

Table1: COVID-19 patients with the classical inflammatory markers out of range. The table summarizes the common diagnostic inflammatory markers analyzed in all 40 COVID-19 patients (Lactate dehydrogenase (LDH), ferritin, lymphocytes number, creatinine, C-reactive protein (PCR), complement 3 (C3), complement 4 (C4), interleuchin6 (IL6)). The patients were clustered based on the age of 60. The analytes were evaluated in COVID-19 patients under 60 years (<60ys) and having an age of 60 or above (≥60ys). The specific reference range value of each analyte is indicated in the first column. Both in all patients and in the patients clustered by age we reported how many patients had values out of the reference range and their relative percentage.

Inflammatory markers	Nomal range	All paents	<60ys	≥ 60ys	p value
LDH	230-500 U/L	690.03±259.18	645.36±202.72	715.58±284.31	0.31 (T-test)
Ferriti	10-291ng/ml	1005.29±892.40	889.90±591.65	1099.61±1011.24	0.26 (T-test)
Lymphocytes number	0.9-5.2 x1000/mcl	3.80±13.80	1.00±0.43	5.31±17.17	0.67 (M-W)
Creatiin	0.4-1 mg/dl	1.13±0.76	0.77±0.15	1.32±0.89	0.69 (M-W)
PCR	0-0.8 mg/dl	10.33±12.78	7.59±10.87	9.21±6.52	0.21 (T-test)
C 3	82-160 mg/dl	145.38±36.45	158.07±31.86	138.23±37.75	**0.02 (T-test)***
C4	12-36 mg/dl	37.35±13.37	37.35±13.79	37.42±13.22	0.40 (T-test)
IL-6	0-5.9 mg/dl	58.59±102.92	11.99±11.01	85.23±123.29	**0.02 (M-W)***

Table 2: List of the inflammatory markers analyzed in the 40 COVID-19 patients. Value of common diagnostic inflammatory markers in all the COVID-19 patients and in the patients clustered by age 60 are summarized in the table. The specific normal range value of each analyte is indicated in the first column. All the values are expressed as mean ± standard deviation. These two subgroups were compared using statistical analysis. When the population had normal distribution (asymmetry between -2 and +2) T-student test was considered (T-test). Mann Whitney (M-W) test was run in the other cases. C3 and IL6 showed statistical significance between the two groups considered. * = statistical significative. (LDH, lactate dehydrogenasi; PCR, C-reactive protein; C3, complement 3; C4, complement 4; IL-6, interleukin6).

Autoanbodies	All Paents (40)		Healthy Subjects (40)		Chi Square (with Yates Correc-on)
	pos	neg	pos	neg	p value
ANA	23 (57.50%)	17 (42.50%)	05 (12.50%)	35(87.50%)	0.0001*
Anti Cardiolipin	05 (12.50%)	35 (87.50%)	05 (12.50%)	35 (87.50%)	0.7353
Anti β2-Glycoprotein	02 (5%)	38 (95%)	01 (2.50%)	39 (97.50%)	1.0000
ENA	01 (2.5%)	39 (97.50%)	00 (0%)	40 (100%)	nv
Anti-PR3	01 (2.5%)	39 (97.50%)	00 (0%)	40 (100%)	nv
Anti-MPO	00 (0%)	40 (100%)	00 (0%)	40 (100%)	nv
ANCA	10 (25%)	30 (75%)	01 (2.50%)	39 (97.50%)	0.0094*
ASCA IgA	10 (25%)	30 (75%)	01 (2.50%)	39 (97.50%)	0.0094*
ASCA IgG	07 (17.5%)	33 (82.50%)	01 (2.50%)	39 (97.40%)	0.0624

Table 3: List of the autoantibodies detected in COVID-19 patients and healthy individual. The table summarizes the number of patients and healthy subjects showing the presence of the most common autoantibodies: anti ANA (antinuclear antibody), anti-Cardiolipin, a□□□□□□-Glycoprotein, anti-ENA (ex-tractable nuclear antigens), anti-PR3 (proteinase 3), anti-MPO (myeloperoxidase), ANCA (anti-neutrophil cytoplasmic antibodies), ASCA (anti-Saccharomyces cerevisiae antibodies) IgA and IgG. The results are expressed as positivity (pos) or negativity (neg) of a patient for an autoantibody, based on the presence and absence of the autoantibody analyzed. The COVID-19 patients and healthy subjects were compared using chi-square statistical analysis with Yates correction. The pres-ence of ANA and ASCA IgA between the two groups considered, was statistically significant. (* = sta-tistical significative; nv = not valuable; p-value <0.01).

IN VITRO

DEFINING THE FEATURES AND DURATION OF ANTIBODY RESPONSES TO SARS-COV-2 INFECTION ASSOCIATED WITH DISEASE SEVERITY AND OUTCOME

Röltgen K, Powell AE, Wirz OF, Stevens BA, Hogan CA, Najeeb J, Hunter M, Wang H, Sahoo MK, Huang C, Yamamoto F, Manohar M, Manalac J, Otrelo-Cardoso AR, Pham TD, Rustagi A, Rogers AJ, Shah NH, Blish CA, Cochran JR, Jardetzky TS, Zehnder JL, Wang TT, Narasimhan B, Gombar S, Tibshirani R, Nadeau KC, Kim PS, Pinsky BA, Boyd SD.. Sci Immunol. 2020 Dec 7;5(54):eabe0240. doi: 10.1126/sciimmunol.abe0240.

Level of Evidence: 3 - Local non-random sample

BLUF

A team of pathologists and biochemists from Stanford University conducted a longitudinal serological analysis of 79 inpatients and 175 outpatients with COVID-19. They found patients with milder infection (outpatients, non-intensive care) had higher ratios of IgG targeting S1 or RBD proteins (Figure 2, 3). While viral RNA loads decreased rapidly after appearance of antibodies (Spearman's correlation coefficients of -0.47 for IgM, -0.43 for IgG, and -0.44 for IgA, $p<0.001$), antibody responses did not predict outcomes in inpatients. SARS-CoV-2 specific antibodies in outpatients progressively declined after the first month of infection (Figure 4). Authors suggest serological responses do not predict COVID-19 outcomes, and that their study begins to clarify characteristics of the humoral response important to understanding long-term effectiveness of vaccinations and encourage further studies on B and T memory cells to better inform vaccination strategies.

ABSTRACT

SARS-CoV-2-specific antibodies, particularly those preventing viral spike receptor binding domain (RBD) interaction with host angiotensin-converting enzyme 2 (ACE2) receptor, can neutralize the virus. It is, however, unknown which features of the serological response may affect clinical outcomes of COVID-19 patients. We analyzed 983 longitudinal plasma samples from 79 hospitalized COVID-19 patients and 175 SARS-CoV-2-infected outpatients and asymptomatic individuals. Within this cohort, 25 patients died of their illness. Higher ratios of IgG antibodies targeting S1 or RBD domains of spike compared to nucleocapsid antigen were seen in outpatients who had mild illness versus severely ill patients. Plasma antibody increases correlated with decreases in viral RNAemia, but antibody responses in acute illness were insufficient to predict inpatient outcomes. Pseudovirus neutralization assays and a scalable ELISA measuring antibodies blocking RBD-ACE2 interaction were well correlated with patient IgG titers to RBD. Outpatient and asymptomatic individuals' SARS-CoV-2 antibodies, including IgG, progressively decreased during observation up to five months post-infection.

FIGURES

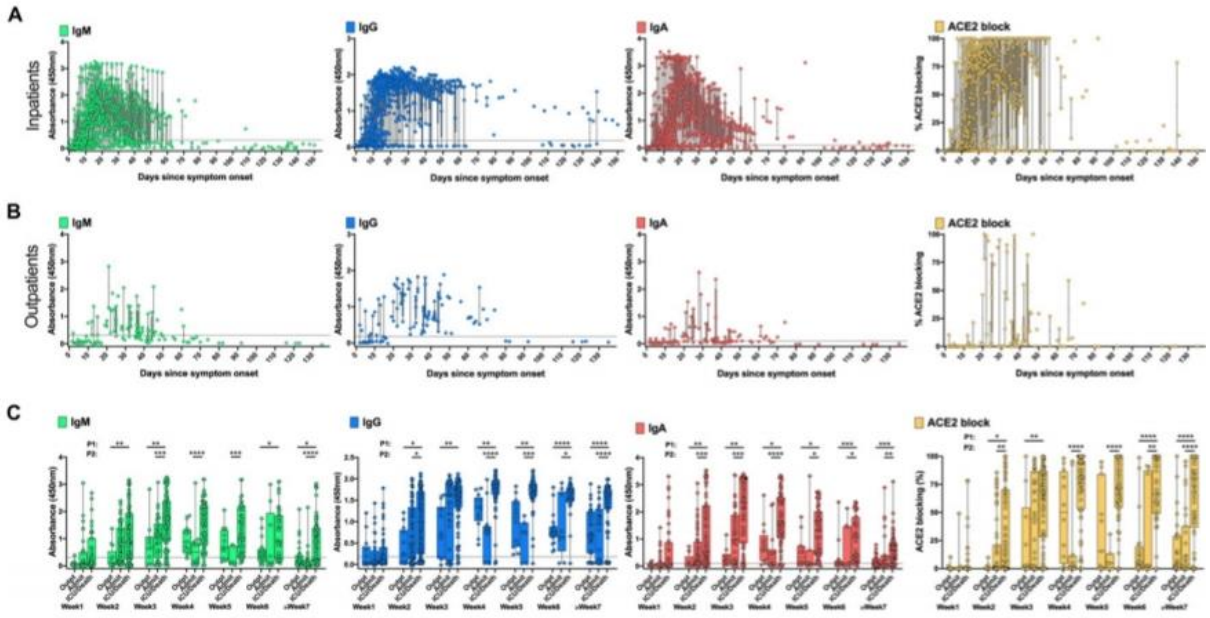


Figure 2: "Development of anti-SARS-CoV-2 RBD antibody responses in COVID-19 patients. 828 longitudinal plasma samples collected from 80 COVID-19 inpatients and deceased individuals (714 samples) (A) and 86 outpatients (114 samples) (B) were tested by ELISA at a dilution of 1:100 for the presence of SARS-CoV-2 RBDspecific IgM, IgG, and IgA antibodies and for antibodies blocking binding of ACE2 to RBD. ELISA data stratified by the 86 outpatients (Outpt), 35 hospitalized patients who did not require ICU care (Admit), and the 20 ICU patients and 25 patients who died, from week 1 to ≥ 7 weeks post-onset of symptoms (C). Boxes indicate the interquartile range and whiskers show the minimum and maximum values for each group. Dotted lines denote the assay cutoff. Mean values for duplicate measurements are shown. Statistical testing comparisons are P1 = Outpt vs Admit/ICU/Deceased, P2 = Admit vs ICU/Deceased, by two-sided Wilcoxon rank sum test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. Data for 14 samples from 2 patients (one admitted non-ICU and one deceased patient) are not plotted because the time of symptom onset was unknown. Mean ELISA OD450 values of duplicate measurements are shown for each sample".

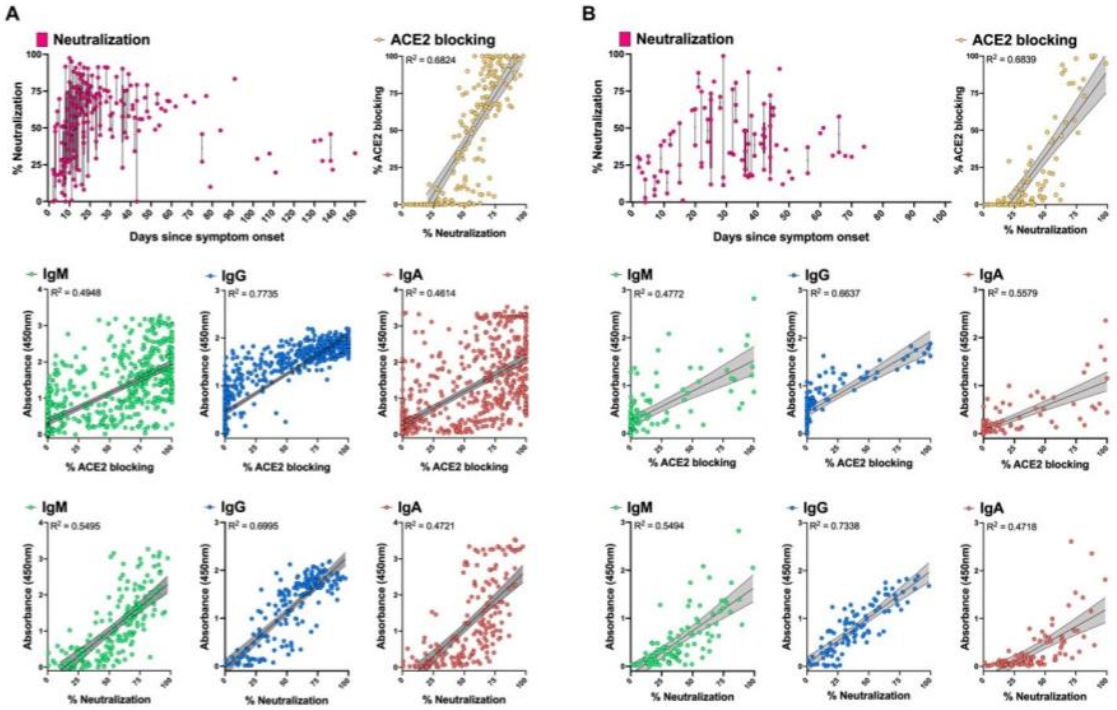


Figure 3: " Correlation of spike-pseudotyped viral neutralization, RBD-ACE2 blocking and RBD-specific serology results. Plasma samples from inpatients (n = 188) (A) and outpatients (n = 96) (B) collected at different time points post-onset of symptoms were tested at a dilution of 1:1250 for their pseudovirus neutralization activity. Correlations with RBD IgM, IgG, IgA (1:100 diluted plasma samples), and RBD-ACE2 blocking ELISA (1:10 diluted plasma samples) data were assessed with simple linear regression and 95% confidence bands (grey shading) of the best-fit line. Correlations between RBD IgM, IgG, and IgA data and RBD-ACE2 blocking ELISA results were done on the full sample set from inpatients (n = 714) and outpatients (n = 114). Plots show mean ELISA OD450 values of duplicate measurements and average percent neutralization from duplicate testing in each of two replicate experiments".

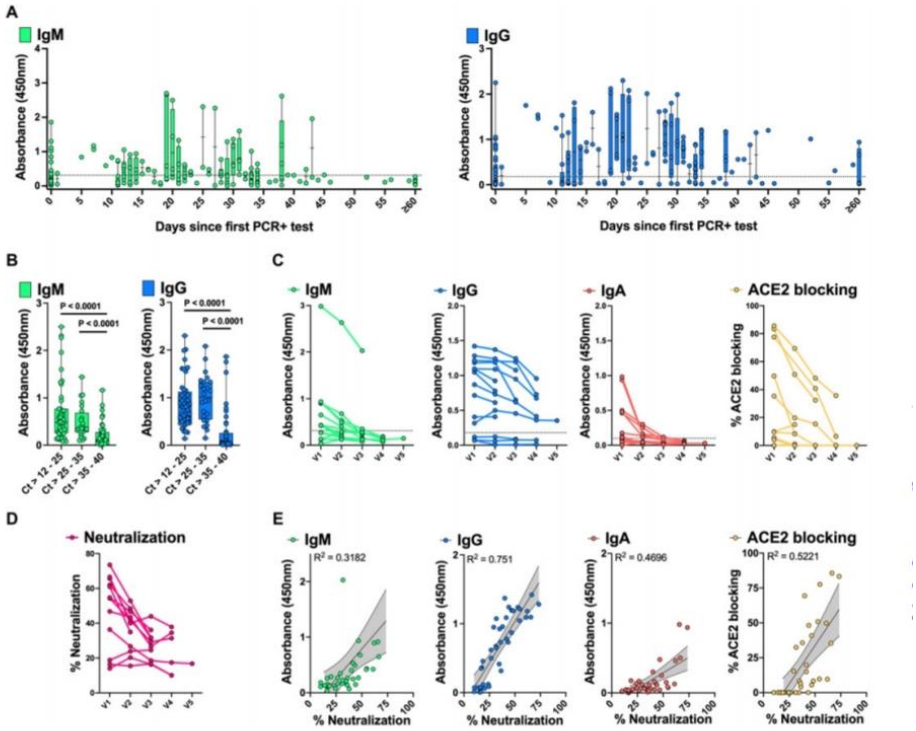


Figure 4: "Development of anti-SARS-CoV-2 spike RBD antibody responses in SARS-CoV-2 rRT-PCR+ asymptomatic individuals and outpatients over time. 176 plasma samples from 136 SARS-CoV-2 rRT-PCR+ individuals were tested for RBD IgM and IgG. The x-axis indicates the time following the first positive rRT-PCR test (A). Dotted lines denote the assay cutoff for positive results. RBD IgM and IgG are shown for the latest available timepoint for subjects with low (Ct >12-25), middle (Ct >25-35) and high (Ct >35-40) SARS-CoV-2 rRT-PCR Ct at diagnosis (B). 45 plasma samples collected from 14 rRT-PCR+ asymptomatic individuals and outpatients sampled at monthly intervals (V1 = enrollment, V2 to V5 = months 1 to 4 post-enrollment) were tested for RBD IgM, IgG, IgA at a dilution of 1:100, as well as RBD-ACE2 blocking antibodies at a dilution of 1:10 (C). The 45 plasma samples were further tested for pseudoviral neutralization at a dilution of 1:1250 (D). Box-whisker ELISA OD450 and blocking/neutralization percent plots show the interquartile range as the box and the minimum and maximum values as the ends of the whiskers. Correlations between virus neutralization and RBD IgM, IgG, IgA, and RBDACE2 blocking are shown with superimposed simple linear regression and 95% confidence bands (grey shading) of the best-fit line (E). Plots show mean ELISA OD450 values of duplicate measurements and average percent neutralization from duplicate testing in each of two replicate experiments".

MANAGEMENT

THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES' INTERIM RECOMMENDATION FOR ALLOCATING INITIAL SUPPLIES OF COVID-19 VACCINE - UNITED STATES, 2020

Dooling K, McClung N, Chamberland M, Marin M, Wallace M, Bell BP, Lee GM, Talbot HK, Romero JR, Oliver SE.. MMWR Morb Mortal Wkly Rep. 2020 Dec 11;69(49):1857-1859. doi: 10.15585/mmwr.mm6949e1.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

Guidelines and recommendations from the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention provides a recommendation on prioritizing the initial vaccine distribution to both healthcare workers and residents of long-term care facilities since there will be a limited supply in the first month. This decision was made considering scientific evidence of SARS-CoV-2 epidemiology, vaccination program implementation, and ethical principles, although they acknowledge that this recommendation may be altered by new information about SARS-CoV-2 or the vaccine as it becomes available.

ABSTRACT

The emergence of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), has led to a global pandemic that has disrupted all sectors of society. Less than 1 year after the SARS-CoV-2 genome was first sequenced, an application* for Emergency Use Authorization for a candidate vaccine has been filed with the Food and Drug Administration (FDA). However, even if one or more vaccine candidates receive authorization for emergency use, demand for COVID-19 vaccine is expected to exceed supply during the first months of the national vaccination program. The Advisory Committee on Immunization Practices (ACIP) advises CDC on population groups and circumstances for vaccine use. ACIP convened on December 1, 2020, in advance of the completion of FDA's review of the Emergency Use Authorization application, to provide interim guidance to federal, state, and local jurisdictions on allocation of initial doses of COVID-19 vaccine. ACIP recommended that, when a COVID-19 vaccine is authorized by FDA and recommended by ACIP, both 1) health care personnel and 2) residents of long-term care facilities (LTCFs) be offered vaccination in the initial phase of the COVID-19 vaccination program (Phase 1a**). In its deliberations, ACIP considered scientific evidence of SARS-CoV-2 epidemiology, vaccination program implementation, and ethical principles. The interim recommendation might be updated over the coming weeks based on additional safety and efficacy data from phase III clinical trials and conditions of FDA Emergency Use Authorization.

ACUTE CARE

CRITICAL CARE

EFFECT OF ARTIFICIAL LIVER BLOOD PURIFICATION TREATMENT ON THE SURVIVAL OF CRITICAL ILL COVID-19 PATIENTS

Xiahong D, Zhang Y, Liang Y, Ying-An J, Liang C, Ye C, Ming L, Chunming G, Jia S, Shulin X, Yongguo L, Jianzhou L, Chenliang Z, Xiaoyang Z, Nan C, Yuanchun L, Jing L, Yuanyuan Z, Xiaobei C, Danhua Z, Hainv G, Lingling T, Mengfei Z, Li L.. Artif Organs. 2020 Dec 16. doi: 10.1111/aor.13884. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A prospective study conducted between January 28 - May 30, 2020 by multiple infectious disease centers in China to investigate the efficacy of liver blood purification treatment on the survival of severe/critical COVID-19 patients with serum inflammatory factors greater than or equal to five times the upper limit. A total of 101 critical COVID-19 patients were enrolled in the study and divided into either the treatment group or the control group. The authors demonstrate that artificial liver therapy clears inflammatory mediators through blocking the cytokine storm thus preventing theses cases from worsening any further and improving the survival rate.

SUMMARY

Patients were considered severe if they met theses conditions:
- Respiratory distress: respiratory rate less than 30 times/minute.
- Oxygen saturation less than 93% at rest.
- Alveolar oxygen partial pressure/fraction of inspiration oxygen less than or equal to 300 mmHg.

Patients were considered critical if they met these conditions:
- Respiratory failure requiring mechanical ventilation.
- Shock.
- Other organ failure requiring ICU monitoring and treatment.

Along with a comprehensive treatment, patients in the treatment group received the artificial liver therapy which included basic plasma exchange. Patients in the control group only received the comprehensive treatment. The study demonstrated a significant drop in serum IL-6 levels in patients in the treatment group as compared to the control group (Figure 1).

ABSTRACT

OBJECTIVE: To investigate the effect of artificial liver blood purification treatment on the survival of severe/critical patients with COVID-19. METHODS: A total of 101 severe and critical patients with SARS-CoV-2 infection were enrolled in this open, case-control, multicentre, prospective study. According to the patients' and their families' willingness, they were divided into two groups. One was named the treatment group, in which the patients received artificial liver therapy plus comprehensive treatment, while the other was named the control group, in which the patients received only comprehensive treatment. Clinical data and laboratory examinations, as well as the 28-day mortality rate, were collected and analysed. RESULTS: This study involved 101 severe/critical patients with COVID-19, among which 50 were in the treatment group and 51 were in the control group. Baseline data comparisons on average age, sex, pre-treatment morbidity, initial symptoms, vital signs, pneumonia severity index (PSI) score, blood routine examination and biochemistry indices et al. showed no difference between the two groups. Cytokine storm was detected, with a significant increase of serum IL-6 level. The serum IL-6 level decreased from 119.94 pg/mL to 20.49 pg/mL in the treatment group and increased from 40.42 pg/mL to 50.81 pg/mL in the control group ($p<0.05$), indicating that artificial liver therapy significantly decreased serum IL-6. The median duration of viral nucleic acid persistence was 19 days in the treatment group (ranging from 6-67 days) and 17 days in the control group (ranging from 3-68 days), no significant difference was observed ($p=0.36$). As of 28-day follow-up,17 patients in the treatment group experienced a median weaning time of 24 days, while 11 patients in the control group experienced a median weaning time of 35 days, with no significant difference between the two groups ($p=0.33$). The 28-day mortality rates were 16% (8/50) in the treatment group and 50.98% (26/51) in the control group, with a significant difference ($z=3.70$, $p<0.001$). CONCLUSION: Cytokine storm is a key factor in the intensification of COVID-19 pneumonia. The artificial liver therapy blocks the cytokine storm by clearing inflammatory mediators, thus preventing severe cases from progressing to critically ill stages and markedly reducing short-term mortality.

FIGURES

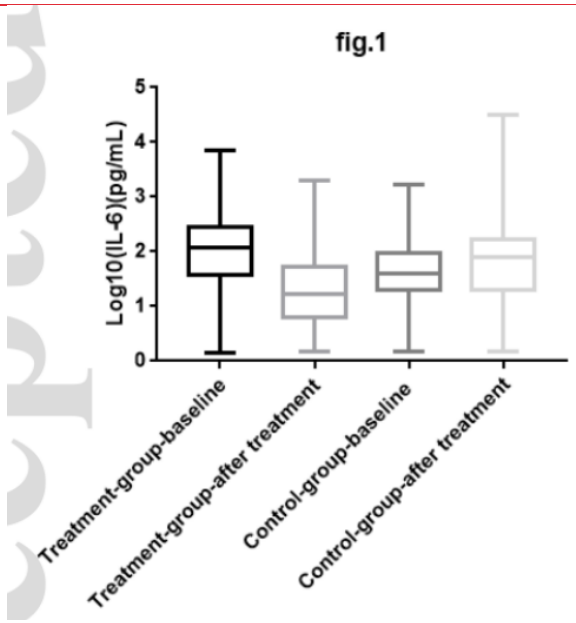


Figure 1. Comparison of serum IL-6 level changes between the artificial liver treatment group and the control group. The serum average IL-6 level decreased from 119.94 pg/mL to 20.49 pg/mL in the treatment group and increased from 40.42 pg/mL to 50.81 pg/mL in the control group($p<0.05$), indicating that artificial liver therapy decreased the serum level of IL-6.

NONINVASIVE MECHANICAL VENTILATION IN COVID-19 ERA: PROPOSAL FOR A CONTINUOUS POSITIVE AIRWAY PRESSURE CLOSED-LOOP CIRCUIT MINIMIZING AIR CONTAMINATION, OXYGEN CONSUMPTION AND NOISE

Cavaglià M, Olivieri C, Morbiducci U, Raparelli T, Jacazio G, Ivanov A, Chiesa A, Savino D, Chiarenza SM, Romiti A, Romiti A, Ferrara M, Musso G, Audenino A.. Artif Organs. 2020 Dec 16. doi: 10.1111/aor.13888. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

In this article, investigators from Turin, Italy propose a non-invasive continuous airway pressure (NIV-CAP) with a novel closed-loop configuration (Figure 1) which can be combined with existing CPAP machines, allowing for automatic control of patient breathing and minimizing aerosol production, oxygen consumption, and noise. This proposed apparatus was simulated with a healthy volunteer, resulting in reduction of oxygen feeding compared to standard NIV-CPAP, suggesting this adaptation of closed-loop circuitry as an efficient and practical option for COVID-19 patients requiring supplemental oxygen requirements.

ABSTRACT

Non-invasive Continuous Positive Airway Pressure (NIV-CPAP) is effective in patients with hypoxemic respiratory failure. Building evidence during the COVID-19 emergency reported that around 50% of patients in Italy treated with NIV-CPAP avoided the need for invasive mechanical ventilation. Standard NIV-CPAP systems operate at high gas flow rates responsible for noise generation and inadequate humidification. Furthermore, open configuration systems require a high concentration of oxygen to deliver the desired FiO2 . Concerns outlined the risk for aerosolization in the ambient and the possible pressure drop in hospital supply pipes. A new NIV-CPAP system is proposed that includes automatic control of patient respiratory parameters. The system operates as a closed-loop breathing circuit that can be assembled, combining a sleep apnea machine with existing commercially available components. Analytical simulation of breathing patient and simulation with a healthy volunteer at different FiO2 were performed. Inspired and expired oxygen fraction, inspired and expired carbon dioxide pressure were recorded at different CPAP levels with different oxygen delivery. Among the main findings, we report (1) a significant (up to 30-fold) reduction in oxygen feeding compared to standard open high flow NIV-CPAP systems, to assure the same FiO2 levels, and (2) a negligible production of the noise generated in ventilatory systems, and consequent minimization of patients' discomfort. The proposed NIV-CPAP circuit, reshaped in closed-loop configuration with the blower outside of the circuit, has the advantages of minimizing aerosol generation, environmental contamination, oxygen consumption, and noise to the patient. The system is easily adaptable and can be implemented using standard CPAP components.

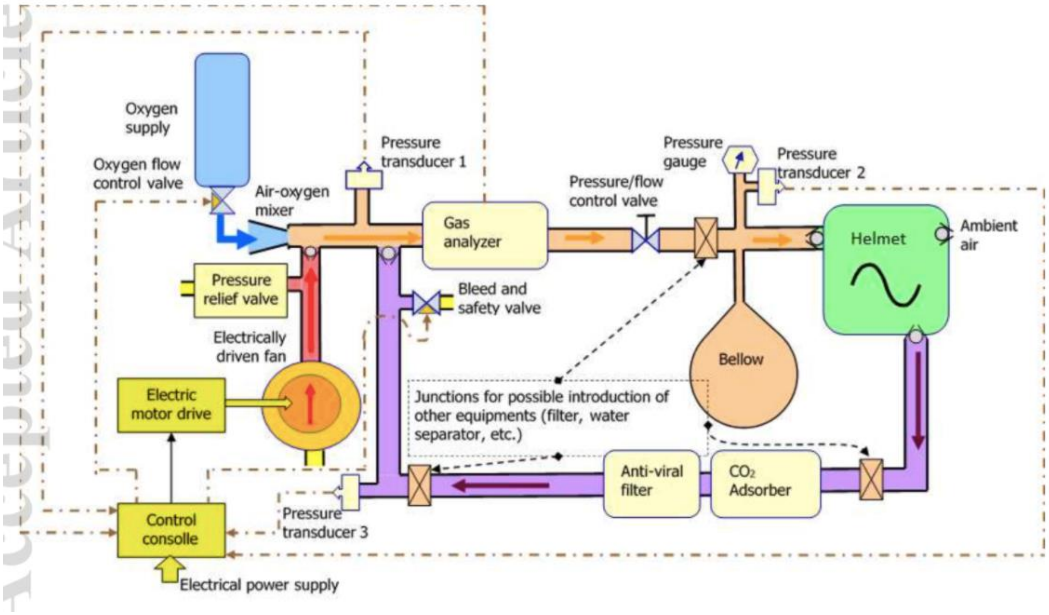


Figure 1. Schematics of the closed-loop NIV-CPAP circuit: pressurized limb (red); oxygen supply equipped with air-oxygen mixer (light blue) inspiratory limb with bellow (orange); gas analyzer (light yellow); patient interface (green); expiratory limb (violet); CO2 adsorber (light yellow); antiviral filter (light yellow). Two safety devices limit the overpressure, i.e., the pressure relief valve (light yellow) and the bleed and safety valve. An ambient air valve prevents negative pressures in the helmet. Two of the three pressure transducers are optional. The flow control valve can be used in the circuit's open-loop operation (bleed valve open). The control console drives fan and oxygen supply sources based on pressure transducers and gas analyzer data.

DEVELOPMENTS IN TREATMENTS

OXFORD-ASTRAZENECA COVID-19 VACCINE EFFICACY

Knoll MD, Wonodi C.. Lancet. 2020 Dec 8:S0140-6736(20)32623-4. doi: 10.1016/S0140-6736(20)32623-4. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A review of the efficacy and safety of the Oxford-AstraZeneca COVID-19 vaccine (ChAdOx1 nCoV-19), a non-profit vaccine aimed at global supply and equitable access, compiles results from four randomized, controlled trials which were conducted in the UK, South Africa, and Brazil to show an overall 70.4% efficacy (with a 95.8% confidence interval of 54.8 to 80.6) and 84 serious adverse events noted among 12,174 ChAdOx1 nCoV-19 recipients, suggesting the Oxford-AstraZeneca vaccine may soon be a frontrunner among the COVID-19 vaccine trials.

ENDOTHELIAL PULSATILE SHEAR STRESS IS A BACKSTOP FOR COVID-19

Sackner MA, Adams JA.. Emerg Top Life Sci. 2020 Dec 11;4(4):379-387. doi: 10.1042/ETLS20200260.
Level of Evidence: 5 - Mechanism-based reasoning

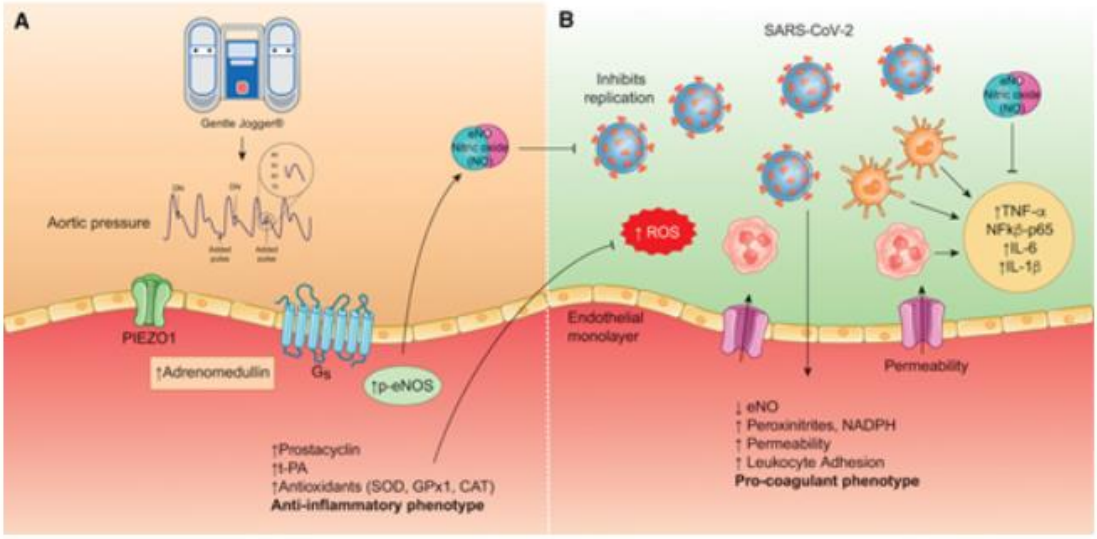
BLUF

Physicians from Mt. Sinai Medical Center of Greater Miami, Florida reviewed the mechanisms of pulsatile shear stress (PSS) treatment for COVID-19 patients delivered by either motorized platform, external counterpulsation (EECP), and/or Passive Stimulated Jogging Device, and the potential benefits regarding viral replication, non-cardiogenic pulmonary edema, endothelial dysfunction, coagulopathy, oxidative stress, hyperinflammation, cytokine storm, myocardial injury, and hyperglycemia in non-diabetics. The primary mechanism is that by increasing muscular activity, PSS acts on the endothelium to increase nitric oxide production, inhibiting SARS-CoV-2 replication (Figure 1); there are yet to be in vivo studies on this topic.

ABSTRACT

There has not been any means to inhibit replication of the SARS-CoV-2 virus responsible for the rapid, deadly spread of the COVID-19 pandemic and an effective, safe, tested across diverse populations vaccine still requires extensive investigation. This review deals with the repurpose of a wellness technology initially fabricated for combating physical inactivity by increasing muscular activity. Its action increases pulsatile shear stress (PSS) to the endothelium such that the bioavailability of nitric oxide (NO) and other mediators are increased throughout the body. In vitro evidence indicates that NO inhibits SARS-CoV-2 virus replication but there are no publications of NO delivery to the virus in vivo. It will be shown that increased PSS has potential in vivo to exert anti-viral properties of NO as well as to benefit endothelial manifestations of COVID-19 thereby serving as a safe and effective backstop.

Figure 1.



A model of pulsatile shear stress (PSS) effects on a normal (A) and SARS-CoV-2-activated (B) endothelial monolayer. The left side of the diagram (A) depicts a normal endothelial cell monolayer. Gentle Jogger (Jogging Device) induces added pulses to the normal circulation [9]. The dichrotic notch (DN) for each aortic pulse waveform is shown along with the added pulsations induced by Gentle Jogger. Pulsations derived from the normal circulation and those produced by the Gentle Jogger, produce PSS on the vascular endothelium monolayer which activates the cation channel PIEZO1. The latter increases production of adrenomedullin, which via an intermediary step (activates the heterotrimeric G protein (Gs) receptor, leading to activation of protein kinase A(PKA) which activates eNOS by phosphorylation, thus increasing endothelial-derived nitric xide (eNO) [10]. PSS, increases prostacyclin, tissue plasminogen activator (tPA), antioxidants (superoxide dismutase (SOD), glutathione peroxidase 1 (GPx1), catalase (CAT)) and produces an anti-inflammatory endothelium phenotype. The right side (B) depicts an activated endothelium from SARS-CoV-2, in which the endothelium monolayer loses its barrier function with increased permeability, reactive oxygen species (ROS) peroxinitrites and NADPH (reduced nicotinamide adenine dinucleotide phosphate) are produced, and the endothelial cell manifests a pro-coagulant phenotype. Bioavailability of nitric oxide is decreased. Additionally, neutrophils and macrophages are stimulated by the virus to produce an increase in the following cytokines; tumor necrosis alpha (TNF-α), nuclear translocation of the NF-kβ-p-65 (nuclear factor kappa beta), and interleukin 6 (IL-6), interleukin 1 beta (IL-1β) and ROS. eNO produced by PSS, inhibits replication of the virus and decreases the production of cytokines. PSS is a means to widely distribute beneficial endothelial derived mediators.

PERSISTENCE OF SYMPTOMS AND QUALITY OF LIFE AT 35 DAYS AFTER HOSPITALIZATION FOR COVID-19 INFECTION

Jacobs LG, Gourna Paleoudis E, Lesky-Di Bari D, Nyirenda T, Friedman T, Gupta A, Rasouli L, Zetkulic M, Balani B, Ogedegbe C, Bawa H, Berrol L, Qureshi N, Aschner JL.. PLoS One. 2020 Dec 11;15(12):e0243882. doi: 10.1371/journal.pone.0243882. eCollection 2020.
Level of Evidence: 3 - Local non-random sample

BLUF

Investigators from Hackensack Meridian School of Medicine and Hospital in New Jersey conducted a single center prospective cohort study of 183 COVID-19 patients admitted to Hackensack Meridian Hospital between March 22 and April 16, 2020, in order to identify persistent physical symptoms (Table 3), psychological health, social relationships, and activities of daily living (Table 5) all pertaining to their self-reported quality of life 35 ± 5 days after hospital discharge (Table 6). The results revealed 16.9% of participants reported their mental health as poor or fair, impairing their daily living, physical and mental health, and quality of life, suggesting the importance of early intervention for both physical and mental symptoms, along with social support, as an essential part of full recovery from COVID-19.

ABSTRACT

BACKGROUND: Characterizing the prevalence and persistence of symptoms associated with COVID-19 infection following hospitalization and their impact is essential to planning post-acute community-based clinical services. This study seeks to identify persistent COVID-19 symptoms in patients 35 days post-hospitalization and their impact on quality of life, health, physical, mental, and psychosocial function. METHODS AND FINDINGS: This prospective cohort study used the PROMIS Instruments to identify symptoms and quality of life parameters in consecutively enrolled patients between March 22 and April 16, 2020, in New Jersey. The 183 patients (median age 57 years; 61.5% male, 54.1% white) reported persistent symptoms at 35 days, including fatigue (55.0%), dyspnea (45.3%), muscular pain (51%), associated with a lower odds rating general health (41.5%, OR 0.093 [95% CI: 0.026, 0.329], p = 0.0002), quality of life (39.8%; OR 0.116 [95% CI: 0.038, 0.364], p = 0.0002), physical health (38.7%, OR 0.055 [95% CI: 0.016, 0.193], p <0.0001), mental health (43.7%, OR 0.093 [95% CI: 0.021, 0.418], p = 0.0019) and social active role (38.7%, OR 0.095 [95% CI: 0.031, 0.291], p<0.0001), as very good/excellent, particularly adults aged 65 to 75 years (OR 8 666 [95% CI: 2 216, 33 884], p = 0 0019). CONCLUSIONS: COVID-19 symptoms commonly persist to 35 days, impacting quality of life, health, physical and mental function. Early post-acute evaluation of symptoms and their impact on function is necessary to plan community-based services.

FIGURES

Table 3. Participant-reported symptoms persisting from hospital discharge to 35 days in COVID-19 patients.

Symptom[a]	Ever Experienced, no. (% of total)	2 weeks,[b] no./ever experienced (%)	3 weeks, no./ever experienced (%)	35 ± 5 days,[c] no./ever experienced (%)
Fatigue	149 (83.2)	120/149 (80.5)	91/148 (61.1)	82/149 (55.0)
Shortness of breath	128 (71.1)	94/128 (73.3)	69/127 (54.0)	58/128 (45.3)
Cough	110 (61.4)	78/110 (70.9)	55/110 (50.0)	46/110 (41.8)
Lack of taste	79 (44.4)	45/79 (57.0)	28/79 (35.4)	18/79 (22.8)
Muscular pain	77 (43.0)	57/77 (74.0)	41/77 (53.2)	39/77 (50.6)
Diarrhea	64 (36.0)	32/64 (50.0)	13/64 (20.3)	7/64 (10.9)
Lack of smell	65 (36.7)	39/65 (60.0)	25/65 (38.5)	17/65 (26.2)
Phlegm	61 (34.7)	46/61 (75)	31/61 (50.8)	27/61 (44.3)
Headache	59 (33.2)	42/59 (71.2)	29/59 (49.2)	23/59 (39.0)
Joint pain	53 (29.8)	46/53 (86.8)	29/53 (54.7)	29/53 (54.7)
Confusion	37 (21.1)	25/37 (67.6)	19/37 (51.4)	16/37 (43.2)
Eye irritation	35 (19.8)	20/35 (57.1)	18/35 (51.4)	15/35 (42.9)
Fever	38 (22.0)	21/38 (55.3)	5/38 (13.2)	2/38 (5.3)
Ulcer	10 (5.7)	5/10 (50.0)	3/10 (30.0)	2/10 (20.0)

Footnotes

[a] Report of symptoms using PROMIS® survey questions, [12, 13] retrospective except at the time of survey regarding the period of time described.

[b] % = (number of participants reporting symptoms which had not stopped within indicated time period *100)/ (total number of participants ever reporting the symptom).

[c] % = (number of participants reporting symptoms present at the time of survey*100/total number of participants ever reporting the symptom).

Table 3. Participant-reported symptoms persisting from hospital discharge to 35 days in COVID-19 patients.

Table 5. COVID-19 patient self-rated quality of life and activities of daily living at day 35.

Quality of life and daily living activity outcomes[a]	Rating	no. (%)
General health	poor, fair	37 (20.2)
	good	70 (38.2)
	very good, excellent	76 (41.5)
Quality of life	poor, fair	42 (23.2)
	good	67 (37.0)
	very good, excellent	72 (39.8)
Physical health	poor, fair	49 (27.1)
	good	62 (34.2)
	very good, excellent	70 (38.7)
Mental health	poor, fair	31 (16.9)
	good	72 (39.3)
	very good, excellent	80 (43.7)
Social Relationships	poor, fair	110 (60.4)
	very good, excellent	72 (39.6)
Social Active Role	poor, fair	57 (31.5)
	good	54 (29.8)
	very good, excellent	70 (38.7)
Physical activity	not at all, a little	25 (13.8)
	moderately	45 (24.9)
	mostly, completely	111 (61.3)
Emotional	always, often	26 (14.2)
	sometimes	64 (35.0)
	rarely, never	93 (50.8)
Fatigue	severe, very severe	15 (8.2)
	moderately	60 (32.8)
	none, mild	108 (59.0)
Dressing	no or a little difficulty	177 (96.7)
	some/much difficulty	6 (3.3)
Walking	no or a little difficulty	146 (84.4)
	some/much difficulty	27 (15.6)
Stairs	no or a little difficulty	115 (70.1)
	some/much difficulty	49 (29.9)
Meal preparation	no or a little difficulty	148 (93.7)
	some/much difficulty	10 (6.3)
Wash dishes	no or a little difficulty	153 (95.6)
	some/much difficulty	7 (4.4)
Sweep	no or a little difficulty	133 (88.1)
	some/much difficulty	18 (11.9)
Make bed	no or a little difficulty	150 (93.8)
	some/much difficulty	10 (6.2)
Lift	no or a little difficulty	129 (79.6)
	some/much difficulty	33 (20.4)
Lift and carry	no or a little difficulty	120 (74.5)
	some/much difficulty	41 (25.5)
Walk fast	no or a little difficulty	74 (54.4)
	some/much difficulty	62 (45.6)

Footnotes

[a] Report of quality of life and daily living activities using PROMIS® survey questions, [12, 13] retrospective except at the time of survey.

Table 5. COVID-19 patient self-rated quality of life and activities of daily living at day 35.

Table 6. Associations between quality of life outcomes and persistent symptoms of COVID-19 patients at day 35.

Quality of life outcome variable	Outcome comparison category	Odds ratio (95% CI)	P-value
General health	good	0.530 (0.136, 2.057)	0.3587
(ref. cat.: poor, fair)[a]	very good, excellent	0.093 (0.026, 0.329)	0.0002
Quality of life	good	0.536 (0.159, 1.809)	0.3149
(ref. cat.: poor, fair)	very good, excellent	0.116 (0.038, 0.364)	0.0002
Physical health	good	0.384 (0.098, 1.504)	0.1694
(ref. cat.: poor, fair)	very good, excellent	0.055 (0.016, 0.193)	<0.0001
Mental health	good	0.286 (0.061, 1.342)	0.1125
(ref. cat.: poor, fair)		0.093 (0.021, 0.418)	0.0019
Social relationships	very good, excellent	0.245 (0.123, 0.486)	
(ref. cat.: poor, fair)			
Social active role	good	0.196 (0.060, 0.637)	
(ref. cat.: poor, fair)	very good, excellent	0.095 (0.031, 0.291)	
Daily physical activity	moderately	0.584 (0.058, 5.925)	
(ref. cat.: a little not at all)	mostly, completely	0.059 (0.008, 0.451)	
Emotional	sometimes	0.876 (0.252, 3.051)	
(ref. cat: always, often)	rarely, never	0.301 (0.096, 0.947)	
Fatigue	moderately	0.786 (0.085, 7.276)	
(ref. cat.: severe, very severe)	none, mild	0.104 (0.013, 0.819)	

[a]Abbreviations ref. cat. reference category, CI Confidence interval.

Table 6. Associations between quality of life outcomes and persistent symptoms of COVID-19 patients at day 35.

COVID-19'S IMPACT ON HEALTHCARE WORKFORCE

BURNOUT, DEPERSONALIZATION, AND ANXIETY CONTRIBUTE TO POST-TRAUMATIC STRESS IN FRONTLINE HEALTH WORKERS AT COVID-19 PATIENT CARE, A FOLLOW-UP STUDY

Miguel-Puga JA, Cooper-Bribiesca D, Avelar-Garnica FJ, Sanchez-Hurtado LA, Colin-Martínez T, Espinosa-Poblano E, Anda-Garay JC, González-Díaz JI, Segura-Santos OB, Vital-Arriaga LC, Jáuregui-Renaud K.. Brain Behav. 2020 Dec 15:e02007. doi: 10.1002/brb3.2007. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers from Hospital de Especialidades del Centro Medico Nacional siglo XXI, Ciudad de México, Mexico conducted a series of survey questionnaires to 204 frontline health care workers at institutions that were reconstructed to care for COVID-19 patients during the height of the pandemic, in order to determine if working conditions and situations contributed to anxiety, depression, dissociative symptoms (depersonalization/derealization), development of PTSD, sleep changes, stress, and burnout. Mental health parameters were assessed at three different time periods (at the time of reconstruction, during the peak of COVID-19 patients, and when their institution opened back up to non-COVID-19 patients). Regression analysis of responses (Table 3) revealed 35 participants met criteria for PTSD, with pre-existing anxiety as a risk factor and pre-existing resilience as a protective factor, as well as statistically significant poor sleep quality during the pandemic, suggesting the importance of psychological screenings to protect the mental health of those most vulnerable and help mitigate medical errors caused by burnt-out medical professionals.

ABSTRACT

INTRODUCTION: We designed a follow-up study of frontline health workers at COVID-19 patient care, within the same working conditions, to assess the influence of their general characteristics and pre-existing anxiety/depression/dissociative symptoms and resilience on the development of symptoms of post-traumatic stress disorder (PTSD), while monitoring their quality of sleep, depersonalization/derealization symptoms, acute stress, state anxiety, and burnout. METHODS: In a Hospital reconfigured to address the surge of patients with COVID-19, 204 frontline health workers accepted to participate. They completed validated questionnaires to assess mental health: before, during, and after the peak of inpatient admissions. After each evaluation, a psychiatrist reviewed the questionnaires, using the accepted criteria for each instrument. Correlations were assessed using multivariable and multivariate analyses, with a significance level of .05. RESULTS: Compared to men, women reporting pre-existing anxiety were more prone to acute stress; and younger age was related to both pre-existent common

psychological symptoms and less resilience. Overall the evaluations, sleep quality was bad on the majority of participants, with an increase during the epidemic crisis, while persistent burnout had influence on state anxiety, acute stress, and symptoms of depersonalization/derealization. PTSD symptoms were related to pre-existent anxiety/depression and dissociative symptoms, as well as to acute stress and acute anxiety, and negatively related to resilience. CONCLUSIONS: Pre-existent anxiety/depression, dissociative symptoms, and coexisting acute anxiety and acute stress contribute to PTSD symptoms. During an infectious outbreak, psychological screening could provide valuable information to prevent or mitigate against adverse psychological reactions by frontline healthcare workers caring for patients.

FIGURES

Variables	Evaluation 1 *Estimate ± SE*	Evaluation 2 *Estimate ± SE*	Evaluation 3 *Estimate ± SE*
Psychological screening			
Hospital Anxiety and Depression Scale	0.105 ± 0.030	0.084 ± 0.018	0.023 ± 0.010
Wald statistic (*p* value)	12.14 (**.0004**)	20.81 (**.000005**)	4.85 (**.02**)
Dissociative Experiences Scale	−0.095 ± 0.020	−0.040 ± 0.010	−0.000 ± 0.008
Wald statistic (*p* value)	21.25 (**.000004**)	14.92 (**.0001**)	0.002 (.95)
Resilience Scale	−0.007 ± 0.007	−0.015 ± 0.006	0.010 ± 0.004
Wald statistic (*p* value)	0.85 (.35)	4.72 (**.02**)	6.65 (**.009**)
Follow-up			
Pittsburgh Sleep Quality Index	0.005 ± 0.042	0.076 ± 0.038	0.007 ± 0.033
Wald statistic (*p* value)	0.02 (.88)	3.92 (**.047**)	0.05 (.81)
Depersonalization/derealization scale	0.084 ± 0.026	0.009 ± 0.009	0.005 ± 0.005
Wald statistic (*p* value)	10.12 (**.001**)	1.10 (**.29**)	1.22 (.26)
Stanford Acute Stress questionnaire	0.018 ± 0.004	0.017 ± 0.005	0.012 ± 0.003
Wald statistic (*p* value)	16.56 (**.00004**)	12.03 (**.0005**)	15.38 (**.00008**)
State-Trait Anxiety Inventory	−0.187 ± 0.054	−0.111 ± 0.025	0.128 ± 0.028
Wald statistic (*p* value)	10.12 (**.001**)	19.50 (**.00001**)	20.90 (**.000004**)
Burnout Measure	0.178 ± 0.126	0.064 ± 0.111	0.150 ± 0.082
Wald statistic (*p* value)	2.00 (.15)	0.33 (.56)	3.28 (.06)
General characteristics			
Gender	−0.062 ± 0.178	−0.197 ± 0.370	0.208 ± 0.165
Wald statistic (*p* value)	0.122 (.72)	0.28 (.59)	1.59 (.20)
Age	0.040 ± 0.019	−0.006 ± 0.012	−0.001 ± 0.009
Wald statistic (*p* value)	4.29 (**.038**)	0.25 (.61)	0.01 (.88)
Occupation			
Clinical & support categories	−0.062 ± 0.198	−0.050 ± 0.379	−0.051 ± 0.164
Wald statistic (*p* value)	0.10 (.75)	0.017(.89)	0.09 (.75)
Technical & support categories	−0.065 ± 0.194	0.788 ± 0.385	0.163 ± 0.123
Wald statistic (*p* value)	0.11 (.73)	4.17 (**.040**)	1.77 (.18)

Note: The coefficient estimates and standard error (*SE*) of the estimates are shown with the Wald statistic and the *p* values.

Table 3. Results of regression analysis on the evidence of PTSD after the peak of inpatient admission; including the general characteristics of the 204 participants, the scores on the psychological screening inventories, and the scores on the questionaries administered (1) before, (2) during, and (3) after the peak of inpatient admissions.

ACKNOWLEDGEMENTS

CONTRIBUTORS

Ellen Reidy
Kersti Bellardi
Krithika Kumarasan
Sarala Kal
Sokena Zaidi
Tasha Ramparas
Tyler Gallagher
Veronica Graham
Zainab Awan

EDITORS

John Michael Sherman
Maresa Woodfield
Stephen Ferraro

SENIOR EDITORS

Allison Hansen
Cameron Richards
Kyle Ellingsen

SENIOR EXECUTIVE EDITOR

Thamanna Nishath

CHIEF EDITOR

Jasmine Rah

ADVISOR

Will Smith