The Daily COVID-19 Literature Surveillance Summary

February 23, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Epidemiology

- Internet search patterns reveal clinical course of COVID-19 disease progression and pandemic spread across 32 countries. Authors from the Predictive Medicine Group at Boston Children's Hospital analyzed internet search patterns in over 32 countries, revealing important epidemiological data that could be used to identify patterns of COVID-19 transmission. Internet search histories were temporally correlated with documented COVID-19 cases and deaths, revealing increased internet searches for COVID-19 symptoms an average of 18 days prior to the documented rise in COVID-19 test positivity. The data also demonstrated a "clear temporal association" between internet searches and the clinical course of disease, with progression of searches on initial symptoms occurring 5.2 days before a rise in searches for shortness of breath, and 22 days before a rise in reported COVID-19 deaths. These results highlight how real-time analysis of internet search data can be a useful tool in identifying COVID-19 transmission during the critical initial days of an outbreak; however, this approach may raise ethical debates on internet privacy and data collection.

Transmission & Prevention

- Social distancing can positively alter the clinical course of COVID-19 in young adults. Physicians from the Swiss Armed Forces assessed the spread of COVID-19 illness among three companies of soldiers at a Swiss military base (n=508); company 1 had their own barracks while companies 2 and 3 shared barracks. A soldier in company 3 developed COVID-19 on March 11, 2020. On day 35 of the outbreak, authors tested 363 asymptomatic soldiers from all 3 groups and found evidence of past or current infection in 15% (13/88) of those from company 1, 64% in company 2, and 59% in company 3. Symptomatic infections were documented in 0% of company 1, 27% of company 2, and 31 % of company 3. Authors suggest the relative lack of COVID-19 illness in company 1 compared to 2 and 3 supports the effectiveness of social distancing and hygiene measures both in preventing disease spread and mitigating disease severity.

R&D: Diagnosis & Treatments

- Can culturable SARS-CoV-2 in hospitalized patients with COVID-19 be helpful in determining illness progression? Researchers from multiple South Korean institutions describe a case series investigating viral shedding by analyzing serial respiratory cultures in 21 hospitalized patients with mild-to-moderate COVID-19. Findings include a median time from symptom onset to viral clearance of 7 days in culture (95% CI, 5-10 days) and 34 days on real-time PCR (95% CI lower boundary 24 days), with viable virus identified until 3 days after fever resolution. Viral load and cycle-threshold values below 28.4 were positively correlated, and the incidence of culture positivity decreased with greater time from onset of symptoms. These findings can be used to guide isolation periods and risk estimation of secondary transmission in COVID-19 patients, but further research with a larger and more diverse patient population can allow for better extrapolation.

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TRENDS IN US ALCOHOL CONSUMPTION FREQUENCY DURING THE FIRST WAVE OF THE SARS-COV-2 PANDEMIC

McKetta S, Morrison CN, Keyes KM.. Alcohol Clin Exp Res. 2021 Feb 15. doi: 10.1111/acer.14575. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Epidemiologists from Columbia University in New York and Monash University in Australia used a self-reported longitudinal survey of 7,397 adults (Table 1) to analyze trends in alcohol use between March 10 and June 8, 2020. They found the number of drinking days increased each day over the study period (0.3% increased risk per calendar day), with a faster increase in states with a lower COVID-19 burden compared to states with a higher burden (Figure 1). Authors suggest the increase in alcohol consumption during the first pandemic wave warrants further consideration of strategies to screen for and manage substance use disorders during the pandemic.

ABSTRACT

BACKGROUND: The SARS-CoV-2 pandemic created disruptions and stressors which may have influenced alcohol consumption frequency trends. Varying COVID-19 health burden and alcohol policies may have contributed to different consumption trends between states. The aim of this study is to assess trends in alcohol consumption and moderation by state of residence. METHODS: We examined trends in adult drinking days, during the first wave of the pandemic (March 10 to June 8) using longitudinal data from Understanding America Study (N=6,172 unique participants; N=28,059 observations). Because state mandates were responsive to disease burden, we modelled interaction by COVID-19 burden, defined as if the state had the median (or higher) daily incidence of COVID-19 cases on the survey date, and state random effects. We controlled for individual sociodemographics, perceived personal/familial COVID-19 burden, mental health symptomology, and risk avoidance. RESULTS: Drinking days increased throughout the duration (incidence risk ratio [IRR] for drinking per increase in one calendar day = 1.003, 95% CI 1.001, 1.004); trends were heterogeneous by disease burden, with individuals living in states with lower COVID-19 burden increasing (IRR=1.005, 95% CI 1.003, 1.007) faster relative to those living in states with higher COVID-19 burden (IRR = 1.000, 95% CI 0.998, 1.002). Trends were heterogenous between states, but there was no evidence of systematic geographic clustering of state trends. CONCLUSIONS: Drinking days increased during the first months of the COVID-19 pandemic, particularly among residents of states with lower disease burden.

FIGURES

Table 1: Demographic and outcome characteristics of respondents, stratified by whether or not state had median cumulative incidence of COVID-19 cases at the time of the survey, March 10, 2020 – June 8, 2020

	State had <median COVID-19 cases (N=8,021 observations)	State had ≥median COVID-19 cases (N=20,038 observations)	
Number of drinking days (mean, S.D.)	1.43 (2.15)	1.57 (2.20)	p<0.001
Male gender	3,373 (42.1%)	8,490 (42.4%)	p=0.63
Age (mean, S.D.)	52.2 (15.7)	50.8 (16.1)	p<0.001
Children live in the house	2,948 (36.8%)	7,913 (39.5%)	p<0.001
White race	6,595 (82.2%)	15,739 (78.6%)	p<0.001
Hispanic	738 (9.2%)	3,263 (16.3%)	P<0.001
Respondent avoids public spaces	5,215 (65.0%)	17,535 (87.5%)	p<0.001
Respondent has a job	4,572 (57.0%)	10,102 (50.4%)	p<0.001
Respondent has high personal/familial perceived COVID-19 burden	749 (9.3%)	3,862 (19.3%)	p<0.001
Depression PHQ4 ≥3	791 (9.9%)	2,427 (12.1%)	P<0.001
Anxiety PHQ4 ≥3	1,159 (14.5%)	3,270 (16.3%)	P<0.001

Table 1: Demographic and outcome characteristics of respondents, stratified by whether or not state had median cumulative incidence of COVID-19 cases at the time of the survey, March 10, 2020 – June 8, 2020

Figure 1: Predicted count of drinking days over time and state-level COVID-19 presence, March 10, 2020 - June 8, 2020; marginal estimates and with interaction by disease burden

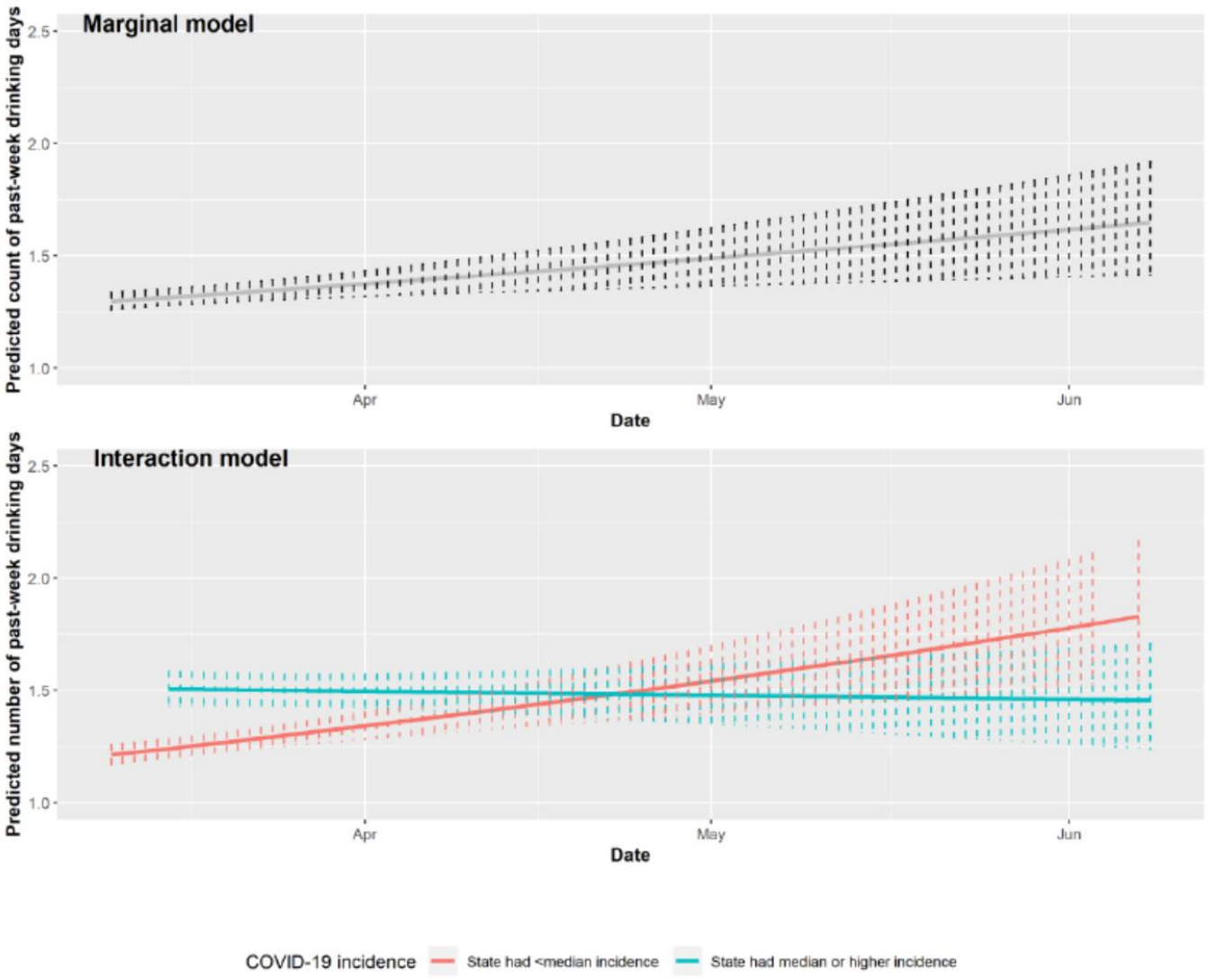

Figure 1: Predicted count of drinking days over time and state-level COVID-19 presence, March 10, 2020 – June 8, 2020; marginal estimates and with interaction by disease burden

VACCINATING CHILDREN AGAINST COVID-19 - THE LESSONS OF MEASLES

Klass P, Ratner AJ.. N Engl J Med. 2021 Feb 18;384(7):589-591. doi: 10.1056/NEJMp2034765. Epub 2021 Jan 20.
Level of Evidence: 5 - Expert Opinion

BLUF

In this perspective article, physicians from Grossman School of Medicine detail the recent history of the public view on the measles vaccine, including the roll out, social and political campaigns, and consequences of noncompliance, drawing comparisons to COVID-19 vaccinations in pediatric populations in the near future. The authors urge for coordinated federal and local support when the time comes to efficiently roll out COVID-19 vaccine to children, developing platforms to deliver truth and reassurance, halting disinformation campaigns, continuing research in pediatric populations to support vaccine benefits, and striving to normalize gratitude towards those children willing to get vaccinated, suggesting a proud display of "SARS stars" or "Corona Diplomas".

CABIN CREW HEALTH AND FITNESS-TO-FLY: OPPORTUNITIES FOR RE-EVALUATION AMID COVID-19

Grout A, Leggat PA.. Travel Med Infect Dis. 2021 Jan 12:101973. doi: 10.1016/j.tmaid.2021.101973. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A literature review conducted at The College of Public Health at James Cook University Johannesburg, South Africa found airlines lacked internationally compatible regulations which assess the crew's capability to reduce the spread of COVID-19, screening of airline crew for potential infections, and assessment of education pertaining to risk factors for infectious diseases. Further research on effective means of assessment is suggested.

ABSTRACT

Aircrew fitness-to-fly is among the elements that make aviation the safest form of long-distance transport. The health of cabin crew is a crucial determinant in carrying out safety-related duties. 'Fitness-to-fly' is associated with defined workplace conditions, for which airlines have a legal duty to ensure fitness for employment. We explored the literature on fitness-to-fly to obtain a pragmatic assessment of the challenges for aeromedical examinations. Regulations promulgated by aviation regulatory authorities and airline-internal policies have similar status and meaning, yet there is no harmonised approach internationally, and an inability to conform periodic medical assessments to actual operational fitness. The COVID-19 pandemic has highlighted the need to better understand fitness-to-fly criteria. Fitness-to-fly measures are mainly based on self-reported data and there is a need for a 'safety' factor for self-reports. Aeromedical evaluations should evolve from meeting medical standards to include pandemics as an element of the overall risk of aircraft operations. Re-evaluating criteria for fitness-to-fly assessment will further the goal of linking research to the actual needs of public health decisionmakers. If airlines are to resume operations at pre-pandemic levels, they must demonstrate to the public and public health agencies that fitness-to-fly assessment is appropriate and effective.

EPIDEMIOLOGY

INTERNET SEARCH PATTERNS REVEAL CLINICAL COURSE OF COVID-19 DISEASE PROGRESSION AND PANDEMIC SPREAD ACROSS 32 COUNTRIES

Lu T, Reis BY.. NPJ Digit Med. 2021 Feb 11;4(1):22. doi: 10.1038/s41746-021-00396-6.
Level of Evidence: 3 - Local non-random sample

BLUF

Authors from the Predictive Medicine Group at Boston Children's Hospital analyzed internet search patterns in over 32 countries from January to April 2020, revealing important epidemiological data that could be used to identify patterns of COVID-19 transmission. Internet search histories were temporally correlated with documented COVID-19 cases and deaths, revealing increased internet searches for COVID-19 symptoms an average of 18 days prior to the documented rise in COVID-19 test positivity (Figure 2). The data also demonstrated a "clear temporal association" between internet searches and the clinical course of disease, with progression of searches on initial symptoms occurring 5.2 days before a rise in searches for shortness of breath, and 22 days before a rise in reported COVID-19 deaths (Figure 1). These results highlight how real-time analysis of internet search data can be a useful tool in identifying COVID-19 transmission during the critical initial days of an outbreak; however, this approach may raise ethical debates on internet privacy and data collection.

ABSTRACT

Effective public health response to novel pandemics relies on accurate and timely surveillance of pandemic spread, as well as characterization of the clinical course of the disease in affected individuals. We sought to determine whether Internet search patterns can be useful for tracking COVID-19 spread, and whether these data could also be useful in understanding the clinical progression of the disease in 32 countries across six continents. Temporal correlation analyses were conducted to characterize the relationships between a range of COVID-19 symptom-specific search terms and reported COVID-19 cases and deaths for each country from January 1 through April 20, 2020. Increases in COVID-19 symptom-related searches preceded increases in reported COVID-19 cases and deaths by an average of 18.53 days (95% CI 15.98-21.08) and 22.16 days (20.33-23.99), respectively. Cross-country ensemble averaging was used to derive average temporal profiles for each search term, which were combined to create a search-data-based view of the clinical course of disease progression. Internet search patterns revealed a clear temporal pattern of disease progression for COVID-19: Initial symptoms of fever, dry cough, sore throat and chills were followed by shortness of breath an average of 5.22 days (3.30-7.14) after initial symptom onset, matching the clinical course reported in the medical literature. This study shows that Internet search data can be useful for characterizing the detailed clinical course of a disease. These data are available in real-time at population scale, providing important benefits as a complementary resource for tracking pandemics, especially before widespread laboratory testing is available.

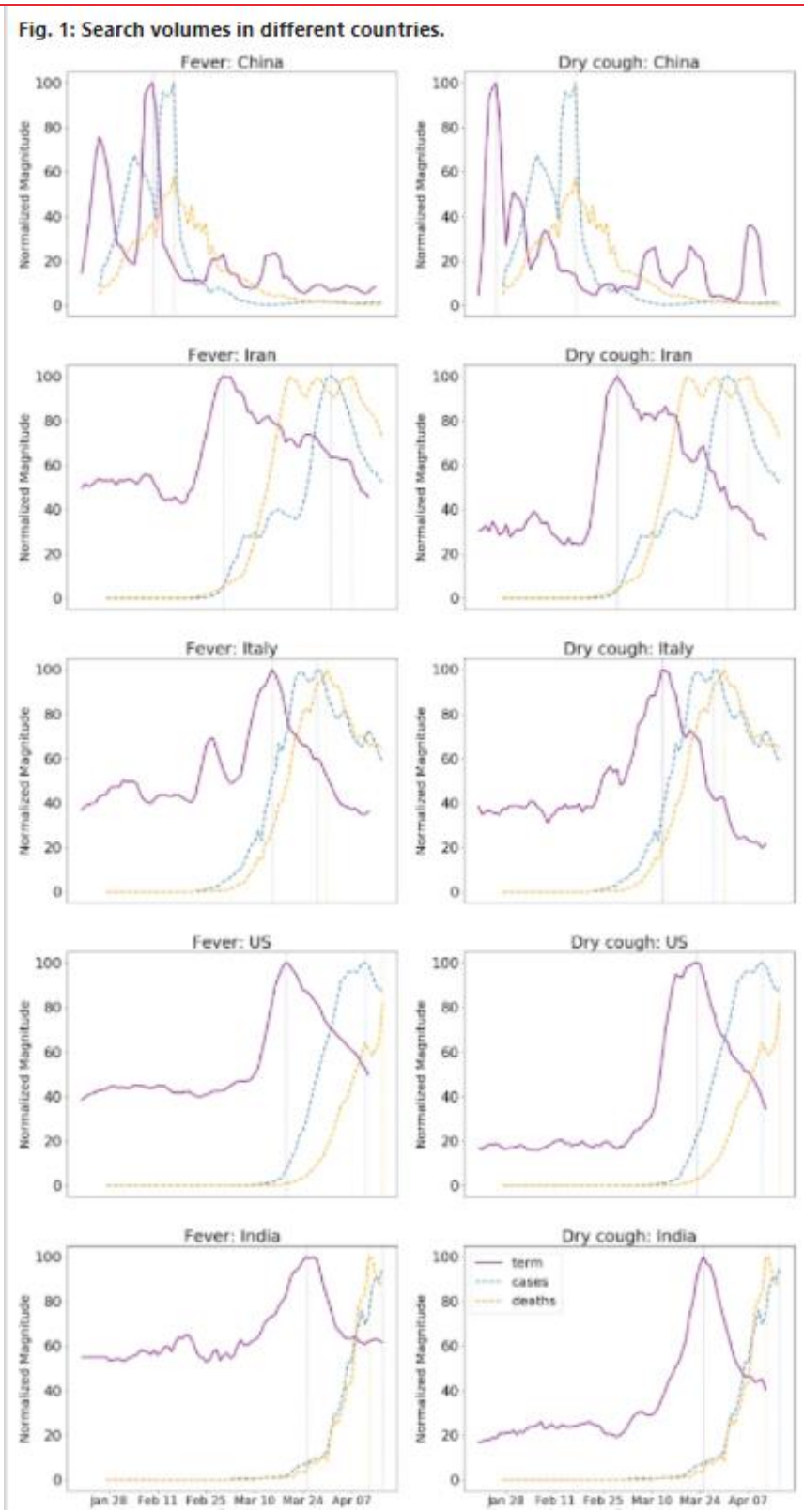

Figure 1. Search volumes (purple) for the terms "fever" (left) and "dry cough" (right), alongside reported COVID-19 cases (cyan) and deaths (orange) for China, Iran, Italy, US and India. Even though outbreaks occur at different times in different countries, the relationships between the search terms and reported COVID-19 cases and deaths remain similar across countries. To highlight the temporal relationships between the curves, the magnitude of each curve was independently normalized to fit the vertical dimensions of the plot.

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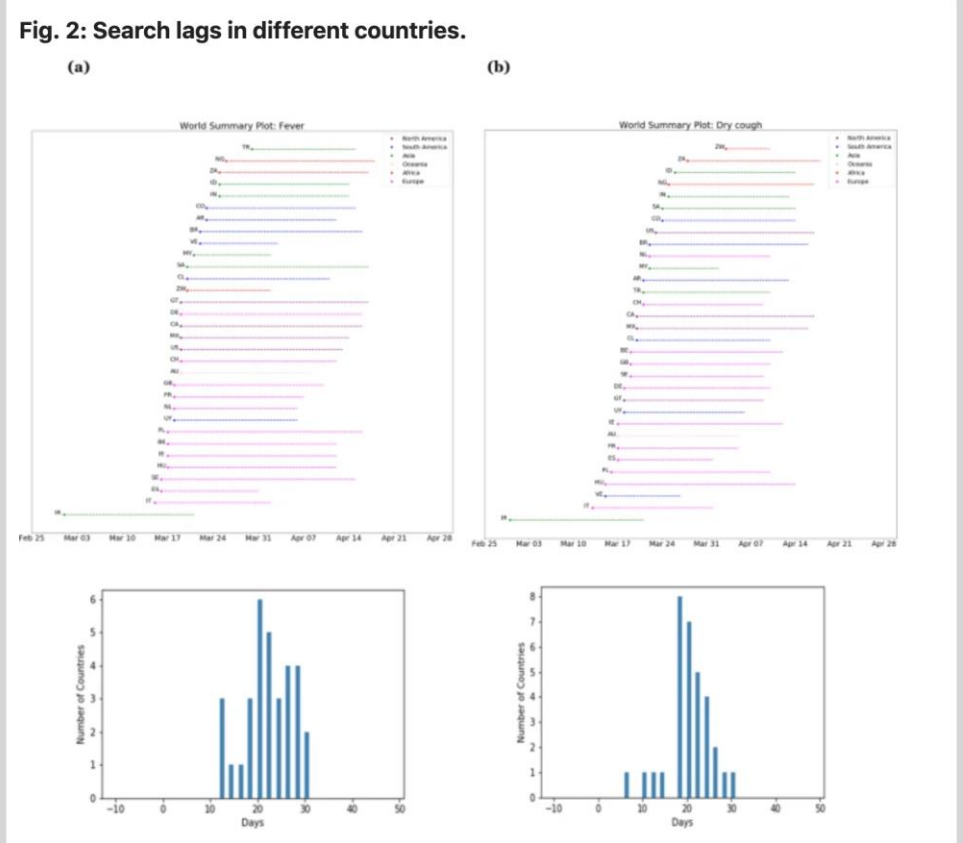

Figure 2. **a** Lags between searches for "fever" and reported COVID-19 deaths across 32 countries, with a histogram showing the distribution of these lags. Each country is labeled with its ISO Alpha-2 country code. **b** The same plots shown for searches for "dry cough".

QUANTIFYING THE TRANSMISSION ADVANTAGE ASSOCIATED WITH N501Y SUBSTITUTION OF SARS-COV-2 IN THE UNITED KINGDOM: AN EARLY DATA-DRIVEN ANALYSIS

Zhao S, Lou J, Cao L, Zheng H, Chong MKC, Chen Z, Chan RWY, Zee BCY, Chan PKS, Wang MH.. J Travel Med. 2021 Jan 28:taab011. doi: 10.1093/jtm/taab011. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

Physicians and microbiologists from the Chinese University of Hong Kong used SARS-CoV-2 sequencing data to compare the new N501Y mutation against the prior N501N variant. The authors reconstructed the variant-specified instantaneous reproduction number and estimated the proportion of 501Y variants (Figure 1). They found the new N501Y variant is 52% (95%CI:46,58) more transmissible than the N501N variant. They suggest the N501Y variant is more infectious than others, but due to limitations in surveillance data recommend further studies to fully understand the implications of the N501Y variant on clinical severity.

ABSTRACT

The emerging N501Y mutation in SARS-CoV-2, which becomes prevalent in the UK rapidly, is one of the major challenges of COVID-19 control. To explore the transmission advantage, we estimate that the N501Y substitution increases the infectivity by 52% (95%CI: 46, 58) in terms of the reproduction number.

FIGURES

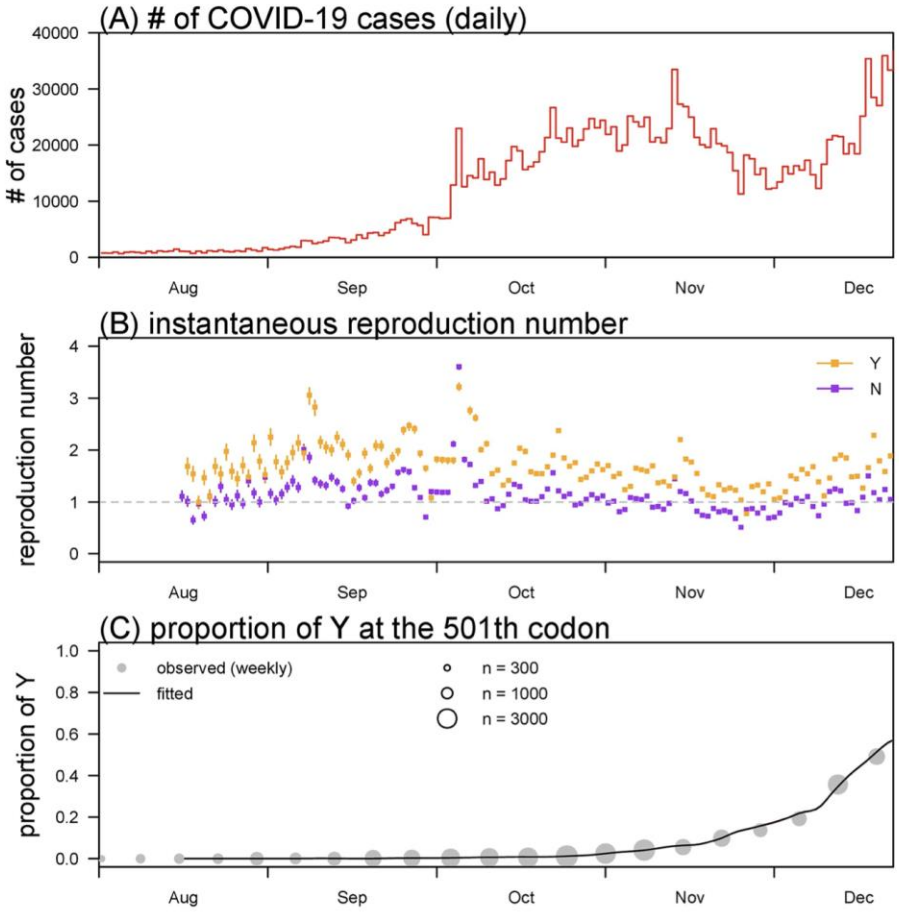

Figure 1. The daily number of COVID-19 cases (panel A), the reconstructed reproduction number (R_t, panel B) and proportion of the Y on the 501th codon of the S protein (panel C). Panel A shows the daily number of COVID-19 time series in the UK. Panel B shows the estimated reproduction numbers of Y (in orange) and N (in purple). The dots are the estimates, and bars are the 95% confidence intervals. Panel C shows the observed (dots) and fitted (curve) proportion of the Y on the 501th codon of the S protein

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

NOSOCOMIAL TRANSMISSION OF CORONAVIRUS DISEASE 2019: A RETROSPECTIVE STUDY OF 66 HOSPITAL-ACQUIRED CASES IN A LONDON TEACHING HOSPITAL

Rickman HM, Rampling T, Shaw K, Martinez-Garcia G, Hail L, Coen P, Shahmanesh M, Shin GY, Nastouli E, Houlihan CF.. Clin Infect Dis. 2021 Feb 16;72(4):690-693. doi: 10.1093/cid/ciaa816.
Level of Evidence: 4 - Local non-random sample

BLUF

A study conducted at multiple hospitals in London retrospectively analyzed 435 hospitalized COVID-19 patients in March-April 2020, finding that 15% of inpatient cases were hospital-acquired, with 55% occurring due to contact with a COVID-19-positive patient in the same bay, and a 36% case fatality rate (See Figure 1). These findings suggest a high incidence and mortality from nosocomial COVID-19 infection and emphasize need for personal protective equipment, infection prevention and control measures, and increasing hospital capacity to isolate the most vulnerable patients from suspected COVID-19 cases.

ABSTRACT

COVID-19 can cause deadly healthcare-associated outbreaks. In a major London teaching hospital, 66/435 (15%) of COVID-19 inpatient cases between 2 March and 12 April 2020 were definitely or probably hospital-acquired, through varied transmission routes. The case fatality was 36%. Nosocomial infection rates fell following comprehensive infection prevention and control measures.

FIGURES

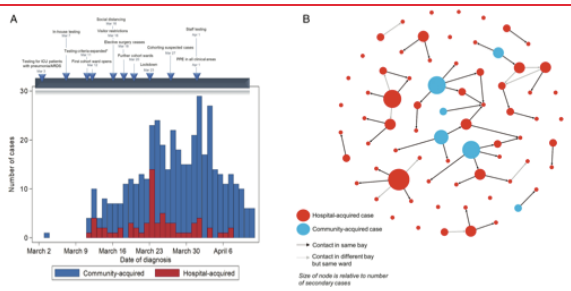

Figure 1a. Numbers of community- and hospital-acquired cases admitted to hospital between 2 March and 6 April 2020, with associated timetable of local and national infection prevention and control measures implemented during this time period. “Hospital-acquired” cases include definite and probable cases.
ICU: intensive care unit. ARDS: acute respiratory distress syndrome. PPE: personal-protective equipment.
*Testing criteria prior to 11th March required an epidemiological link with a case of COVID-19 or a high- risk country; following 11th March they were extended to all admitted patients with ARDS, influenza-like illness or pneumonia.
Figure 1b. Network representation of all definite and probable hospital-acquired cases (red), and community-acquired cases identified as potential index cases (blue) between 2 March and 6 April 2020. Black links represent a possible transmission within the same bay; grey links represent transmission in the same ward, with the earliest compatible case on the ward identified as the index case. Direction of arrow represents possible direction of transmission based on dates of symptom onset and the size of the node is proportionate to its number of identified possible secondary cases (out-degree).

PEDIATRICS

INFLAMMATORY SYNDROME IN CHILDREN ASSOCIATED WITH COVID-19 COMPLICATED BY ACUTE MYOCARDIAL INFARCTION

Reffo E, Stritoni V, Di Salvo G.. Eur Heart J. 2021 Feb 20:ehab077. doi: 10.1093/eurheartj/ehab077. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Pediatric intensivists and a pediatric cardiologist from University Hospital Padua in Italy present the case of a previously healthy 4-year-old child that presented with symptoms of an inflammatory syndrome (fever, conjunctivitis, and skin rash) and positive anti-SARS-CoV-2 IgG. Six days after admission, the child developed irritability and vomiting with ST-segment elevations and troponin of 2801 ng/L (see summary). Successful thrombolysis with alteplase, heparin, and aspirin was performed. The authors believe this is the first reported case of acute myocardial infarction in the context of SARS-CoV-2 associated pediatric multisystem inflammatory syndrome, and suggest providers are aware of this potential complication.

SUMMARY

The patient presented with:
- positive anti-SARS-CoV-2 IgG (108 U/mL)
- fever
- conjunctivitis
- skin rash
- elevated inflammatory markers (CRP 190 mg/L, neutrophilia 16.75 109/L)
- normal ECG
- echocardiogram showing "dilatation of the left descending coronary artery (Z score +3) with normal ventricular function (ejection fraction 57%)"

On day 6:
- ECG with ST-elevation
- troponin I of 2801 ng/L
- Echo showing "reduced left ventricular ejection fraction 35%, akinetic septum, and apex, a thrombus occluding a gigantic aneurysmally dilated left descending coronary artery"

COVID-19 INDUCES A HYPERACTIVE PHENOTYPE IN CIRCULATING PLATELETS

Comer SP, Cullivan S, Szklanna PB, Weiss L, Cullen S, Kelliher S, Smolenski A, Murphy C, Altaie H, Curran J, O'Reilly K, Cotter AG, Marsh B, Gaine S, Mallon P, McCullagh B, Moran N, Ní Áinle F, Kevane B, Maguire PB; COCOON Study investigators.. PLoS Biol. 2021 Feb 17;19(2):e3001109. doi: 10.1371/journal.pbio.3001109. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Molecular biologists and hematologists from University College Dublin, among others, evaluated platelet parameters in patients with severe (n=34) and non-severe (n=20) COVID-19 compared to 20 non-COVID-19 medical inpatients (see summary). They measured a "30 to 90 fold increased agonist-induced ADP release" (Figure 2) and significantly elevated hyperactive circulating PF4, sP-selection, and TPO levels (Figure 3) in severe COVID-19 patients compared to non-COVID-19 patients. Mean platelet volume and platelet-to-neutrophil ratio were associated with disease severity (Figure 1). Authors suggest platelet hyperactivity may contribute to hypercoagulability in COVID-19 and may contribute to disease severity.

SUMMARY

Authors defined disease severity as follows:
1. severe COVID-19 = "requiring critical care support" (n = 34)
2. nonsevere COVID-19 = "not requiring critical care" (n = 20)

ABSTRACT

Coronavirus Disease 2019 (COVID-19), caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has affected over 30 million globally to date. Although high rates of venous thromboembolism and evidence of COVID-19-induced endothelial dysfunction have been reported, the precise aetiology of the increased thrombotic risk associated with COVID-19 infection remains to be fully elucidated. Therefore, we assessed clinical platelet parameters and circulating platelet activity in patients with severe and nonsevere COVID-19. An assessment of clinical blood parameters in patients with severe COVID-19 disease (requiring intensive care), patients with nonsevere disease (not requiring intensive care), general medical in-patients without COVID-19, and healthy donors was undertaken. Platelet function and activity were also assessed by secretion and specific marker analysis. We demonstrated that routine clinical blood parameters including increased mean platelet volume (MPV) and decreased platelet:neutrophil ratio are associated with disease severity in COVID-19 upon hospitalisation and intensive care unit (ICU) admission. Strikingly, agonist-induced ADP release was 30- to 90-fold higher in COVID-19 patients compared with hospitalised controls and circulating levels of platelet factor 4 (PF4), soluble P-selectin (sP-selectin), and thrombopoietin (TPO) were also significantly elevated in COVID-19. This study shows that distinct differences exist in routine full blood count and other clinical laboratory parameters between patients with severe and nonsevere COVID-19. Moreover, we have determined all COVID-19 patients possess hyperactive circulating platelets. These data suggest abnormal platelet reactivity may contribute to hypercoagulability in COVID-19 and confirms the role that platelets/clotting has in determining the severity of the disease and the complexity of the recovery path.

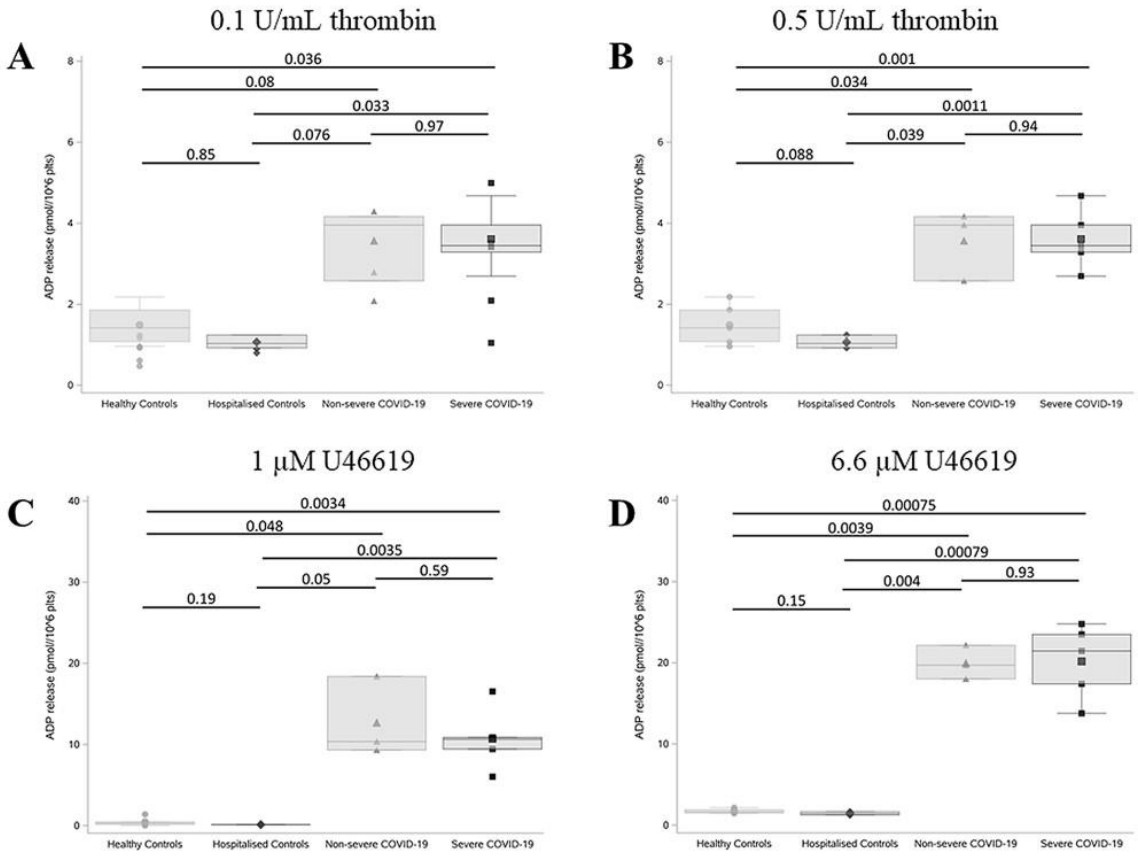

Figure 2. Agonist-induced ADP release was dramatically higher in COVID-19 patients compared with non-COVID-19 hospitalised patients. Platelet dense granule release was measured in duplicate in severe (n = 5) and nonsevere (n = 4) COVID-19 patients compared to hospitalised (n = 3) and healthy controls (n = 6). Platelets were stimulated with 0.1 U/ml thrombin (A), 0.5 U/ml thrombin (B), 1 μM U46619 (C), and 6.6 μM U46619 (D) and ATP release (surrogate for ADP) was measured using a Chronolume luciferase assay. ADP release is expressed as pmol/106 platelets. Boxplots represent the data median (line inside the box) and the IQR (outline of the box) together with data maximum and data minimum (whiskers) and individual observations (see individual data in S1 Data). Statistical analysis was performed using a two-tailed t test and p-values were adjusted for multiple comparisons using a Holm–Bonferroni post hoc test. COVID-19, Coronavirus Disease 2019; IQR, interquartile range. show less

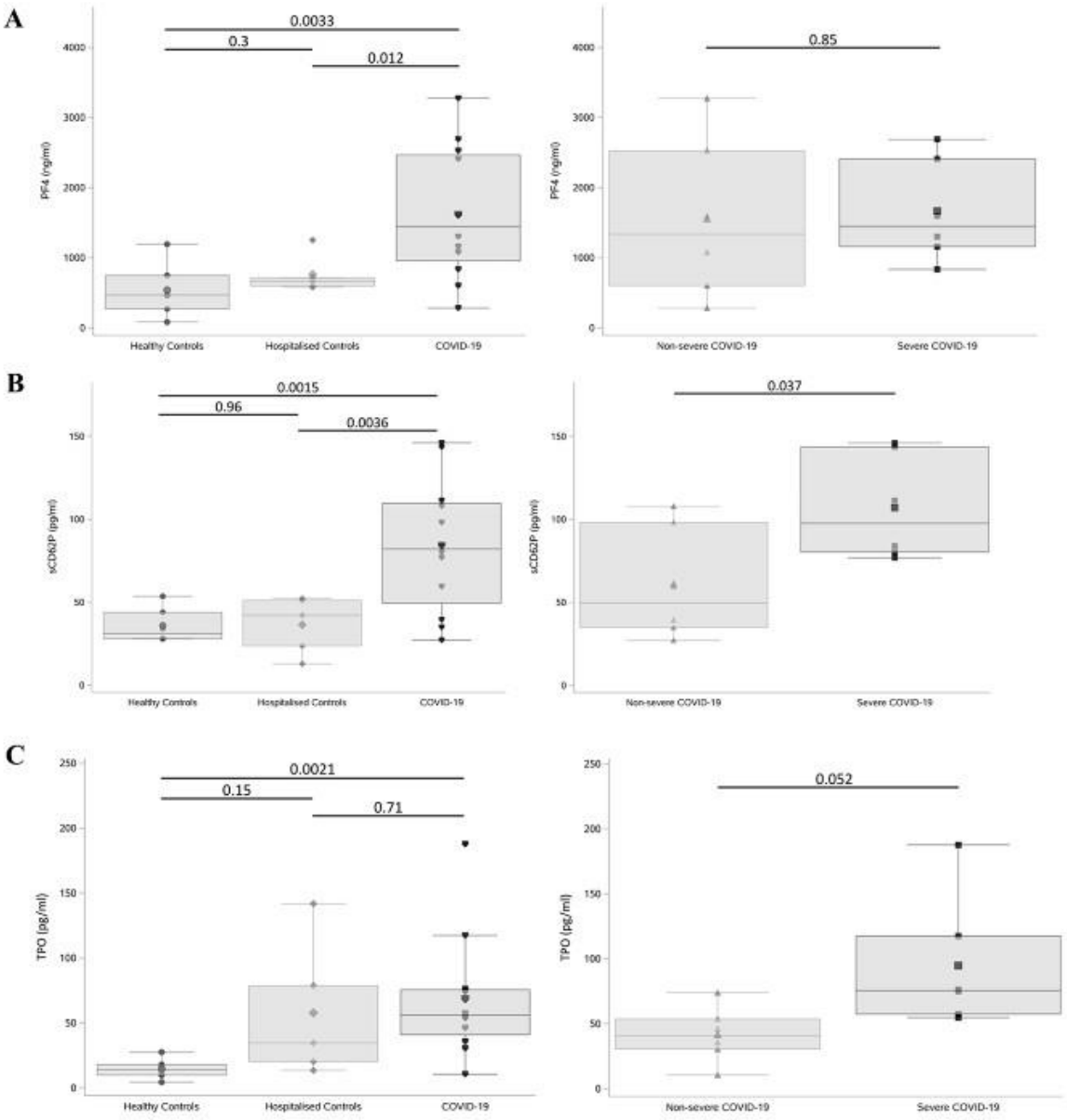

Fig 3. Circulating levels of PF4, sP-selectin levels, and TPO were significantly elevated in COVID-19. (A) PF4, (B) sP-selectin (sCD62P), and (C) TPO plasma levels from patients with severe (n = 6) and nonsevere (n = 6) COVID-19 compared to hospitalised (n = 6) and healthy (n = 6) controls were measured in triplicate by ELISA. Boxplots represent the data median (line inside the box) and the IQR (outline of the box) together with data maximum and data minimum (whiskers) and individual observations (see individual data in S1 Data). Statistical analysis was performed using a two-tailed t test, and p-values were adjusted for multiple comparisons using a Holm–Bonferroni post hoc test. COVID-19, Coronavirus Disease 2019; ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; PF4, platelet-factor 4; sP-selectin, soluble P-selectin; TPO, thrombopoietin.

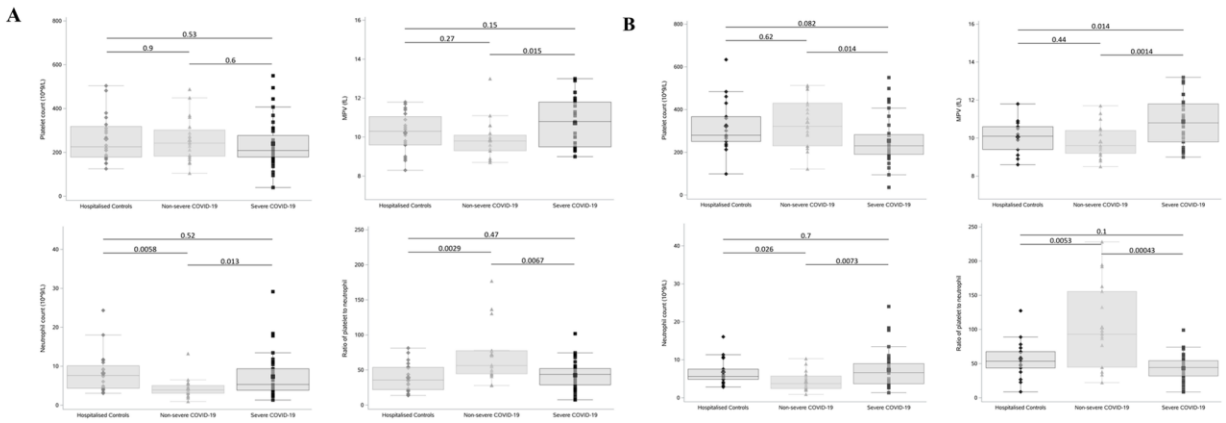

Fig 1. Routine clinical laboratory parameters are associated with disease severity in COVID-19.
Platelet counts, MPV, Neutrophil counts, and PNRs of patients with severe (n = 34) or nonsevere (n = 20) COVID-19 and hospitalised controls (n = 20). (A) On the day of admission, patients who subsequently developed severe COVID-19 had significantly higher MPV (p = 0.015) and neutrophil counts (p = 0.013) and significantly lower PNR (p = 0.0067) compared to those who did not subsequently develop severe COVID-19. (B) On day 7 of hospitalisation, nonsevere COVID-19 patients had a significantly higher platelet count compared to severe COVID-19 patients on the day of transfer to intensive care (p = 0.014). Boxplots represent the data median (line inside the box) and the IQR (outline of the box) together with data maximum and data minimum (whiskers) and individual observations (see individual data in S1 Data). Statistical analysis was performed using a two-tailed t test, and p-values were adjusted for multiple comparisons using a Holm–Bonferroni post hoc test. COVID-19, Coronavirus Disease 2019; IQR, interquartile range; MPV, mean platelet volume; PNR, platelet-to-neutrophil ratio.

A REVIEW OF PERSISTENT POST-COVID SYNDROME (PPCS)

Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S, Lybeck M, Reid TR.. Clin Rev Allergy Immunol. 2021 Feb 20. doi: 10.1007/s12016-021-08848-3. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A review article by physician researchers from various California institutions details the proposed mechanism of "persistent post-COVID syndrome" (PPCS) which affects patients recovering from severe COVID-19, including immune dysregulation driven by TGF-beta signaling leading to long-term fibrosis, suppressed immunity, and catabolism syndrome (Figure 2). The authors suggest tailored and specific care for PPCS patients (Table 2), stressing the importance for regular follow-up and treatment of co-morbid conditions.

ABSTRACT

Persistent post-COVID syndrome, also referred to as long COVID, is a pathologic entity, which involves persistent physical, medical, and cognitive sequelae following COVID-19, including persistent immunosuppression as well as pulmonary, cardiac, and vascular fibrosis. Pathologic fibrosis of organs and vasculature leads to increased mortality and severely worsened quality of life. Inhibiting transforming growth factor beta (TGF-beta), an immuno- and a fibrosis modulator, may attenuate these post-COVID sequelae. Current preclinical and clinical efforts are centered on the mechanisms and manifestations of COVID-19 and its presymptomatic and prodromal periods; by comparison, the postdrome, which occurs in the aftermath of COVID-19, which we refer to as persistent post-COVID-syndrome, has received little attention. Potential long-term effects from post-COVID syndrome will assume increasing importance as a surge of treated patients are discharged from the hospital, placing a burden on healthcare systems, patients' families, and society in general to care for these medically devastated COVID-19 survivors. This review explores underlying mechanisms and possible manifestations of persistent post-COVID syndrome, and presents a framework of strategies for the diagnosis and management of patients with suspected or confirmed persistent post-COVID syndrome.

FIGURES

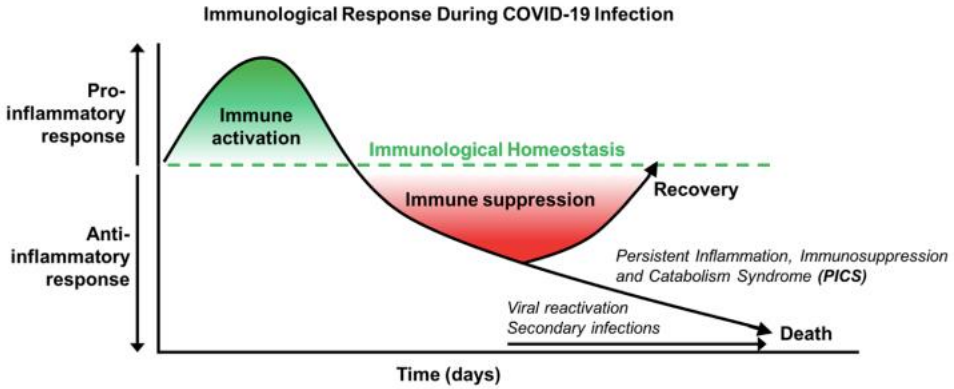

Figure 2. Simplified net immunological response in COVID-19 by analogy with sepsis. Immunologic response in COVID-19 over time: initially, the proinfammatory response predominates. Anti-infammatory cytokines are expressed to dampen the cytokine storm. With chronic immunosuppression, persistent infammation immunosuppression and catabolism syndrome (PICS) dominates. Early deaths may be caused by cytokine storm while later deaths, which occur during the anti-infammatory phase, may be caused by secondary infections.

Table 2 Recommendations for the management of patients with suspected or confirmed persistent post-COVID-19 syndrome (PPCS)

1. Physician examination of patient with mapping of current symptomatic status or medical concerns
2. Establish COVID-19 exposure status and potential disease history through oral history and possible clinical testing
3. Screen for possible non-COVID-19 co-morbidities or chronic medical conditions
4. Administer appropriate medical treatments for acute symptoms or established underlying chronic conditions
5. Educate patient in the possible manifestations of persistent post-COVID-19 also known as *long COVID-19* sequelae
6. Continue regular patient follow-up and encourage patient to seek medical care at onset of worsening symptoms

Table 2. Recommendations for the management of patients with suspected or confirmed persistent post-COVID-19 syndrome (PPCS).

PROSTATE ADENOCARCINOMA AND COVID-19: THE POSSIBLE IMPACTS OF TMPRSS2 EXPRESSIONS IN SUSCEPTIBILITY TO SARS-COV-2

Cheng J, Zhou J, Fu S, Fu J, Zhou B, Chen H, Fu J, Wei C.. J Cell Mol Med. 2021 Feb 20. doi: 10.1111/jcmm.16385. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Genetics and oncology experts from Southwest Medical University in China, among others, evaluated expression of the TMPRSS2, a cellular protease associated with both prostate adenocarcinoma (PRAD) and SARS-CoV-2 viral entry. After analysis of multiple international genetic databases, they found TMPRSS2 is expressed in many normal tissues (see summary) with increased expression in PRAD tissue (Figure 2). Functional analysis confirmed its involvement in SARS-CoV-2 viral entry, peptidase activity, and membrane structure. Authors suggest patients with PRAD may may be at increased risk for SARS-CoV-2 infection and that androgen-mediated treatments may provide protection for this group by decreasing the amount of susceptible tissue.

SUMMARY

Authors found TMPRSS2 is expressed in "small intestine, prostate, pancreas, salivary gland, colon, stomach, seminal vesicle and lung."

ABSTRACT

TMPRSS2 (OMIM: 602060) is a cellular protease involved in many physiological and pathological processes, and it facilitates entry of viruses such as SARS-CoV-2 into host cells. It is important to predict the prostate's susceptibility to SARS-CoV-2

infection in cancer patients and the disease outcome by assessing TMPRSS2 expression in cancer tissues. In this study, we conducted the expression profiles of the TMPRSS2 gene for COVID-19 in different normal tissues and PRAD (prostate adenocarcinoma) tumour tissues. TMPRSS2 is highly expressed in normal tissues including the small intestine, prostate, pancreas, salivary gland, colon, stomach, seminal vesicle and lung, and is increased in PRAD tissues, indicating that SARS-CoV-2 might attack not only the lungs and other normal organs, but also in PRAD cancer tissues. Hypomethylation of TMPRSS2 promoter may not be the mechanism for TMPRSS2 overexpression in PRAD tissues and PRAD pathogenesis. TMPRSS2 expresses eleven isoforms in PRAD tissues, with the TMPRSS2-001 isoform expressed highest and followed by TMPRSS2-201. Further isoform structures prediction showed that these two highly expressed isoforms have both SRCR_2 and Trypsin (Tryp_SPc) domains, which may be essential for TMPRSS2 functional roles for tumorigenesis and entry for SARS-CoV-2 in PRAD patients. Analyses of functional annotation and enrichment in TMPRSS2 showed that TMPRSS2 is mostly enriched in regulation of viral entry into host cells, protein processing and serine-type peptidase activity. TMPRSS2 is also associated with prostate gland cancer cell expression, different complex(es) formation, human influenza and carcinoma, pathways in prostate cancer, influenza A, and transcriptional misregulation in cancer. Altogether, even though high expression of TMPRSS2 may not be favourable for PRAD patient's survival, increased expression in these patients should play roles in susceptibility of the SARS-CoV-2 infection and clinical severity for COVID-19, highlighting the value of protective actions of PRAD cases by targeting or androgen-mediated therapeutic strategies in the COVID-19 pandemic.

FIGURES

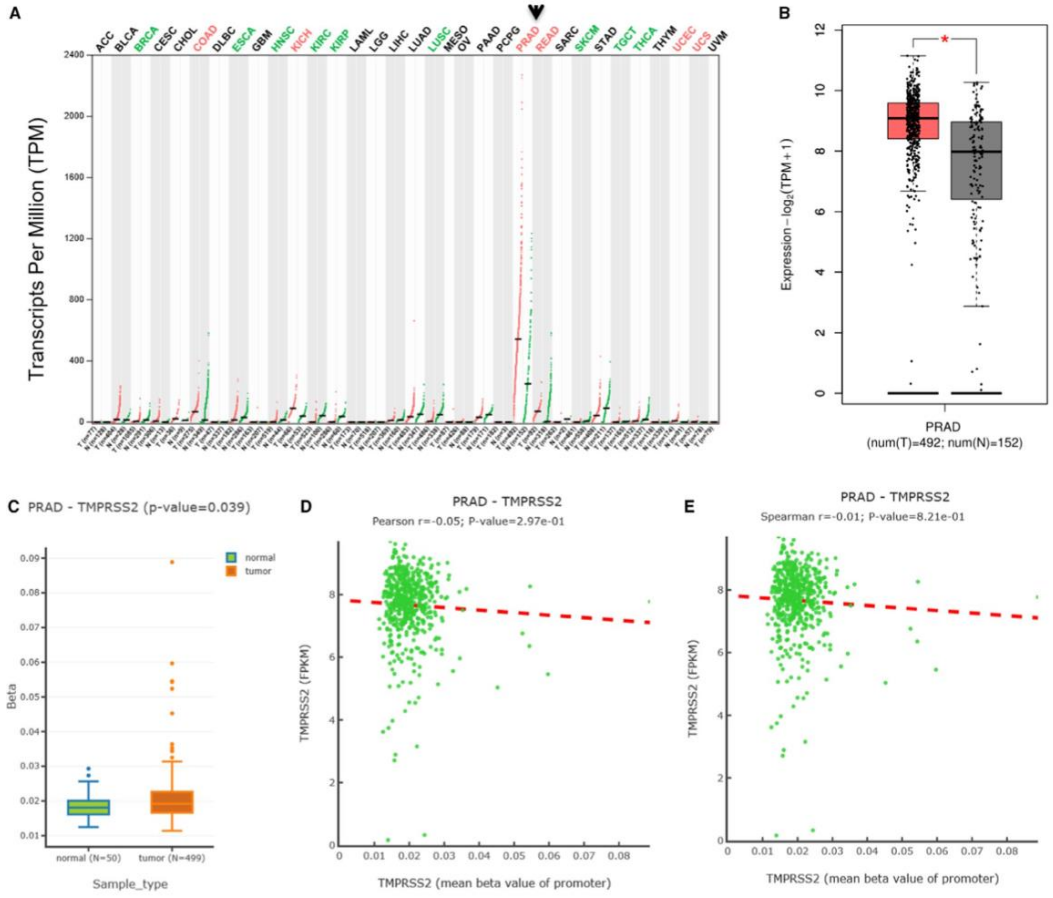

FIGURE 2 *TMPRSS2* expression and its promoter methylation status in tumour tissues of prostate adenocarcinoma (PRAD) and corresponding normal tissues. A, Expression profile for *TMPRSS2* in 32 different tumour tissues and their corresponding normal tissues (TCGA normal and GTEx data). Tissue-wise expression using profiles. B, Expression profile for *TMPRSS2* in PRAD tumour tissues and the corresponding normal tissues (TCGA normal and GTEx data) (*: $P < .01$). Tissue-wise expression using box plots. C, The promoter methylation status for the regulating *TMPRSS2* expression from PRAD. D, Pearson analysis for correlation between the mRNA expression and the methylation status for *TMPRSS2* from PRAD. E, Spearman analysis for correlation between the mRNA expression and the methylation status for the *TMPRSS2* gene from PRAD

SOCIAL DISTANCING ALTERS THE CLINICAL COURSE OF COVID-19 IN YOUNG ADULTS: A COMPARATIVE COHORT STUDY

Bielecki M, Züst R, Siegrist D, Meyerhofer D, Crameri GAG, Stanga Z, Stettbacher A, Buehrer TW, Deuel JW.. Clin Infect Dis. 2021 Feb 16;72(4):598-603. doi: 10.1093/cid/ciaa889.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

Physicians from the Swiss Armed Forces assessed the spread of COVID-19 illness among three companies of soldiers at a Swiss military base (n=508)(Table 1); company 1 had their own barracks while companies 2 and 3 shared barracks. A soldier in company 3 developed COVID-19 on March 11, 2020. On day 35 of the outbreak, authors tested 363 asymptomatic soldiers from all 3 groups and found evidence of past or current infection in 15% (13/88) of those from company 1, 64% in company 2, and 59% in company 3. Symptomatic infections were documented in 0% of company 1, 27% of company 2, and 31 % of company 3 (Figures 1, 2). Authors suggest the relative lack of COVID-19 illness in company 1 compared to 2 and 3 supports the effectiveness of social distancing and hygiene measures both in preventing disease spread and mitigating disease severity.

ABSTRACT

BACKGROUND: Social distancing and stringent hygiene seem effective in reducing the number of transmitted virus particles, and therefore the infectivity, of coronavirus disease 2019 (COVID-19) and could alter the mode of transmission of the disease. However, it is not known if such practices can change the clinical course in infected individuals. METHODS: We prospectively studied an outbreak of COVID-19 in Switzerland among a population of 508 predominantly male soldiers with a median age of 21 years. We followed the number of infections in two spatially separated cohorts with almost identical baseline characteristics with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before and after implementation of stringent social distancing. RESULTS: Of the 354 soldiers infected prior to the implementation of social distancing, 30% fell ill from COVID-19. While no soldier in a group of 154, in which infections appeared after implementation of social distancing, developed COVID-19 despite the detection of viral RNA in the nose and virus-specific antibodies within this group. CONCLUSIONS: Social distancing not only can slow the spread of SARS-CoV-2 in a cohort of young, healthy adults but can also prevent the outbreak of COVID-19 while still inducing an immune response and colonizing nasal passages. Viral inoculum during infection or mode of transmission may be key factors determining the clinical course of COVID-19.

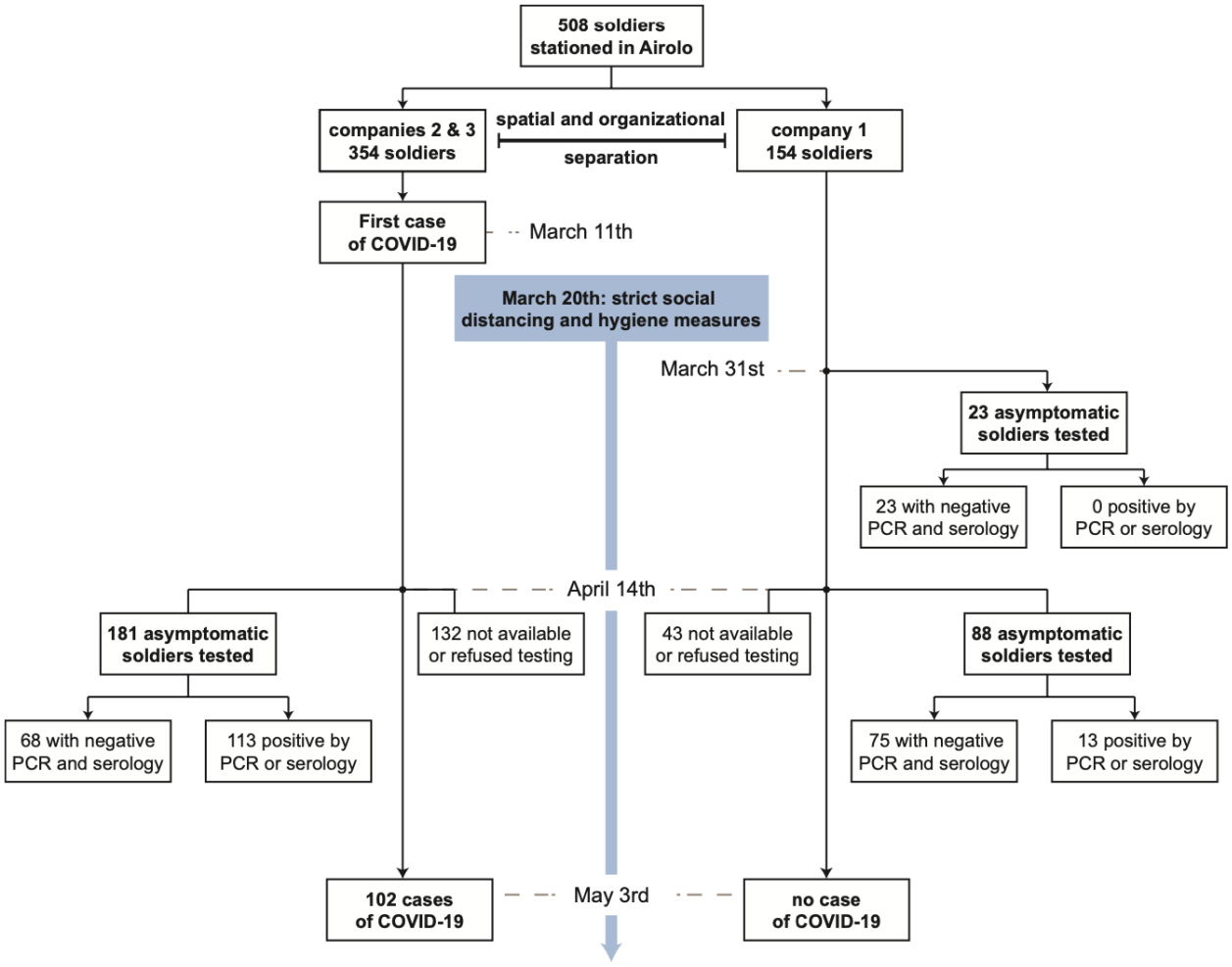

Figure 2. Flowchart of the study. A total of 354 soldiers of companies 2 and 3 were spatially and organizationally separated from 154 soldiers of company 1. On 11 March, the first case of COVID-19 was diagnosed in the left cohort; thus, infection in this group must have occurred prior to or on this date. On 20 March, strict social and hygiene measures were implemented in both cohorts. On 31 March, 23 asymptomatic soldiers from company 1 were tested, of whom all showed negative serology and PCR. On 14 April we conducted a cross-sectional testing on all soldiers who agreed to take part in our study. From company 1, 88 soldiers were tested; 13 were positive by PCR or by serology. Of 181 asymptomatic soldiers from companies 2 and 3, 113 were positive by either serology or PCR. We continued to follow up both cohorts for 19 more days; none of the tested soldiers developed COVID-19 during this time. While in companies 2 and 3 102 cases of COVID-19 were diagnosed, company 1 remained without cases. This finding infers a profound impact of social distancing and stringent hygiene measures on the outbreak of COVID-19 in an infected cohort. While companies 2 and 3 were infected prior to the enforcement of such methods, nearly one-third of all soldiers developed COVID-19 and a high level of seroconversion was observed; the cohort to the right was infected after 31 March and thus after the enforcement of social distancing and hygiene measures. Despite 15% asymptomatically infected soldiers in company 1 on 14 April, we did not observe a single case of COVID-19 in this cohort. This demonstrates that enforcing social distancing before infection can lead to milder clinical courses of COVID-19. Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction.

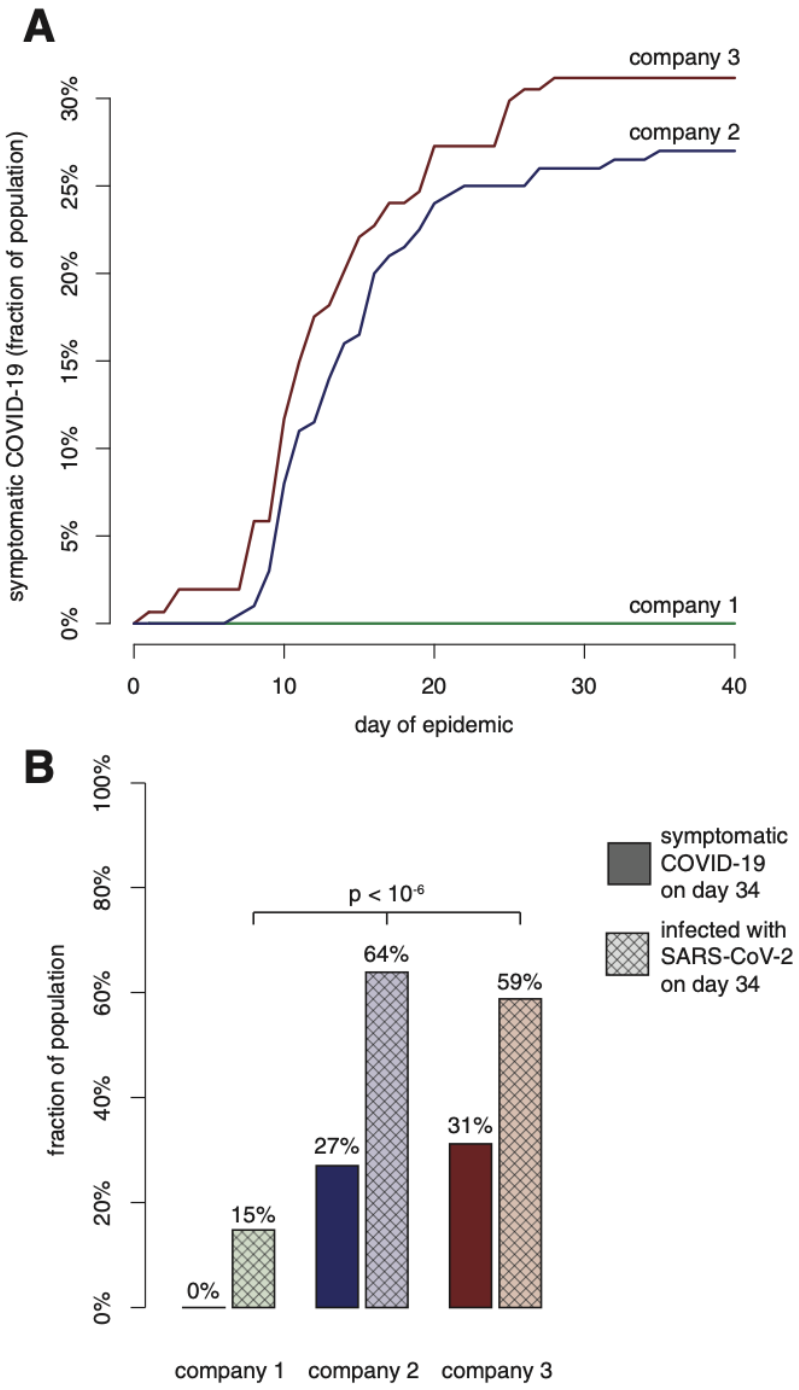

Figure 1. *A*, Epidemic curve of patients with COVID-19 as a fraction of the total population of the 3 companies. While company 1 (green), organizationally and spatially separated from the others, had no case of COVID-19, companies 2 (blue) and 3 (red) show a very similar course where one-third of the population were symptomatic for COVID-19. *B*, Symptomatic cases of COVID-19 and rate of infection among the 3 companies. The rate of infected persons was significantly smaller in company 1 than in the other companies (Fisher's exact test) and was determined on day 34 by combined nasopharyngeal swab and serological testing; a person was considered infected if either returned a positive result. The fraction of symptomatic patients among the infected was significantly larger in companies 2 and 3 than in company 1 ($P = .02$). Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Baseline Characteristics of the Study Population on 31 March 2020

	Company 1	Company 2	Company 3	Others	All
Soldiers, n	154	200	154	76	584
Males, n (%)	154 (100)	174 (87)	138 (90)	60 (79)	526 (90)
Age, years	20.4 (18–27)	20.4 (18–28)	21.0 (18–27)	20.6 (19–54)	20.6 (18–54)
COVID-19,[a] n (%)	0 (0)	54 (27)	48 (31)	4 (5.3)	107 (18)
Exposed to SARS-CoV-2,[b] n/N (%)	13/88 (15)	83/130 (64)	30/51 (59)	22/57 (39)	148/326 (45)
Date of first exposure to SARS-CoV-2	Between 31 March and 14 April	Before 18 March	Before 11 March	Variable	…
COVID-19	Not affected	Affected		…	…

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

[a]Symptomatic patients between 11 March and 3 May 2020.

[b]On 14 April, by positive serology test for immunoglobulin A, G, or M or detection of SARS-CoV-2 in nasopharyngeal swabs.

CAN COVID VACCINES STOP TRANSMISSION? SCIENTISTS RACE TO FIND ANSWERS

Mallapaty S.. Nature. 2021 Feb 19. doi: 10.1038/d41586-021-00450-z. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

A journalist writing for Nature discusses current efforts to delineate whether current COVID-19 vaccines can prevent transmission of SARS-CoV-2. The author notes that while initial research is promising in showing a decline in the number of asymptomatic-carriers post-vaccination and decreased viral loads (see summary), more research needs to be conducted to assess the true efficacy of vaccines and their ability to prevent disease transmission.

SUMMARY

Preliminary analyses suggest some vaccines have a transmission blocking effect; however, this effect cannot with certainty be determined to be due to the vaccine or other efforts such as quarantine or social distancing:
- The Moderna vaccine has shown a 2/3 decrease in the number of asymptomatic carriers after the primary vaccine dose, however, these patients were only tested twice
- TheAstraZeneca vaccine showed an approximate 50% reduction in asymptomatic infections
- Research has shown that there was a drop in viral load after the first Pfizer vaccine dose, which may translate into less ability to spread infection

To really assess the ability of the vaccine to cut down on transmission, researchers are now studying close-contacts of those vaccinated via the PANTHER program. There are similar close-contact monitoring studies of vaccinated individuals in the works in Israel and Brazil.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

ANALYSIS OF ASYMPTOMATIC AND PRESYMPTOMATIC TRANSMISSION IN SARS-COV-2 OUTBREAK, GERMANY, 2020

Bender JK, Brandl M, Höhle M, Buchholz U, Zeitlmann N.. Emerg Infect Dis. 2021 Feb 18;27(4). doi: 10.3201/eid2704.204576. Online ahead of print.
Level of Evidence: 4 - Local non-random sample

BLUF

A case study conducted at the Robert Koch Institute during early 2020 by the European Centre for Disease Prevention and Control found that, when contact tracing 59 patients clustered from one patient's exposure, pre-symptomatic transmission occurred more frequently than symptomatic transmission (Table 2). This suggests early detection of COVID-19 cases and prompt initiation of contact tracing may reduce high transmission.

SUMMARY

- From the period of February 29, 2020, to the end of March, 2020, the researchers analyzed the cluster of 59 cases as confirmed by the local public health authority.

- The retrospective cohort study classified patients as asymptomatic, symptomatic, and further based on contact exposure in the pre-symptomatic or symptomatic phase.

- The notable 75% transmission in the cohort from the pre-symptomatic patients may be explained by the peak infectiousness around the date of symptom onset, but is notably higher than other studies.

- An important limitation of the study is that, the nature of the study is not generalizable, with the study occurring during the winter timeframe, as well as underestimation and omission of non-applicable cases.

ABSTRACT

We determined secondary attack rates (SAR) among close contacts of 59 asymptomatic and symptomatic coronavirus disease case-patients by presymptomatic and symptomatic exposure. We observed no transmission from asymptomatic case-patients and highest SAR through presymptomatic exposure. Rapid quarantine of close contacts with or without symptoms is needed to prevent presymptomatic transmission.

FIGURES

Clinical symptoms of source case	No. contacts tested positive or experienced respiratory symptoms	Total no. contacts	SAR, %	RR (95% CI)
Household contacts SAR_{lab}				
Asymptomatic	0	4	0	Reference
Symptomatic, phase not specified or both†	4	28	14.3	0.8 (0.09–∞)
Total	4	32	12.5	
Household contacts SAR_{res}				
Asymptomatic	0	7	0	Reference
Symptomatic, phase not specified or both	12	35	34.3	3.4 (0.56–∞)
Total	12	42	28.6	
Other contacts SAR_{lab}				
Asymptomatic cases	0	22	0	Reference
Symptomatic, phase not specified or both	3	25	12.0	3.4 (0.36–∞)
Symptomatic, presymptomatic phase only	15	72	20.8	6.5 (1.1–∞)
Symptomatic, symptomatic phase only	2	29	6.9	1.8 (0.14–∞)
Total	20	148	13.5	
Other contacts SAR_{res}				
Asymptomatic cases	2	52	3.8	Reference
Symptomatic, phase not specified or both	4	22	18.2	4.7 (0.68–52)
Symptomatic, presymptomatic phase only	22	67	32.8	8.5 (2.1–75)
Symptomatic, symptomatic phase only	1	29	3.5	0.90 (0.02–17)
Total	29	170	17.1	

Table 2. Secondary attack rates among contacts of coronavirus disease case-patients in a district in southern Germany

PROMOTING VERSATILE VACCINE DEVELOPMENT FOR EMERGING PANDEMICS

Monrad JT, Sandbrink JB, Cherian NG.. NPJ Vaccines. 2021 Feb 11;6(1):26. doi: 10.1038/s41541-021-00290-y.
Level of Evidence: 5 - Expert Opinion

BLUF

An international group of researchers discuss strategies for optimizing future vaccine development. These strategies include a more flexible vaccine platform that would allow for increased vaccine research on "prototype pathogens" that could be applied to future emerging infectious diseases, thus increasing pandemic preparedness. They also discuss how both national and private institutions could cooperate to enhance global health security and create a more efficient system for understanding and responding to novel pathogens, potentially providing large-scale economic benefits.

ABSTRACT

The ongoing COVID-19 pandemic has demonstrated the importance of rapid and versatile development of emergency medical countermeasures such as vaccines. We discuss the role of platform vaccines and prototype pathogen research in modern vaccine development, and outline how previous pathogen-specific funding approaches can be improved to adequately promote vaccine R&D for emerging pandemics. We present a more comprehensive approach to financing vaccine R&D, which maximises biomedical pandemic preparedness by promoting flexible vaccine platforms and translatable research into prototype pathogens. As the numerous platform-based SARS-CoV-2 vaccines show, funders can accelerate pandemic vaccine development by proactively investing in versatile platform technologies. For certain emerging infectious diseases, where vaccine research can translate to other related pathogens with pandemic potential, investment decisions should reflect the full social value of increasing overall preparedness, rather than just the value of bringing a vaccine to market for individual pathogens.

DERMATOLOGY

RAPIDLY PROGRESSIVE ALOPECIA AREATA TOTALIS IN A COVID-19 PATIENT, UNRESPONSIVE TO TOFACITINIB

Ferreira SB, Dias MFRG, Berbert Ferreira R, Neves Neto AC, Trüeb RM, Lupi O.. J Eur Acad Dermatol Venereol. 2021 Feb 15. doi: 10.1111/jdv.17170. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

This letter to the editor from Maringá, Brazil describes a 24-year-old female being treated for alopecia areata totalis (Figure 1) with tofacitinib, an oral JAK 1/3 inhibitor of IL-2, IL-7 and L-6, who discontinued use following SARS-CoV-2 infection and subsequently experienced severe anagen effluvium unresponsive to tofacitinib despite 3 months of reinitiating therapy (Figure 2). The authors hypothesize that SARS-CoV-2 infection may trigger inflammation and hair follicle cell death via direct viral insult in a mechanism of action similar to that of Dengue virus and suggest careful consideration before discontinuing long-term immunosuppressants in COVID-19 patients.

FIGURES

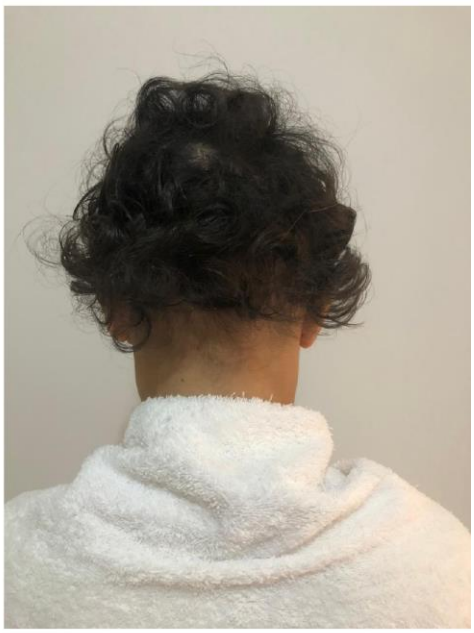

Figure 1. Patient, before the pandemic, with a full-grown hair and no signs of disease activity, using tofacitinib 5mg BID.

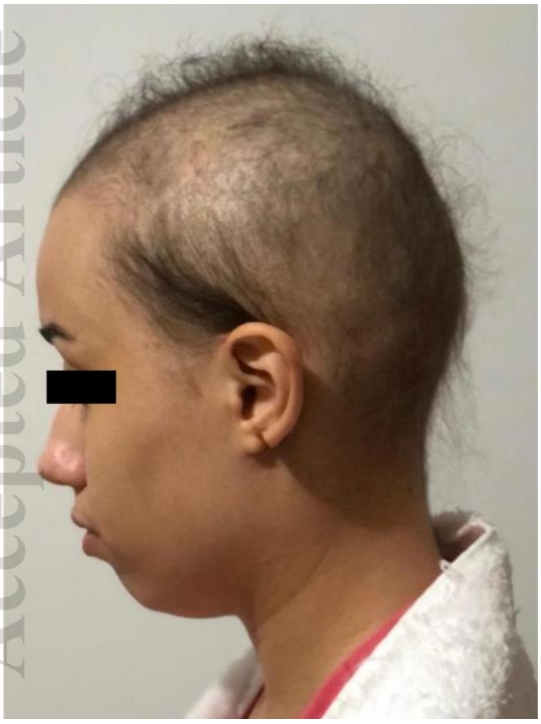

Figure 2. Active alopecia areata 90 days after reintroduction of tofacitinib 5mg BID. Dermoscopy shows exclamation mark hairs, black and yellow dots.

SURGICAL SUBSPECIALTIES

NEUROSURGERY

CSF LEAK AFTER COVID-19 NASOPHARYNGEAL SWAB: A CASE REPORT

Paquin R, Ryan L, Vale FL, Rutkowski M, Byrd JK.. Laryngoscope. 2021 Feb 12. doi: 10.1002/lary.29462. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

A case report from the Medical College of Georgia presents a 38-year-old female with traumatic cerebral spinal fluid (CSF) leak after receiving a nasopharyngeal swab for COVID-19 testing. Imaging revealed a traumatic encephalocele at the cribriform and ethmoid roof junction (Figure 2), which was treated with surgical skull base repair (Figure 3) and resolution of all symptoms after 9 days. The authors found this to be the second case of iatrogenic CSF leak in the literature following nasopharyngeal swabbing and urge increased education and training for healthcare professionals on swabbing techniques. They also suggest patients with known skull base abnormalities may warrant alternative testing.

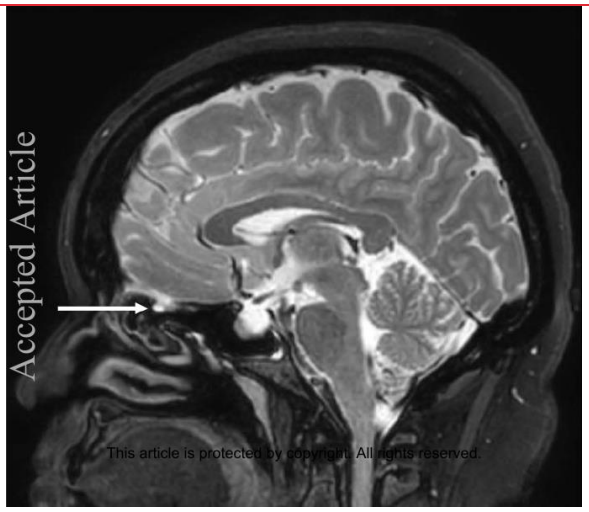

Figure 2. T2 weighted MRI brain in sagittal plane demonstrating encephalocele projecting from the right olfactory fossa (arrow)

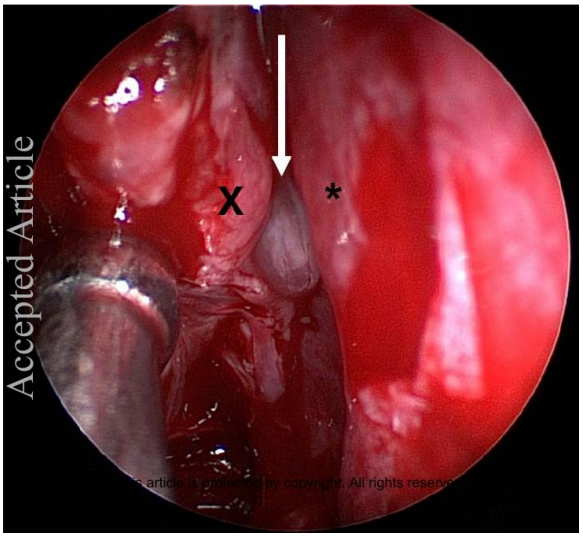

Figure 3. Intraoperative endoscopic view of right nasal cavity with the encephalocele visualized between the cribriform and ethmoid roof (arrow) protruding between the nasal septum (*) and remnant middle turbinate (x)

ENDOCRINOLOGY

MANAGEMENT OF HYPONATRAEMIA AND HYPERNATRAEMIA DURING THE COVID-19 PANDEMIC: A CONSENSUS STATEMENT OF THE SPANISH SOCIETY FOR ENDOCRINOLOGY (ACQUA NEUROENDOCRINOLOGY GROUP)

Fernandez Martinez A, Barajas Galindo D, Ruiz Sanchez J.. Rev Endocr Metab Disord. 2021 Feb 5. doi: 10.1007/s11154-021-09627-3. Online ahead of print.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

A literature review conducted at Hospital Uniervistario de Mostoles during early 2021 by the Acqua Neuroendocrinology Group found that COVID-19 patients with dysnatremia from metabolic disorders are at higher risk for poor outcomes such as mortality or sepsis. This study suggests that the expert-based recommendations summarized below should be followed to enhance clinical outcomes.

SUMMARY

- Patients with disorders of water homeostasis, including Diabetes Insipidus (DI), or syndrome of inappropriate anti-diuretic hormone (SIADH) secretion, can have exacerbated symptoms when infected with COVID-19.

- While patients with DI or SIADH require careful treatment and follow-up appointments to enhance long-term outcomes, reducing clinical attendance protects the patients from risk of infection.

- The Neuroendocrinology Group of the Spanish Society for Endocrinology (SEEN) used evidence-based literature to provide specific recommendations to manage water balance disorders in patients with COVID-19 infections.

- For patients with chronic DI, and no infection, patients should receive follow-up in accordance with typical clinical guidelines, with lab tests and through telemedicine

- In patients with chronic DI and mild to moderate COVID-19, patients should receive one blood and urine test, and be admitted to hospitals if noted for significant changes in plasma sodium levels, new-onset impairment of mental functioning and loss of thirst.

- In patients with chronic DI and severe COVID-19 infections, it is highly recommended to monitor plasma and urine electrolytes daily, especially screening for hyperglycemia in the event that patients also have hypopituitarism.

- It is essential to treat and identify hyponatremia in COVID-19 patients, using electrolyte labs, and continuing to give water, while keeping important treatment interactions between hyponatremia and SARS-CoV-2 pharmacotherapy in mind (Table 1)

- In the case of hypernatremia, it is recommended to follow typical treatment recommendations: prevent thrombosis, measure plasma and urine sodium daily, and reduce high sodium levels to reduce the risk for cerebral edema.

ABSTRACT

SARS-COV2 infection has swiftly become a pandemic disease of historic relevance and widely variable outcomes. This variable prognosis is related both to uneven damage, among others, to lungs, heart and kidneys, and to a multisystemic inflammatory reaction. All these factors are known to disrupt water balance and potentially induce hyponatraemia or hypernatraemia. Water balance disorders are known mortality and morbidity risk factors in several clinical scenarios and their proper management, though often complex and hazardous, can reduce mortality and length of hospitalization. Clinical uncertainty over COVID-19 outcome, the variety of organs involved in both the infection and water balance and difficulties in clinical

examination due to risk of contagion might obstruct proper management of dysnatremic disorders. Thus, the Acqua Neuroendocrinology Group of the Spanish Society for Endocrinology (SEEN) has endeavoured to provide evidence and expert based recommendations on the management of hyponatraemia and hypernatraemia in COVID-19 patients.

FIGURES

Table 1 Pharmacological interactions between COVID-19 and hyponatraemia pharmacotherapy [28, 29, 33]

Hyponatraemia drug	Lopinavir/ritonavir	Tocilizumab	Remdesivir	Hydroxychloroquine	Dexamethasone
Tolvaptan	↑Tolvaptan concentrations (CYP3A4 inhibition)	↓Tolvaptan concentrations (CYP3A4 activation)	↑Tolvaptan concentrations (CYP3A4 inhibition)	None	None
Urea	No clinical experience published in COVID-19				
Furosemide	–	–	–	–	Corticosteroids may ↑hypokalemia

DURATION OF CULTURABLE SARS-COV-2 IN HOSPITALIZED PATIENTS WITH COVID-19

Kim MC, Cui C, Shin KR, Bae JY, Kweon OJ, Lee MK, Choi SH, Jung SY, Park MS, Chung JW.. N Engl J Med. 2021 Feb 18;384(7):671-673. doi: 10.1056/NEJMc2027040. Epub 2021 Jan 27.
Level of Evidence: 4 - Case-series

BLUF

Researchers from multiple South Korean institutions describe a case series investigating viral shedding by analyzing serial respiratory cultures in 21 hospitalized patients with mild-to-moderate COVID-19 between February and June 2020. Findings include a median time from symptom onset to viral clearance of 7 days in culture (95% CI, 5-10 days) and 34 days on real-time PCR (95% CI lower boundary 24 days) (See Figure S1), with viable virus identified until 3 days after fever resolution. Viral load and cycle-threshold values below 28.4 were positively correlated (See Table S3 and Figure 1), and the incidence of culture positivity decreased with greater time from onset of symptoms. These findings can be used to guide isolation periods and risk estimation of secondary transmission in COVID-19 patients, but further research with a larger and more diverse patient population can allow for better extrapolation.

FIGURES

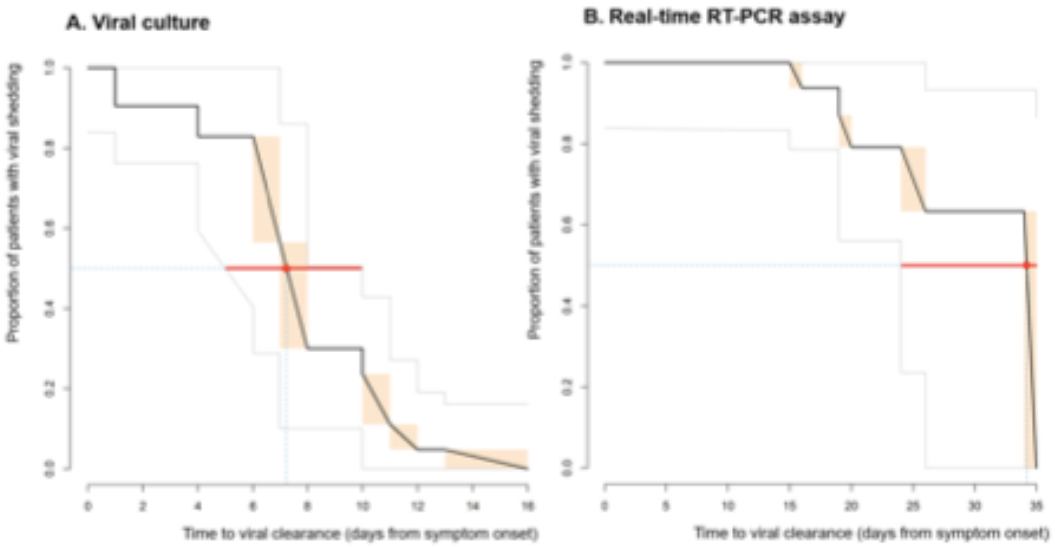

Figure S1. Estimates of the time to viral clearance. The nonparametric maximum-likelihood estimation of the proportion of patients with SARS-CoV-2 shedding in 21 patients hospitalized with COVID-19 in viral culture (Panel A) and real-time reverse transcriptase- polymerase chain reaction (RT-PCR) assay (Panel B) are shown. The orange rectangles represent proportions of patients with the corresponding intervals censored for viral clearance. The gray lines represent the 95% confidence interval (CI) of the fitted distributions. The 95% CI of the time to viral clearance (the red point) for the 50th percentile of the patients is indicated by the red horizontal line. From the date of symptom onset, culture clearance occurred by 7 days (95% CI, 5-10 days) and real-time RT-PCR clearance occurred by 34 days (the lower limit of the 95% CI was 24 days, but the upper limit of the 95% CI was not computable) in 50% of the patients.

Variables	Number of tested real-time RT-PCR assay	Number of positive viral culture / number of tested viral culture	Culture positivity rates (%)
Time from symptom onset			
≤ 4 days	21	14/21	67
5-8 days	23	8/20	40
9-12 days	34	7/31	23
13-16 days	34	0/13	0
17-20 days	22	0/4	0
> 20 days	31	0/0	NA
Cycle-threshold value for the N gene of SARS-CoV-2			
≤ 22	11	11/11	100
> 22 and ≤ 24	9	7/	78
> 24 and ≤ 26	6	4/6	67
> 26 and ≤ 28	11	5/11	46
> 28 and ≤ 30	16	2/14	14
> 30 and ≤ 32	14	0/13	0
> 32 and ≤ 34	12	0/7	0
> 34	86	0/18	0
Total	165	29/89	33

Table S3. Culture positivity rates of viable SARS-CoV-2 according to time from symptom onset and cycle-threshold value

Abbreviations: RT-PCR = reverse transcriptase-polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

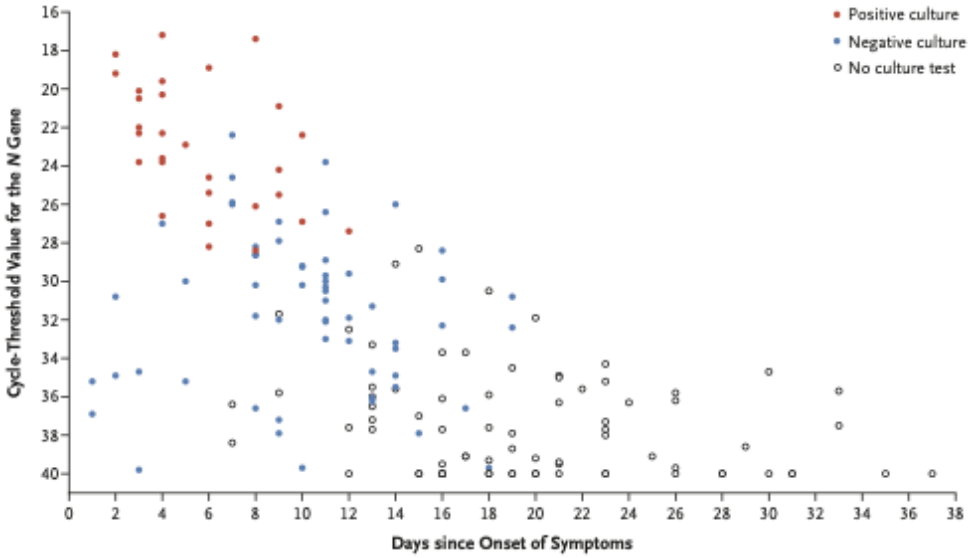

Figure 1. Timing of Presence or Absence of Viable SARS-CoV-2 on Viral Culture and Cycle-Threshold Values for 165 Serial Samples Obtained from 21 Consecutive Patients Hospitalized with Covid-19.
Viral loads were determined with the cycle-threshold value for the N gene of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).4 Sampling intervals ranged from 1 to 5 days (median, 2). Each circle represents a sample obtained on the specified day. Viral culture was positive only in samples with a cycle-threshold value of 28.4 or less and in those that were obtained as long as 12 days after symptom onset. Covid-19 denotes coronavirus disease 2019.

LOW DIAPHRAGM MUSCLE MASS PREDICTS ADVERSE OUTCOME IN PATIENTS HOSPITALIZED FOR COVID-19 PNEUMONIA: AN EXPLORATORY PILOT STUDY

Corradi F, Isirdi A, Malacarne P, Santori G, Barbieri G, Romei C, Bove T, Vetrugno L, Falcone M, Bertini P, Guarracino F, Landoni G, Forfori F; and the UCARE (Ultrasound in Critical care and Anesthesia Research Group).. Minerva Anestesiol. 2021 Feb 17. doi: 10.23736/S0375-9393.21.15129-6. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

A comparative pilot study conducted at the University of Pisa from March 5 through 30, 2020 by the Department of Surgical, Medical, Molecular Pathology and Critical Care Medicine found that, upon measurements of 77 patients admitted to hospitals with confirmed COVID-19 infections, patients with adverse outcomes had thinner diaphragms compared to those with non-adverse outcomes (2.0 vs. 2.2 mm, P=0.001; Table 1). This study suggests that respiratory failure risk should be evaluated with an assessment that includes diaphragmatic thickness and diaphragmatic ultrasound.

SUMMARY

- In addition to findings of the thinner diaphragm, additional strong predictors of adverse outcomes included elevated lymphocyte counts, and end-expiratory decreased pressure. (Table 1).

-End-expiratory diaphragmatic thickness was the strongest predictor of adverse outcomes (P=0.018;Table 1).

ABSTRACT

BACKGROUND: The aim of this study was to evaluate whether measurement of diaphragm thickness (DT) by ultrasonography may be a clinically useful noninvasive method for identifying patients at risk of adverse outcomes defined as need of invasive mechanical ventilation or death. METHODS: We prospectively enrolled 77 patients with laboratory-confirmed Covid-19 infection admitted to our intermediate care unit in Pisa between March 5 and March 30, 2020, with follow up until hospital discharge or death. Logistic regression was used identify variables potentially associated with adverse outcomes and those P <0.10 were entered into a multivariate logistic regression model. Cumulative probability for lack of adverse outcomes in patients with or without low baseline diaphragm muscle mass was calculated with the Kaplan-Meier product-limit estimator. RESULTS: The main findings of this study are that 1) patients who developed adverse outcomes had thinner diaphragm than those who did not (2.0 vs. 2.2 mm, P=0.001), 2) DT and lymphocyte count were independent significant predictors of adverse outcomes, with end-expiratory DT being the strongest (ss=-708; OR=0.492; P=0.018). CONCLUSIONS: Diaphragmatic ultrasound may be a valid tool to evaluate the risk of respiratory failure. Evaluating the need of mechanical ventilation treatment should be based not only on PaO2/FiO2, but on a more comprehensive assessment including DT because if the lungs become less compliant a thinner diaphragm, albeit free of intrinsic abnormality, may become exhausted, thus contributing to severe respiratory failure.

FIGURES

Table 1. Clinical characteristics, laboratory data and imaging findings at hospital admission.

Characteristics	All patients (n = 77)	Alive (n = 62)	Dead or intubated (n = 15)	P
Age (years)	59 (51-77)	58 (49-69)	78 (59-82)	0.002
Male sex	51 (66)	40 (65)	11 (73)	0.762
Length of symptoms before admission (days)	6 (2-10)	7 (4-10)	2 (0-4)	0.004
Vital signs				
Temperature (°C)	38 (37.8-38.3)	38 (37.8-38.1)	38 (37.7-38.5)	0.733
Heart rate (bpm)	85 (75-97)	83 (74-95)	97 (76-100)	0.101
Respiratory rate	20 (18-26)	20 (18-25)	22 (18-26)	0.495
Systolic blood pressure (mmHg)	137 (120-148)	136 (123-148)	140 (120-148)	0.882
Diastolic blood pressure (mmHg)	80 (70-90)	80 (71-90)	90 (70-92)	0.587
PaO_2/FiO_2 ratio	290 (233-300)	300 (253-300)	250 (200-300)	0.038
Laboratory Data				
White-cell (x 10^9/L)	6.11 (4.65-7.92)	6.02 (4.56-8.24)	6.97 (4.75-7.58)	0.912
Lymphocyte (x 10^9/L)	1.06 (0.69-1.33)	1.10 (0.70-1.36)	0.85 (0.54-1.17)	0.037
Aspartate aminotransferase (U/L)	32 (26-43)	32 (26-42)	32 (24-90)	0.830
Alanine aminotransferase (U/L)	27 (20-49)	30 (21-49)	21 (14-50)	0.163
Serum creatinine (mg/dL)	1.02 (0.88-1.24)	1.00 (0.86-1.13)	1.24(1-2.57)	0.022
Troponin (ng/L)	10 (6-24)	9 (6-17)	36 (21-86)	0.001
Platelet count (10^3/mcL)	165 (132-200)	166 (139-201)	163 (125-201)	0.553
Bilirubin level (mg/dL)	0.54 (0.38-0.89)	0.54 (0.38-0.93)	0.63 (0.38-0.71)	0.983
Creatine kinase level (U/L)	115 (55-230)	111 (50-236)	120 (55-360)	0.984
Arterial lactate (mg/dL)	1.2 (0.9-2.4)	0.9 (0.8-2.4)	1.85 (1-3.3)	0.230
Procalcitonin (ng/mL)	0.09 (0.06-0.21)	0.08 (0.06-0.19)	0.1 (0.09-0.54)	0.206
C reactive protein (mg/L)	4.19 (2.12-6.65)	4.3 (2.4-10.8)	5.95 (2.65-9.42)	0.341
D-Dimer (mg/L)	0.57 (0.23-0.99)	0.49 (0.22-0.95	0.79 (0.58-0.79)	0.476
Quantitative CT				
Mean lung density (HU)	-772 (-822 / -709)	-775 (-833 / -725)	-715 (-812/-660)	0.173
Lung weight (grams)	957 (829-1159)	957 (828-1159)	958 (872-1329)	0.682
Diaphragmatic US				
End-expiratory DT (mm)	2.2 (2.0-2.2)	2.2 (2.2-2.2)	2.0 (1.9-2.1)	0.0012

PROLONGED ELEVATION OF D-DIMER LEVELS IN CONVALESCENT COVID-19 PATIENTS IS INDEPENDENT OF THE ACUTE PHASE RESPONSE

Townsend L, Fogarty H, Dyer A, Martin-Loeches I, Bannan C, Nadarajan P, Bergin C, O' Farrelly C, Conlon N, Bourke NM, Ward SE, Byrne M, Ryan K, O' Connell N, O' Sullivan JM, Ni Cheallaigh C, O' Donnell JS.. J Thromb Haemost. 2021 Feb 15. doi: 10.1111/jth.15267. Online ahead of print.

Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

An experiment conducted at St. James's Hospital Dublin by the Department of Infectious Diseases from May to September 2020 found that, upon investigation of the immune mechanisms responsible for acute COVID-19 disease in 150 patients, 25.3% of investigated patients presented with increased D-dimer levels up to four months post-infection (Figure 1), suggesting this particular immune marker may hold high relevance when investigating long-term clinical management of patients.

SUMMARY

- The goal of the study was to investigate which biological mechanisms were responsible for long-term effects of infections with COVID-19

- The sample size of 150 patients, post-initial diagnosis, were analyzed not only for inflammatory markers, but also clinically, by chest x-ray, and 6-minute walk tests

- The elevation of D-dimers was especially pronounced in patients who required hospital care for infections, as well as those over the age of 50 ($p<0.001$)

ABSTRACT

BACKGROUND: Persistent fatigue, breathlessness and reduced exercise tolerance have been reported following acute COVID-19 infection. Although immuno-thrombosis has been implicated in acute COVID-19 pathogenesis, the biological mechanisms underpinning Long COVID remain unknown. We hypothesized that pulmonary microvascular immuno-thrombosis may be important in this context. METHODS: 150 COVID-19 patients were reviewed at St James's Hospital Dublin between May and September 2020 at a median of 80.5 (range 44 - 155) days after initial diagnosis. These included patients hospitalized during initial illness (n=69) and others managed entirely as outpatients (n=81). Clinical examination, chest x-ray and 6-minute walk tests were performed. In addition, a range of coagulation and inflammatory markers were assessed. RESULTS: Increased D-dimer levels (>500ng/ml) were observed in 25.3% patients up to four months post-SARS-CoV-2 infection. On univariate analysis, elevated convalescent D-dimers were more common in COVID-19 patients who had required hospital admission and in patients aged more than 50 years ($p<0.001$). Interestingly, we observed that 29% (n=11) of patients with elevated convalescent D-dimers had been managed exclusively as out-patients during their illness. In contrast, other coagulation (PT, APTT, fibrinogen, platelet count) and inflammation (CRP, IL-6 and sCD25) markers had returned to normal in > 90% of convalescent patients. CONCLUSIONS: Elucidating the biological mechanisms responsible for sustained D-dimer increases may be of relevance in Long COVID pathogenesis and has implications for clinical management of these patients.

FIGURES

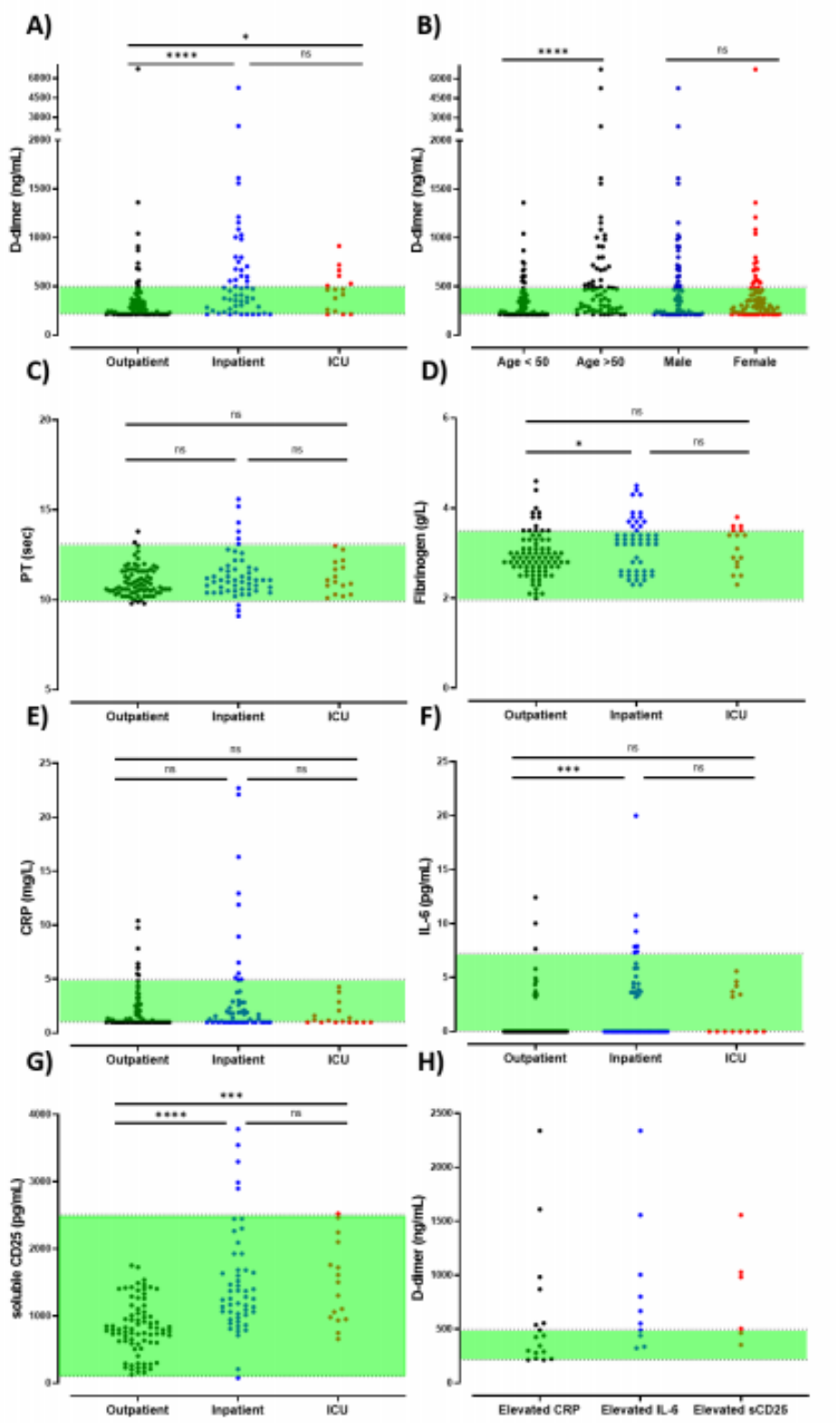

Figure 1: Coagulation and Inflammatory parameters in COVID-19 patients at convalescent follow up.’ Outpatient results are grouped according to whether acute infection was managed as an out-patient, in-patient, or in-patient requiring intensive care unit (ICU) admission showing: A) D-dimers according to initial illness severity, B) D-dimers stratified by age and gender, C) Prothrombin time D) Fibrinogen E) C-reactive protein F) Interleukin-6 G) soluble CD25, H) D-dimers in patients with elevated CRP, IL-6 and sCD25 at convalescence. Dotted lines represent the lower limit of detection and the upper limit of normal for D-dimer and IL-6. Dotted lines represent the upper and lower limit of the normal reference ranges for all other parameters with results in the green shaded areas falling within the normal reference range. Differences assessed by Kruskal-Wallis testing with Dunn’s post-hoc test.

DEVELOPMENTS IN TREATMENTS

NEUTRALIZING MONOCLONAL ANTIBODY FOR MILD TO MODERATE COVID-19

Malani PN, Golub RM.. JAMA. 2021 Jan 21. doi: 10.1001/jama.2021.0585. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

In this letter to the editor, the author from the Division of Infectious Diseases at the University of Michigan details the recent findings from the BLAZE-1 (Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies) trial involving 577 outpatients with mild to moderate COVID-19. Phase 2 results claim statistically significant primary end point for combination therapy of bamlanivimab and etesevimab compared to the placebo group, suggesting promising utilization for this therapy.

STERILIZING IMMUNITY AGAINST SARS-COV-2 INFECTION IN MICE BY A SINGLE-SHOT AND LIPID AMPHIPHILE IMIDAZOQUINOLINE TLR7/8 AGONIST-ADJUVANTED RECOMBINANT SPIKE PROTEIN VACCINE

Jangra S, De Vrieze J, Choi A, Rathnasinghe R, Laghlali G, Uvyn A, Van Herck S, Nuhn L, Deswarte K, Zhong Z, Sanders N, Lienenklaus S, David S, Strohmeier S, Amanat F, Krammer F, Hammad H, Lambrecht BN, Coughlan L, García-Sastre A, de Geest B, Schotsaert M.. Angew Chem Int Ed Engl. 2021 Jan 19. doi: 10.1002/anie.202015362. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A novel in vivo drug study conducted by researchers from Icahn School of Medicine at Mount Sinai in New York and Ghent University in Belgium found the novel drug imidazoquinoline, as an ampiphilic molecule, dramatically attenuates systemic inflammation in mice by entering lymph nodes (Figure 3), suggesting it possesses valuable use as an adjuvant therapy along with approved vaccines.

ABSTRACT

The search for vaccines that protect from severe morbidity and mortality as a result of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19) is a race against the clock and the virus. Here we describe the use of a novel amphiphilic imidazoquinoline (IMDQ-PEG-CHOL) TLR7/8 adjuvant, consisting of an imidazoquinoline conjugated to the chain end of a cholesterol-poly(ethylene glycol) macromolecular amphiphile. This amphiphile is water soluble and exhibits massive translocation to lymph nodes upon local administration, likely through binding to albumin, affording localized innate immune activation and a dramatic reduction in systemic inflammation. The adjuvanticity of IMDQ-PEG-CHOL was validated in the context of a licensed vaccine setting (i.e. the quadrivalent influenza vaccine) and an experimental trimeric recombinant SARS-CoV-2 spike protein vaccine, showing robust IgG2a and IgG1 antibody titers in mice that could neutralize viral infection in vitro and in vivo in a mouse model.

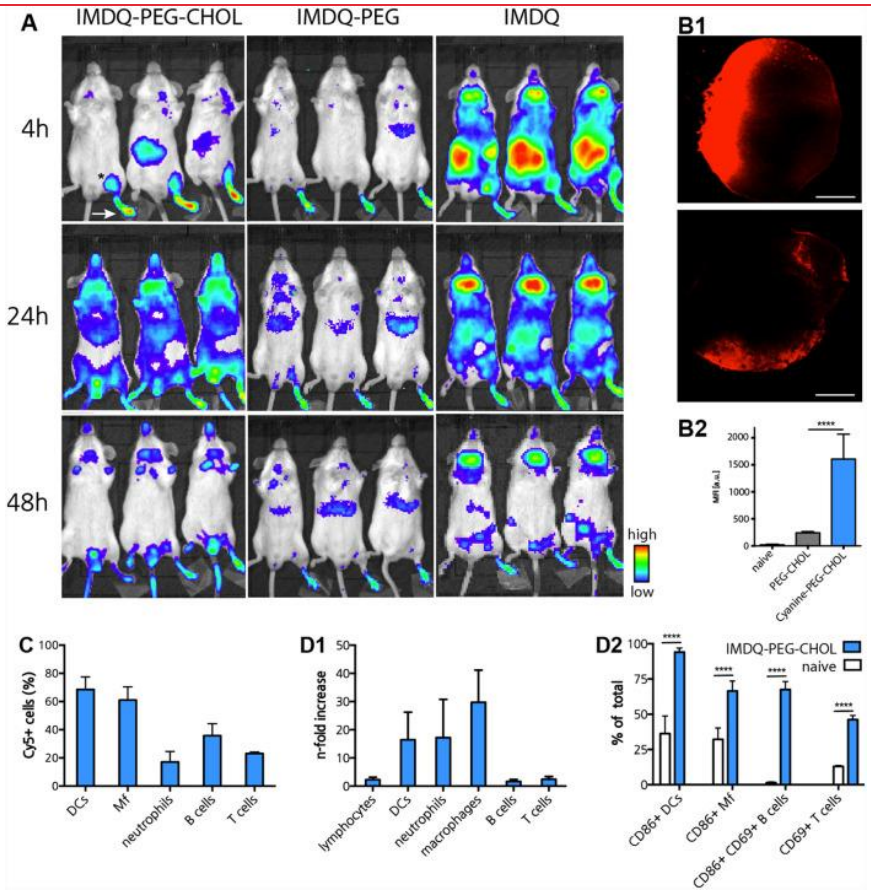

Figure 3. (A) Bioluminescence images of luciferase reporter mice (IFN-beta+/delta-beta-luc); images taken 4, 24 and 48 h post footpad injection of IMDQ-PEG-CHOL, IMDQ-PEG and native IMDQ. (B1) Confocal microscopy images of lymph node tissue sections 48 h post subcutaneous injection of Cyanine5-PEG-CHOL, respectively Cyanine5-PEG, into the footpad of mice. Scale bar represents 100 micron. (B2) Flow cytometry analysis of the draining popliteal lymph node 48 h post subcutaneous injection of Cyanine5-PEG-CHOL, respectively Cyanine5-PEG into the footpad of mice. (n=3, mean + SD; Student's t-test: ****: p<0.0001) (C) Translocation of Cyanine5-PEG-CHOL to the draining popliteal lymph node analyzed 24 h post injection into the footpad, measured by flow cytometry. (n=6, mean + SD) (D) Flow cytometry analysis of the innate immune response in the draining popliteal lymph node 24 h post injection of IMDQ-PEG-CHOL into the footpad (D1) Relative increase in innate immune cell subsets, B and T cell numbers relative to a naïve control and (D2) maturation/activation of innate immune cell subsets, B and T cells (n=6, mean + SD; Student's t-test: ****: p<0.0001).

COVID-19 AND HOW THE WEARING OF FACE COVERINGS CAN AFFECT THOSE WITH AN EXPERIENCE OF TRAUMA

Welfare-Wilson A, Adley L, Bell Z, Luby R.. J Psychiatr Ment Health Nurs. 2021 Feb 15. doi: 10.1111/jpm.12743. Online ahead of print.

Level of Evidence: 5 - Expert Opinion

BLUF

A group of mental health experts from the UK reflects on the unintentional consequences that face coverings may have on individuals who have experienced past trauma and conclude that as the pandemic continues, the implications of face coverings in this population will be an important topic of conversation in mental health circles. They recommend increased utilization of trauma-specific "grounding techniques" in this population to help promote mental wellbeing and resilience.

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CONTRIBUTORS

Brad Mott
Hamza Sultan
Margaret Fahrenbach
Michael Wang
Nicolas Longobardi
Renate Meckl
Sarala Kal
Sokena Zaidi
Veronica Graham

EDITORS

John Michael Sherman
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