The Daily COVID-19 Literature Surveillance Summary

March 16, 2021

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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

Transmission & Prevention

- Microfluidic-based air sampling has potential to be a better method for detecting aerosol SARS-CoV-2. Chemical and biomedical scientists from the Fudan University in Shanghai, China developed a new small-volume rotating microfluidic fluorescence chip-integrated system for detecting aerosolized SARS-CoV-2 suspended in the air. They found it detected virus faster (15 minutes) than current methods (3-4 hours for RT-PCR) while meeting current detection limits with 100% specificity after cross-reaction testing with other airborne pathogens. Authors suggest this system offers a faster on-site option for aerosolized SARS-CoV-2 detection that can improve infection prevention practices.

R&D: Diagnosis & Treatments

- Tocilizumab may influence hypoxia in moderate to severe COVID-19 patients. A randomized, controlled open-label trial conducted by physicians at First Affiliated Hospital of University of Science and Technology of China assessed the effectiveness of tocilizumab therapy to attenuate the cytokine storm in COVID-19 patients. The tocilizumab group (n=34) had no statistically meaningful cure rate versus the control group (n=31) ($p = 0.4133$), but did have statistically significant improvement of hypoxia from day 12 versus the control group ($p = 0.0359$). The implication being that tocilizumab could potentially be effective in improving hypoxia and oxygenation in COVID-19 patients.

TABLE OF CONTENTS

DIGITAL HEALTH SOLUTIONS TO CONTROL THE COVID-19 PANDEMIC IN COUNTRIES WITH HIGH DISEASE PREVALENCE: LITERATURE REVIEW

R Niakan Kalhori S, Bahaadinbeigy K, Deldar K, Gholamzadeh M, Hajesmaeel-Gohari S, Ayyoubzadeh SM.. J Med Internet Res. 2021 Mar 10;23(3):e19473. doi: 10.2196/19473.
Level of Evidence: 5 - Review / Literature Review

BLUF

A literature review conducted by researchers in Iran included 32 papers published from December 2019 to March 15, 2020 regarding digital health applications to manage and control COVID-19 in the 10 most-affected countries. Six domains were established to categorize the applications (See Table 2), with telemedicine visit services most commonly implemented, especially in the US, followed by electronic methods with disease information, preventing disease spread, and methods of protection, with overarching relevance of mobile device, videoconferencing, and telecommunication to limit contact and exposures. The extent of technology development are represented in Figure 1 and this article suggests there will be continued development of digital health products to assist in management and monitoring of viral infection and health crises for the present and future.

ABSTRACT

BACKGROUND: The novel coronavirus disease (COVID-19) as a case of pneumonia becomes a global pandemic, affecting most of the countries around the world. digital health as information technologies that can be applied in three aspects including digital patients, digital devices, and digital clinics could help against this pandemic. OBJECTIVE: Recent reviews have examined the role of digital health in controlling COVID-19 to identify the potential of digital health to fight against the disease. However, this study is aimed at reviewing and analyzing applied digital technology to control the COVID-19 pandemic in ten countries with the highest prevalence of the disease. METHODS: For this review, Google Scholar, PubMed, Web of Science, and Scopus databases were searched in August 2020 to retrieve publications from December 2019 to 15 March 2020. Furthermore, the Google search engine was also investigated to identify additional applications of digital health for COVID-19 pandemic control. RESULTS: 32 papers were included in this review reported 37 digital health applications for COVID-19 control. Most of the projects for COVID-19 fighting were telemedicine visit (N=11, 30%). Digital learning packages for informing about the disease (N=7, 19%), GIS and QR code application for real-time case tracking (N=7, 19%), as well as cloud /mobile based systems for self-care and patient tracking (N=7, 19%) were in the second rank of digital tool applications. projects deployed by collaboration of European countries, USA, Australia, and China. CONCLUSIONS: Having considered the potential of available information technologies across the world in the 21st century, particularly in developed countries, it seems that more digital health products with higher level of intelligence capability have remained to be applied for pandemic and health related crisis management. CLINICALTRIAL:

FIGURES

Domain number	Applied digital health solutions	COVID-19 control approaches	Digital health application projects (N=37), n (%)
1	Digital learning package, mobile apps, and web-based systems	Widespread distribution of information	7 (19)
2	GISs[a], QR[b] codes, and wearable devices	Real-time tracking of transmission, activity tracking, and quarantine-level analysis	7 (19)
3	Web-based systems and mobile apps, videoconferencing, and telephone	Telemedicine visit services and virtual venues for meetings	11 (30)
4	Cloud- and mobile-based systems	Self-care and patient monitoring, training, and diagnosis	7 (19)
5	Intelligent systems and CDSSs[c]	Early warning and detection, screening, and triage	4 (10)
6	Social media	Dynamic burden of the pandemic and analysis of its consequences	1 (3)

Table 2. The frequency of digital health methods and their applications for COVID-19 pandemic control.
aGISs: geographic information systems.
bQR: quick response.
cCDSSs: clinical decision support systems.

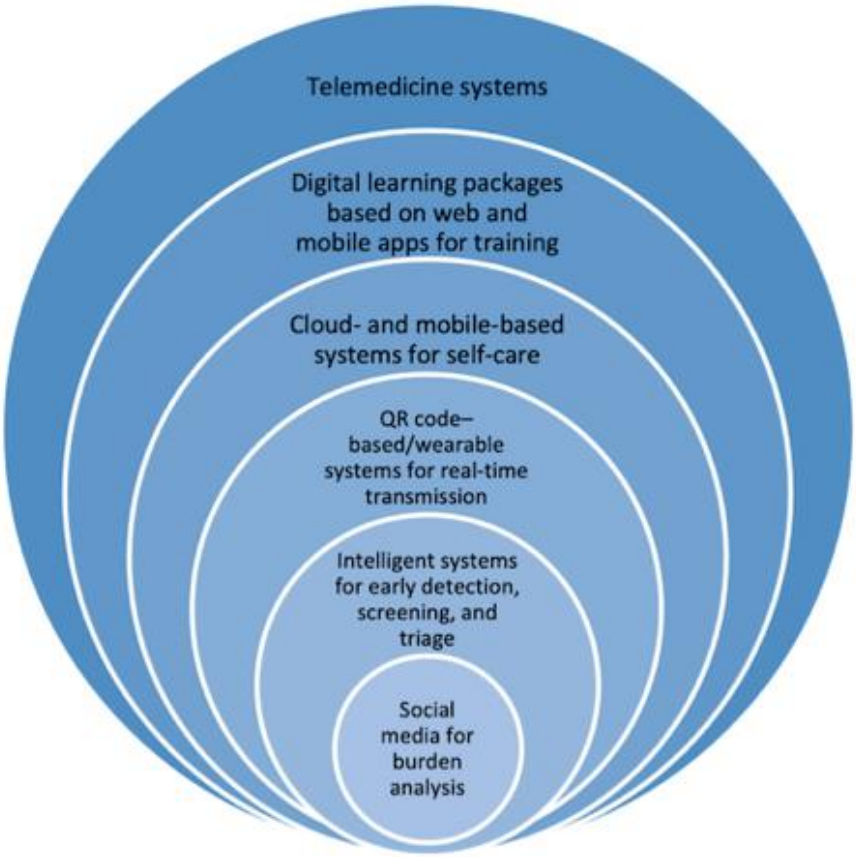


Figure 1. Technologies currently being applied to address the COVID-19 pandemic. QR: quick response.

ADULTS

INDICATORS OF ACUTE KIDNEY INJURY AS BIOMARKERS TO DIFFERENTIATE HEATSTROKE FROM CORONAVIRUS DISEASE 2019: A RETROSPECTIVE MULTICENTER ANALYSIS

Obinata H, Yokobori S, Ogawa K, Takayama Y, Kawano S, Ito T, Takiguchi T, Igarashi Y, Nakae R, Masuno T, Ohwada H.. J Nippon Med Sch. 2021 Mar 11;88(1):80-86. doi: 10.1272/jnms.JNMS.2021_88-107. Epub 2020 Aug 31.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

Researchers from various medical and academic institutions in Tokyo, Japan conducted a retrospective observational study comparing 90 patients from three multicenter (115 hospitals) observational registries of heat-related illness from 2017-2019 vs. 86 COVID-19 patents admitted to either Japan Self Defense Forces Central Hospital or Flowers & Forest Tokyo Hospital between February 1, 2020 and May 1, 2020. The results revealed statistically significant differences between the two groups when comparing systolic blood pressure, oxygen saturation, body temperature, leukocyte count, creatinine, and CRP (Table 1). A multiple logistic regression model revealed creatinine was the most important factor in distinguishing between the two groups (Figure 3), with an average of 2.2 mg/dL in heat-related illness patients vs. 0.85 mg/dL in COVID-19 patients ($p<0.001$), suggesting laboratory findings of early acute kidney injury could be a distinguishing factor between patients with heat-related illness versus patients with COVID-19.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) and heat related-illness are systemic febrile diseases. In the summer during the COVID-19 pandemic, a differential diagnosis between the two conditions is important. However, no studies have compared and distinguished heat-related illness from COVID-19. We aimed to compare the data between patients with early-stage heat-related illness and those with COVID-19. METHODS: This retrospective observational study included 90 patients with early-stage heat-related illness selected from Heatstroke STUDY 2017-2019 (nationwide registries of heat-related illness in Japan) and 86 patients with laboratory-confirmed COVID-19 with complaints of fever or fatigue and were admitted to one of two hospitals in Tokyo, Japan. RESULTS: Amongvital signs, systolic blood pressure (119 vs. 125 mmHg, $p = 0.02$), oxygen saturation (98% vs. 97%, $p < 0.001$), and body temperature (36.6 vs. 37.6 C, $p<0.001$) showed significant between-group differences for the heatstroke and COVID-19 groups, respectively. Numerous intergroup differences in laboratory findings were present, including white blood cell counts (10.8 vs. 5.2 x 103/muL, $p<0.001$), creatinine (2.2 vs. 0.85 mg/dL, $p<0.001$), and C-reactive protein (0.2 vs. 2.8 mg/dL, $p<0.001$), although a logistic regression model achieved an area under the curve (AUC) of 0.966 using these three factors. A Random Forest machine learning model achieved accuracy, precision, recall, and AUC of 0.908, 0.976, 0.842, and 0.978, respectively. Creatinine was the most important feature of this model. CONCLUSIONS: Acute kidney injury was associated with heat-related illness, which could be key in distinguishing or evaluating patients with fever in the summer during the COVID-19 pandemic.

Table 1 Baseline characteristics of patients

	Heat-related illness (n = 90)	COVID-19 (n = 86)	*p*-value
Age, years	48 [35-62]	53 [41-67]	0.09
Male, % (n)	81 (90.0)	58 (67.4)	0.001<
Body mass index	24.0 [21.3-26.2]	23.3 [20.1-26.4]	0.50
Past medical history			
Cardiovascular	3	5	0.42
Respiratory	2	10	0.01
Renal	0	1	0.30
Hepatitis	0	0	N/A
Diabetes mellitus	0	3	0.07
Vital signs			
Systolic blood pressure, mm Hg	119 [108-134]	125 [114-139]	0.02
Diastolic blood pressure, mm Hg	78 [69-91]	80 [72-90]	0.58
Heart rate, bpm	90 [82-103]	88 [78-100]	0.20
Respiratory rate, bpm	19 [16-21]	19 [16-22]	0.54
Oxygen saturation, %	98 [96-99]	97 [95-98]	0.001<
Body temperature, °C	36.6 [36.1-37.0]	37.6 [36.8-38.3]	0.001<
Laboratory findings			
White blood cell count, 10^3 /μL	10.8 [7.2-15.1]	5.2 [4.2-6.6]	0.001<
Hemoglobin, g/dL	16.6 [14.9-17.8]	15.0 [14.1-15.8]	0.001<
Platelet count, 10^4 /μL	26.0 [21.5-29.6]	19.0 [15.9-23.7]	0.001<
Blood urea nitrogen, mg/dL	26.1[19.7-36.8]	14.0 [10.0-17.0]	0.001<
Creatinine, mg/dL	2.2 [1.35-2.9]	0.85 [0.70-1.03]	0.01<
Total bilirubin, mg/dL	1.0 [0.7-1.3]	0.6 [0.4-0.7]	0.001<
Aspartate transaminase, U/L	34 [24-46]	33 [23-57]	0.89
Alanine transaminase, U/L	37 [23-55]	34 [17-51]	0.35
Creatine kinase, mg/dL	259 [170-432]	79 [55-135]	0.001<
C-reactive protein, mg/dL	0.2 [0.1-0.5]	2.8 [0.3-6.3]	0.001<
Prothrombin time (international normalized ratio)	1.00 [0.90-1.10]	1.00 [1.00-1.10]	0.05
D-dimer, μg/mL	0.5 [0.5-0.7]	0.6 [0.5-1.0]	0.04
Sodium, mEq/L	137 [136-140]	139 [136-141]	0.05
Potassium, mEq/L	4.3 [3.9-4.6]	4.1 [3.8-4.3]	0.01<
Chlorine, mEq/L	99 [94-108]	102 [98-104]	0.001<
Glucose, mg/dL	122 [107-153]	104 [93-116]	0.001<

COVID-19: coronavirus disease 2019

Table 1. Baseline characteristics of patients.

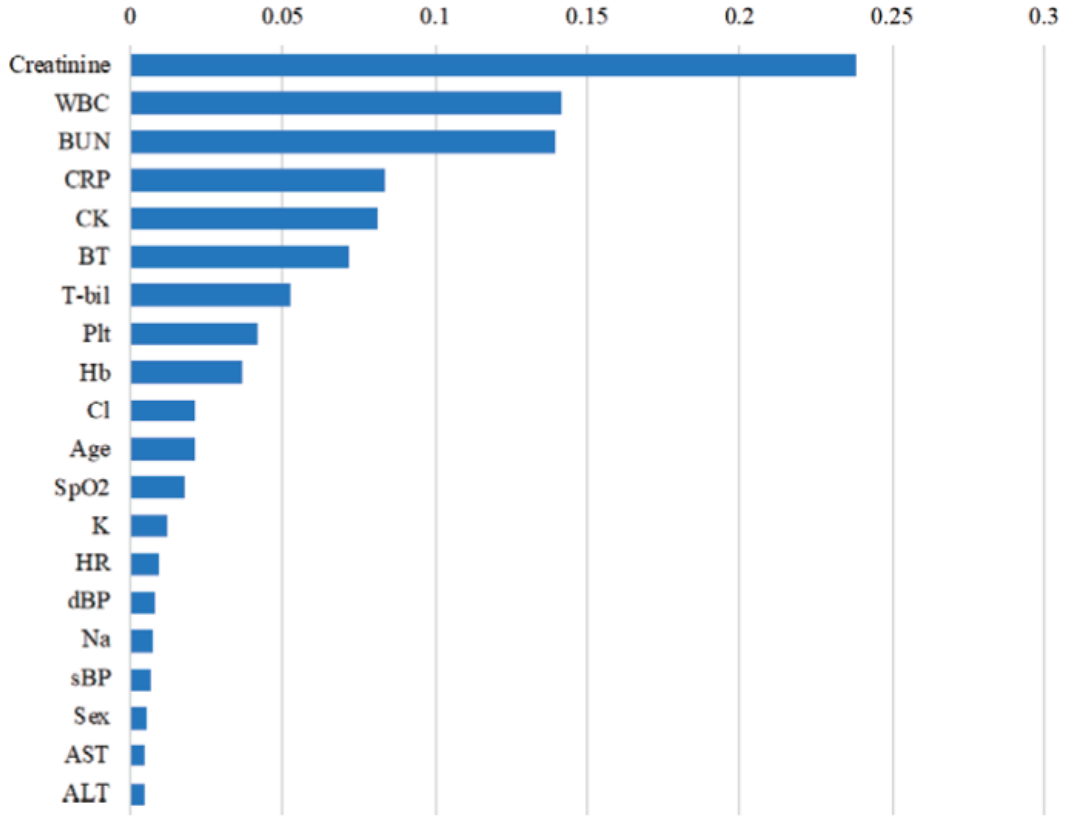


Figure 3. Ranking of feature importance in the Random Forest model. Cre: creatinine; WBC: white blood cell count; BUN: blood urea nitrogen; CRP: C-reactive protein; CK: creatine kinase; BT: body temperature; T-bil: total bilirubin; Plt: platelet count; Hb: hemoglobin; Cl: chlorine; HR: heart rate; dBP: diastolic blood pressure; sBP: systolic blood pressure; AST: aspartate transaminase; ALT: alanine transaminase.

BNT162B2 MRNA COVID-19 VACCINE: FIRST APPROVAL

Lamb YN.. Drugs. 2021 Mar 8. doi: 10.1007/s40265-021-01480-7. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A medical writer affiliated with Spring Nature of Auckland, New Zealand, authored this summary of the development and clinical trials leading up to the approval of BNT162b2 (Figure 1), an immunostimulant (Figure 2), mRNA-based vaccine created by BioNTech and Pfizer for prevention of COVID-19. BNT162b2, administered in two 30µg doses, 21 days apart, was found to be 95% effective in preventing COVID-19 in healthy adults, ranging from 19-55 years of age with no evidence of prior infection and 94.6% effective in patients with and without evidence of prior infection. Adverse events of the vaccine included injection site pain (most common) and systemic symptoms (including fatigue, headaches, muscle pain, join pain, chills, diarrhea and fever) with an onset and resolution typically 1-2 days after receiving the vaccine. BNT162b2 received its first emergency use authorization in the United Kingdom on December 2, 2020 and then received its first conditional approval on December 19, 2020 in Switzerland followed by another conditional approval in the European Union. The immune response elicited by the BNT162b2 vaccine in its recipients can play a key role in building herd immunity.

ABSTRACT

BNT162b2 (Comirnaty ; BioNTech and Pfizer) is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine for the prevention of the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. BNT162b2 encodes the SARS-CoV-2 spike protein, the expression of which elicits immune responses against the antigen in recipients. In early December 2020, BNT162b2 received a temporary emergency use authorization (EUA) in the UK and, subsequently, a series of approvals or authorizations for emergency use in Bahrain, Canada, Mexico, Saudi Arabia and the USA. Soon after, BNT162b2 received conditional marketing authorizations in Switzerland (19 December 2020) and the EU (21 December 2020) for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. BNT162b2 is administered intramuscularly in a two-dose regimen. This article summarizes the milestones in the development of BNT162b2 leading to these first approvals for the prevention of COVID-19.

FIGURES

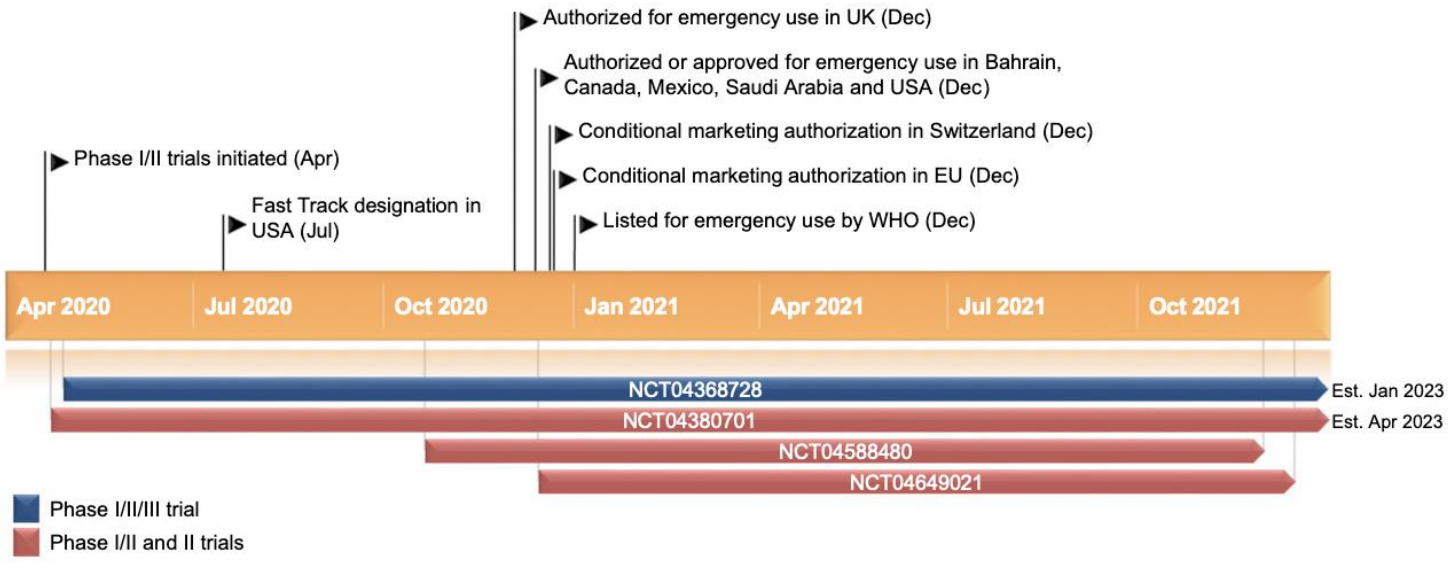
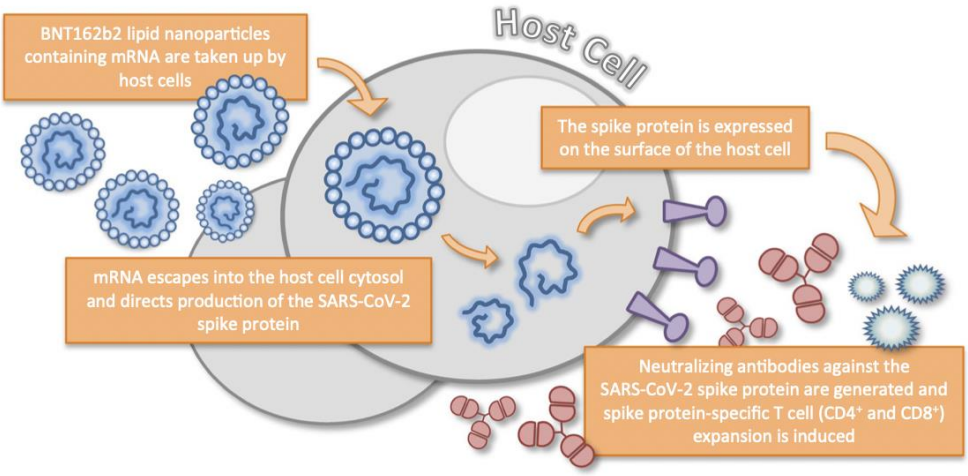


Figure 1. The timeline of events leading up to the approval of the BNT162b2 vaccine is displayed.



Mechanism of action of BNT162b2 following intramuscular administration

Figure 2. The immunostimulant mechanism of action is played.

QUANTIFYING ASYMPTOMATIC INFECTION AND TRANSMISSION OF COVID-19 IN NEW YORK CITY USING OBSERVED CASES, SEROLOGY, AND TESTING CAPACITY

Subramanian R, He Q, Pascual M.. Proc Natl Acad Sci U S A. 2021 Mar 2;118(9):e2019716118. doi: 10.1073/pnas.2019716118.
Level of Evidence: 5 - Modeling

BLUF

Epidemiologists from the Department of Ecology and Evolution at the University of Chicago and Sante Fe Institute conducted a modeling study aimed to quantify the rate of transmission of COVID-19 by asymptomatic and presymptomatic cases in New York City between March 1, 2020 and June 1, 2020. Three different compartmental models were created by modifying the traditional SEIR (susceptible-exposed-infectious-recovered) model. Using the SEPIAR (susceptible-exposed-presymptomatic-infectious-asymptomatic-recovered) model, a Monte Carlo profile was constructed to evaluate transmission of cases and found that presymptomatic and asymptomatic cases together contribute to at least 50% of the force of infection of COVID-19 (Figure 2), suggesting the need for interventions that account for nonsymptomatic cases to further control the transmission of COVID-19.

SUMMARY

-The first model, SEPIAR, incorporated presymptomatic and asymptomatic transmission

-The second model, SEIAR, excluded presymptomatic transmission

-The third model, SEPIR, excluded asymptomatic transmission. (Figure 1)

ABSTRACT

The contributions of asymptomatic infections to herd immunity and community transmission are key to the resurgence and control of COVID-19, but are difficult to estimate using current models that ignore changes in testing capacity. Using a model that incorporates daily testing information fit to the case and serology data from New York City, we show that the proportion of symptomatic cases is low, ranging from 13 to 18%, and that the reproductive number may be larger than often assumed. Asymptomatic infections contribute substantially to herd immunity, and to community transmission together with presymptomatic ones. If asymptomatic infections transmit at similar rates as symptomatic ones, the overall reproductive number across all classes is larger than often assumed, with estimates ranging from 3.2 to 4.4. If they transmit poorly, then symptomatic cases have a larger reproductive number ranging from 3.9 to 8.1. Even in this regime, presymptomatic and asymptomatic cases together comprise at least 50% of the force of infection at the outbreak peak. We find no regimes in which all infection subpopulations have reproductive numbers lower than three. These findings elucidate the uncertainty that current case and serology data cannot resolve, despite consideration of different model structures. They also emphasize how

temporal data on testing can reduce and better define this uncertainty, as we move forward through longer surveillance and second epidemic waves. Complementary information is required to determine the transmissibility of asymptomatic cases, which we discuss. Regardless, current assumptions about the basic reproductive number of severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) should be reconsidered.

FIGURES

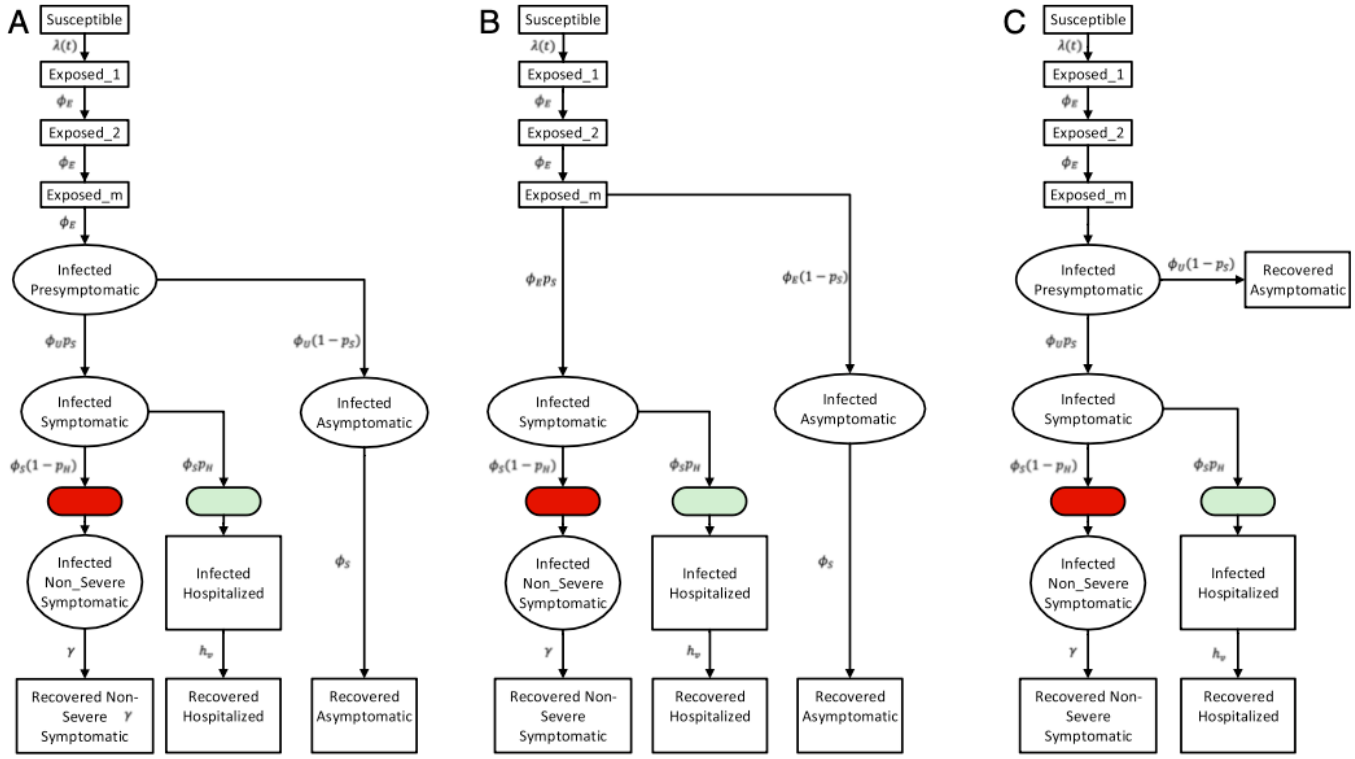


Figure 1. Three different compartmental models were created by modifying the traditional SEIR (susceptible-exposed-infectious-recovered) model. The first model, SEPIAR (A), incorporated presymptomatic and asymptomatic transmission, the second model, SEIAR (B), excluded presymptomatic transmission, and the third model, SEPIR (C), excluded asymptomatic transmission. The circular compartments contribute to the force of infection and the rectangular compartments do not. The point at which severe/hospitalized cases (green ellipse) and non-severe symptomatic cases (red ellipse) are sampled and enter the testing queue is displayed.

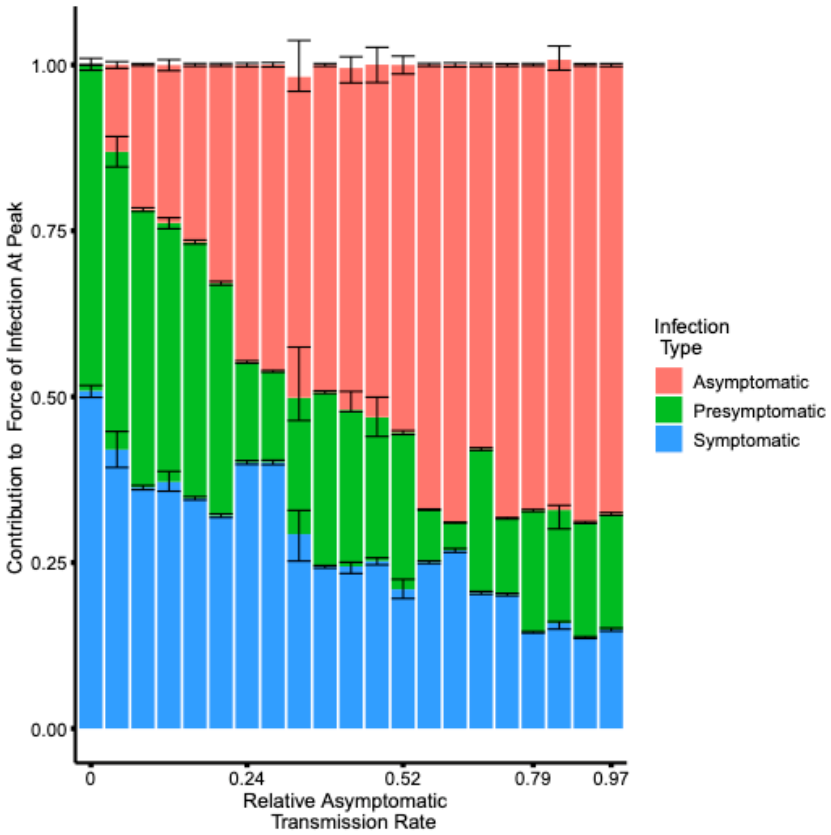


Figure 2. The contribution to the force of infection on April 14, 2020 by asymptomatic, presymptomatic, and symptomatic cases under different relative asymptomatic rates is displayed.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

EXHALED AEROSOL INCREASES WITH COVID-19 INFECTION, AGE, AND OBESITY

Edwards DA, Ausiello D, Salzman J, Devlin T, Langer R, Beddingfield BJ, Fears AC, Doyle-Meyers LA, Redmann RK, Killeen SZ, Maness NJ, Roy CJ.. Proc Natl Acad Sci U S A. 2021 Feb 23;118(8):e2021830118. doi: 10.1073/pnas.2021830118.
Level of Evidence: 3 - Local non-random sample

BLUF

An observational cohort study conducted at two sites in North Carolina and Michigan by researchers from multiple universities investigated respiratory droplet generation and exhalation in 194 human and 8 nonhuman primate subjects and found increased exhaled respiratory droplet number with higher severity of COVID-19 infection (See Figure 1, 3) and increased obesity (See Figure 2). These findings suggest that the propensity of individuals to exhale large numbers of respiratory droplets and the capacity of airway mucus to resist breaking up contribute to the superspreader phenomena of the pandemic, thus stabilization of airway lining mucosal surfaces is an effective approach to decrease COVID-19 infection and transmission.

ABSTRACT

COVID-19 transmits by droplets generated from surfaces of airway mucus during processes of respiration within hosts infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. We studied respiratory droplet generation and exhalation in human and nonhuman primate subjects with and without COVID-19 infection to explore whether SARS-CoV-2 infection, and other changes in physiological state, translate into observable evolution of numbers and sizes of exhaled respiratory droplets in healthy and diseased subjects. In our observational cohort study of the exhaled breath particles of 194

healthy human subjects, and in our experimental infection study of eight nonhuman primates infected, by aerosol, with SARS-CoV-2, we found that exhaled aerosol particles vary between subjects by three orders of magnitude, with exhaled respiratory droplet number increasing with degree of COVID-19 infection and elevated BMI-years. We observed that 18% of human subjects (35) accounted for 80% of the exhaled bioaerosol of the group (194), reflecting a superspreader distribution of bioaerosol analogous to a classical 20:80 superspreader of infection distribution. These findings suggest that quantitative assessment and control of exhaled aerosol may be critical to slowing the airborne spread of COVID-19 in the absence of an effective and widely disseminated vaccine.

FIGURES

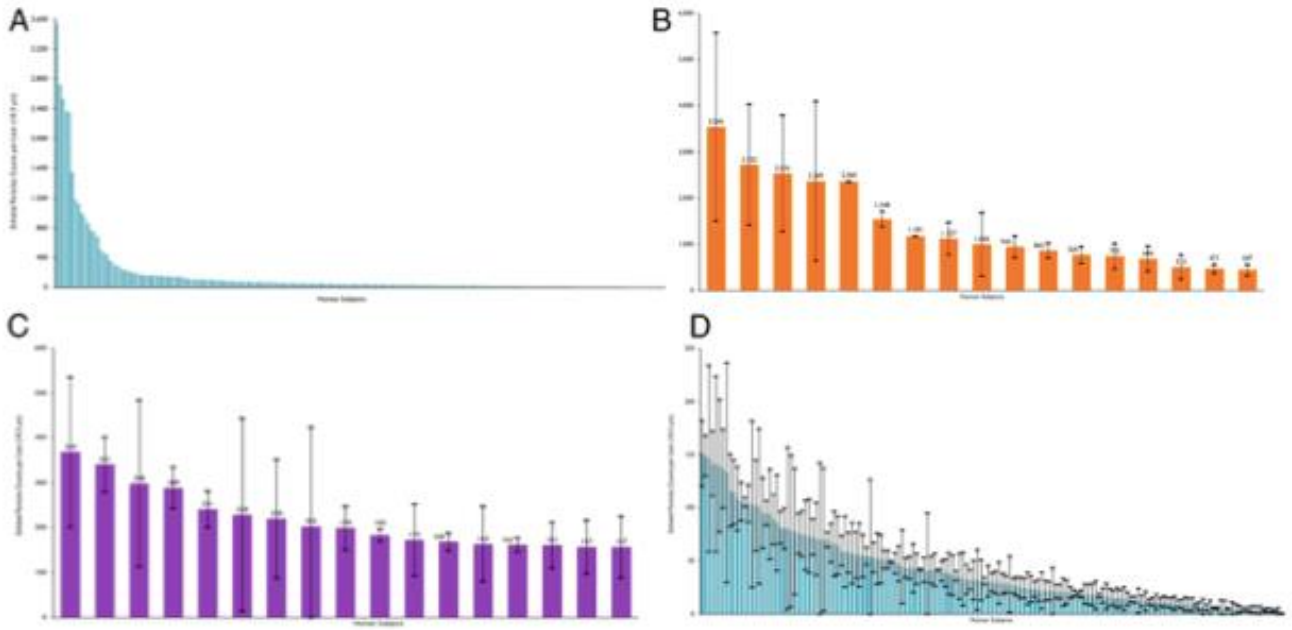


Fig. 1. Exhaled breath particles of 74 essential workers at No Evil Foods and of 120 volunteers at Grand Rapids Community College. (A) All participants; (B) “superspreader” (of aerosol particles) participants (first decile); (C) “superspreader” (of aerosol particles) participants (second decile); and (D) “low spreader” participants. Data represent particle counts per liter of exhaled air (particle diameter larger than 300 nm) for each of the 194 individuals. Error bars represent SD sample calculations based on 3 to 12 exhaled aerosol count measurements, with each measurement an average of counts over a 5-s time interval.

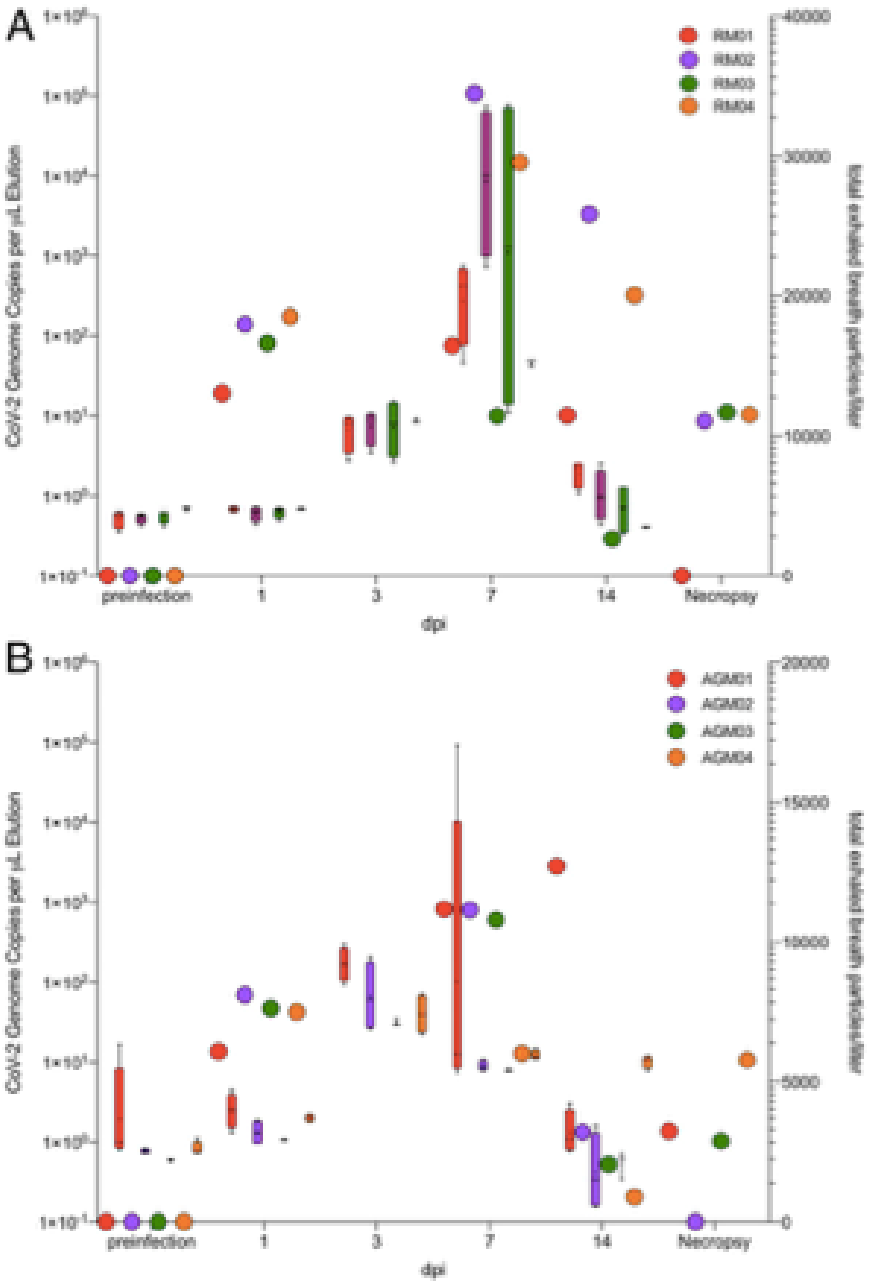


Fig. 3. Exhaled breath particles and corresponding genomic SARS-CoV-2 viral RNA in experimentally infected (A) rhesus macaques (RM) and (B) Af- rican green monkeys (AGM). Both groups are segregated by species (n = 4; n = 8). The corresponding color-matched box-and-whisker plots of total exhaled breath particles represent iterative five 1-min sampling events to genomic viral RNA (color-matched circles) for each animal at each respective time point. Mean calculated correlation between time point-matched ex- haled breath particle production and genomic viral RNA showed statistically significant correlations in 75% of the RM (RM01, r2 = 0.93, P < 0.03; RM02, r2 = 0.99, P < 0.004; RM04, r2 = 0.98, P < 0.0008) and 50% of the AGM (AGM02, r2 = 0.91, P < 0.04; AGM03, r2 = 0.97, P < 0.01).

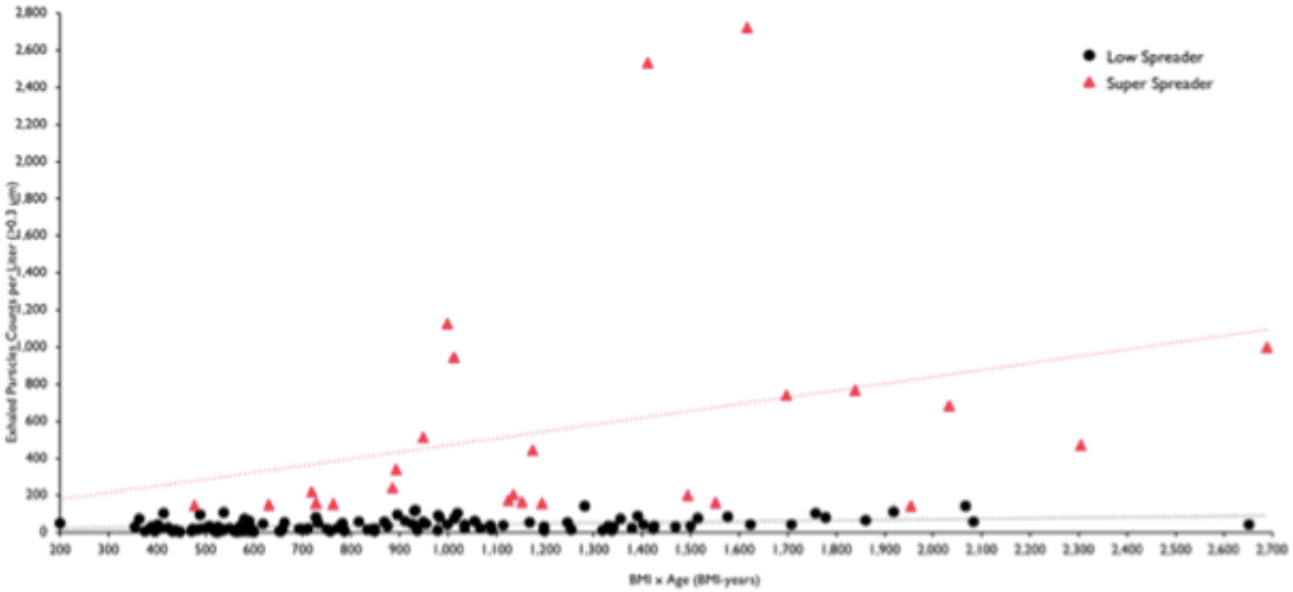


Fig. 2. Exhaled breath particles as a function of BMI-years for volunteers reporting age and BMI (n = 146). Results of linear regression analysis are shown for the exhaled aerosol numbers from the superspreader and low spreader (of aerosol particles) subjects showing significant correlation, particularly for the superspreader subjects (r2 = 0.98).

EFFICIENT MICROFLUIDIC-BASED AIR SAMPLING/MONITORING PLATFORM FOR DETECTION OF AEROSOL SARS-COV-2 ON-SITE

Xiong H, Ye X, Li Y, Qi J, Fang X, Kong J.. Anal Chem. 2021 Mar 9;93(9):4270-4276. doi: 10.1021/acs.analchem.0c05154. Epub 2021 Feb 26.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Chemical and biomedical scientists from the Fudan University in Shanghai, China developed a new small-volume rotating microfluidic fluorescence chip-integrated system for detecting aerosolized SARS-CoV-2 suspended in the air. They found it detected virus faster (15 minutes) than current methods (3-4 hours for RT-PCR) while meeting current detection limits (Table 1) with 100% specificity (Figure 4, 5) after cross-reaction testing with other airborne pathogens. (Figure 4). Authors suggest this system offers a faster on-site option for aerosolized SARS-CoV-2 detection that can improve infection prevention practices.

ABSTRACT

Airborne pathogens have been considered as highly infectious and transmittable between humans. With the pandemic outbreak of the coronavirus disease 2019 (COVID-19), an on-site diagnostic system-integrated airborne pathogen-monitoring machine is recommended by experts for preventing and controlling the early stage beta-coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread. In this work, a small-volume rotating microfluidic fluorescence chip-integrated aerosol SARS-CoV-2 sampling system was constructed to satisfy the demand for rapid on-site sample collection and detection of SARS-CoV-2. The rotating microfluidic fluorescence system with small volume has very high sensitivity in the detection of SARS-CoV-2 (detection limit of 10 copies/muL with the shortest Ct value of 15 min), which is comparable to reverse transcription polymerase chain reaction (RT-PCR). The precision variation coefficients within/between batches are very low [coefficient of variation (CV) % <= 5.0%]. Our work has passed the comprehensive inspection of the microfluidic chip performance by the Shanghai Medical Device Testing Institute [National Medical Inspection (Design) no. 4408] and successfully tested 115 clinical samples. The integrated system exhibits 100% specificity, high sensitivity (10 copies/muL), and good precision (CV % <= 5.0%) in the rapid detection of SARS-CoV-2, thus realizing rapid monitoring and diagnostics of SARS-CoV-2 nucleic acid on-site.

(copies/μL) sample (1, 2-fold)	results: positive amount (12 repetitions) ORF1ab	N	positive rate ORF1ab (%)	N (%)
10	12	12	100	100
5	10	10	83.33	83.33

Table 1. Detection Limit of SARS-CoV-2

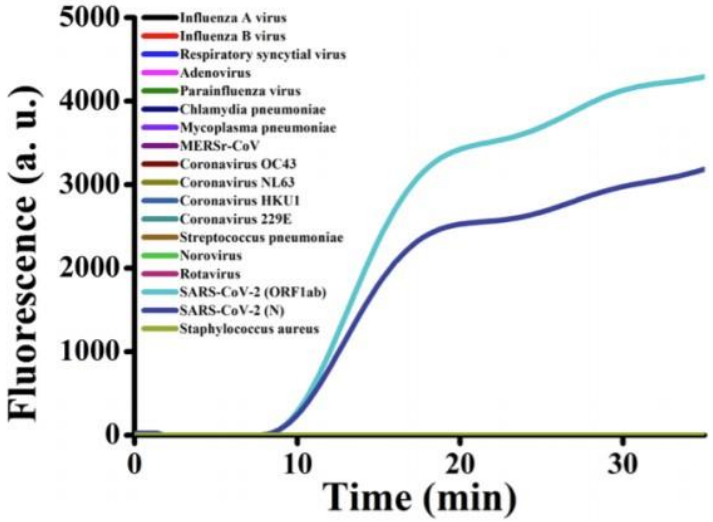


Figure 4. Specificity amplification curves (SARS-CoV-2 targeting ORF1ab and N exhibit positive results; influenza A virus, influenza B virus, respiratory syncytial virus, adenovirus, parainfluenza virus, Chlamydia pneumoniae, Mycoplasma pneumoniae, MERSr-CoV, coronavirus OC43, coronavirus NL63, coronavirus HKU1, coronavirus 229E, Streptococcus pneumoniae, norovirus, rotavirus, and Staphylococcus aureus exhibit negative results).

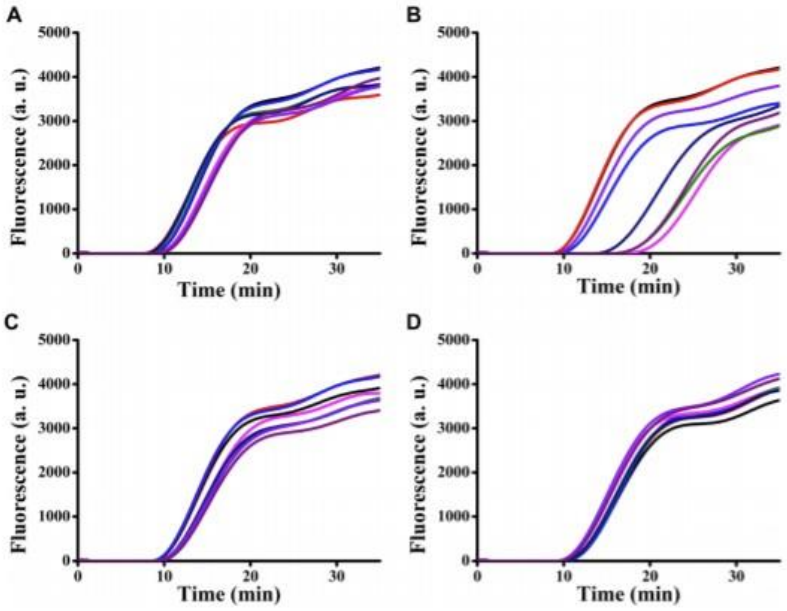


Figure 5. Amplification curves of the (A,B) ORF1ab target in critical concentration references and (C,D) N target in critical concentration references (two experiments with sixteen replicates each).

Figure 5. Amplification curves of the (A,B) ORF1ab target in critical concentration references and (C,D) N target in critical concentration references (two experiments with sixteen replicates each

NEUROLOGY

IMPACT OF SARS-COV-2 ON REPERFUSION THERAPIES FOR ACUTE ISCHEMIC STROKE IN LOMBARDY, ITALY: THE STROKOVID NETWORK

Pezzini A, Grassi M, Silvestrelli G, Locatelli M, Rifino N, Beretta S, Gamba M, Raimondi E, Giussani G, Carimati F, Sangalli D, Corato M, Gerevini S, Masciocchi S, Cortinovis M, La Gioia S, Barbieri F, Mazzoleni V, Pezzini D, Bonacina S, Pilotto A, Benussi A, Magoni M, Premi E, Prelle AC, Agostoni EC, Palluzzi F, De Giuli V, Magherini A, Roccatagliata DV, Vinciguerra L, Puglisi V, Fusi L, Xhani R, Pozzi F, Diamanti S, Santangelo F, Grampa G, Versino M, Salmaggi A, Marcheselli S, Cavallini A, Giossi A, Censori B, Ferrarese C, Ciccone A, Sessa M, Padovani A; STROKOVID group.. J Neurol. 2021 Mar 8. doi: 10.1007/s00415-021-10497-7. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective analysis conducted between March 8th to April 30, 2020 by physicians in Lombardy, Italy looking at the impact of COVID-19 on reperfusion therapies for acute brain ischemia in 296 patients. Among other results (summary below; Table 1), the authors noted that the time from stoke symptom onset to treatment was on average 40 minutes longer in the COVID-19 group (p=0.007), demonstrating that infected patients with stroke who require hospitalization are at an increased risk of sub-optimal outcomes as compared to non-infected patients (Figure 1). As such, the authors emphasize the need for high quality stroke care delivery during this pandemic through implementing plans for intra-hospital stroke management and continuous education and training of healthcare staff.

SUMMARY

-There was no significant difference in demographics between the infected and non-infected group except for an observed increase in prevalence of males (p=0.028) and a higher frequency of atrial fibrillation (p=0.047) in the COVID-19 group.

-For those that underwent endovascular thrombectomy, the percentage of those with collateral filling of less then 50% of the occluded territory or absent collaterals was higher in the COVID-19 infected group.

-COVID-19 patients experienced respiratory and medical complications more often, encountered post-procedural intracranial hemorrhages more frequently (p<0.035), and faced increased hospital mortality (p≤0.001) as compared to the non-infected group (Table 3)

ABSTRACT

Whether and how SARS-CoV-2 outbreak affected in-hospital acute stroke care system is still matter of debate. In the setting of the STROKOVID network, a collaborative project between the ten centers designed as hubs for the treatment of acute stroke during SARS-CoV-2 outbreak in Lombardy, Italy, we retrospectively compared clinical features and process measures of patients with confirmed infection (COVID-19) and non-infected patients (non-COVID-19) who underwent reperfusion therapies for acute ischemic stroke. Between March 8 and April 30, 2020, 296 consecutive patients [median age, 74 years (interquartile range (IQR), 62-80.75); males, 154 (52.0%); 34 (11.5%) COVID-19] qualified for the analysis. Time from symptoms onset to treatment was longer in the COVID-19 group [230 (IQR 200.5-270) minutes vs. 190 (IQR 150-245) minutes; p = 0.007], especially in the first half of the study period. Patients with COVID-19 who underwent endovascular thrombectomy had more frequently absent collaterals or collaterals filling <= 50% of the occluded territory (50.0% vs. 16.6%; OR 5.05; 95% CI 1.82-13.80) and a lower rate of good/complete recanalization of the primary arterial occlusive lesion (55.6% vs. 81.0%; OR 0.29; 95% CI 0.10-0.80). Post-procedural intracranial hemorrhages were more frequent (35.3% vs. 19.5%; OR 2.24; 95% CI 1.04-4.83) and outcome was worse among COVID-19 patients (in-hospital death, 38.2% vs. 8.8%; OR 6.43; 95% CI 2.85-14.50). Our findings showed longer delays in the intra-hospital management of acute ischemic stroke in COVID-19 patients, especially in the early phase of the outbreak, that likely impacted patients outcome and should be the target of future interventions.

	COVID-19 ($n=34$)	Non-COVID-19 ($n=262$)	Univariable OR (95% CI)	p value
Age, years	76 (63–82.25)	74 (61–80)	1.02 (0.99–1.05)	0.242
Sex, male	24 (70.6)	130 (49.6)	2.43 (1.12–5.29)	0.028
Hypertension	25 (73.5)	183 (69.8)	1.19 (0.53–2.68)	0.659
Diabetes	5 (14.7)	44 (16.8)	0.85 (0.31–2.39)	1.000
Hypercholesterolemia	12 (35.3)	89 (34.0)	1.06 (0.50–2.24)	0.850
Smoking habit				
Never smoker	27 (79.4)	168 (66.4)	1	
Former smoker	4 (11.8)	36 (14.2)	0.69 (0.22–2.09)	0.515
Current smoker	3 (8.8)	49 (19.4)	0.38 (0.11–1.30)	0.125
Coronary heart disease	7 (20.6)	46 (17.6)	1.21 (0.50–2.96)	0.638
Atrial fibrillation	12 (35.3)	52 (19.8)	2.20 (1.02–4.73)	0.047
Personal history of ischemic stroke	3 (8.8)	26 (9.9)	0.87 (0.25–3.07)	1.000
Prior antiplatelets	12 (35.3)	92 (35.1)	1.00 (0.47–2.12)	0.984
Prior anticoagulants	5 (14.7)	18 (6.9)	2.33 (0.80–6.76)	0.161
Stroke severity on admission, NIHSS score	12 (7–20.25)	10 (6–16)	1.04 (0.98–1.09)	0.131
Cause of stroke				
Large-vessel disease	3 (8.8)	55 (21.0)	0.33 (0.09–1.21)	0.095
Cardiac embolism	14 (41.2)	85 (32.4)	1.02 (0.46–2.27)	0.950
Small-vessel disease	1 (2.9)	23 (8.8)	0.28 (0.03–2.26)	0.234
Other determined etiology	2 (5.9)	12 (4.6)	1.03 (0.20–5.12)	0.966
Undetermined etiology	14 (41.2)	84 (32.1)	1	
Process measures				
Time from stroke onset to hospital admission, minutes, median (IQR)	84 (63–127.5)	90 (65–125)		0.996
Time from stroke onset to brain imaging, minutes, median (IQR)	138 (112.5–181.5)	131 (102.5–178)		0.389
Time from stroke onset to treatment, minutes, median (IQR)	230 (200.5–270)	190 (150–245)		0.007

NIHSS National Institute of Health Stroke Scale, *IQR* interquartile range

Table 1. Demographic and clinical features of the study group according to COVID-19 status.

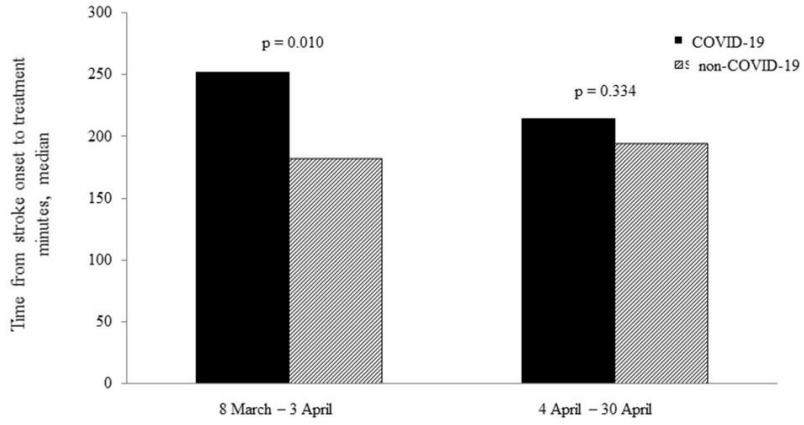


Figure 1. Time from stroke symptoms onset to treatment according to COVID-19 status in the two study periods.

Table 3 In-hospital outcome of acute ischemic stroke patients stratified by COVID-19 status

	COVID-19 ($n=34$)	Non-COVID-19 ($n=262$)	Univariable OR (95% CI)	p value
Stroke severity at 24 h, NIHSS score	10 (4.5–18.5)	5 (2–10)	1.05 (1.01–1.10)	0.014
Any intracranial heamorrhage	12 (35.3)	51 (19.5)	2.24 (1.04–4.83)	0.035
Symptomatic intracranial hemorrhage	4 (11.8)	16 (6.1)	2.04 (0.64–6.50)	0.265
In-hospital recurrence	0 (0.0)	5 (1.9)	0.98 (0.96–0.99)	1.000
Functional independence upon hospital discharge (mRS, 0–2)	9 (30.0)	133 (56.1)	0.33 (0.14–0.76)	0.007
In-hospital death	13 (38.2)	23 (8.8)	6.43 (2.85–14.50)	≤0.001

NIHSS National Institute of Health Stroke Scale, functional independence was defined as a score on the modified Rankin scale of 0–2

HEMATOLOGY AND ONCOLOGY

IBRUTINIB INTERFERES WITH INNATE IMMUNITY IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS DURING COVID-19 INFECTION

Fiorcari S, Atene CG, Maffei R, Debbia G, Potenza L, Luppi M, Marasca R.. Haematologica. 2021 Mar 11. doi: 10.3324/haematol.2020.277392. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Hematologists and oncologists from the University of Modena and Reggio Emilia in Italy conducted an in vitro study of the potential impact of ibrutinib treatment for chronic lymphocytic leukemia (CLL) on immune responses to SARS-CoV-2 using blood samples from CLL patients who had not been diagnosed with COVID-19 (see summary). They found cells treated with ibrutinib appeared to limit the cytokine storm and promote more Th1 immunity (Figure 1, Figure 2). Authors suggest ibrutinib may play a protective role in CLL patients with COVID-19 and argue in favor of its continued use in these patients.

SUMMARY

Blood samples were obtained from patients that matched standard diagnostic criteria for CLL and who have not experienced COVID-19 infection.

Peripheral blood mononuclear cells (PBMCs) were isolated and either used fresh or cryopreserved until they were used. They were treated with ibrutinib or vehicle then stimulated with SARS-CoV-2 Peptide Pools Protein S, S1, S+, N and M (Miltenyi Biotech) and analyzed using CSA for TNF-α and IFN-γ (Miltenyi Biotech). PBMCs were stained with CD14 and CD3 antibody in order to identify both the monocyte and T populations.

PBMCs before and after 3 months of ibrutinib therapy were stored in liquid nitrogen.

FIGURES

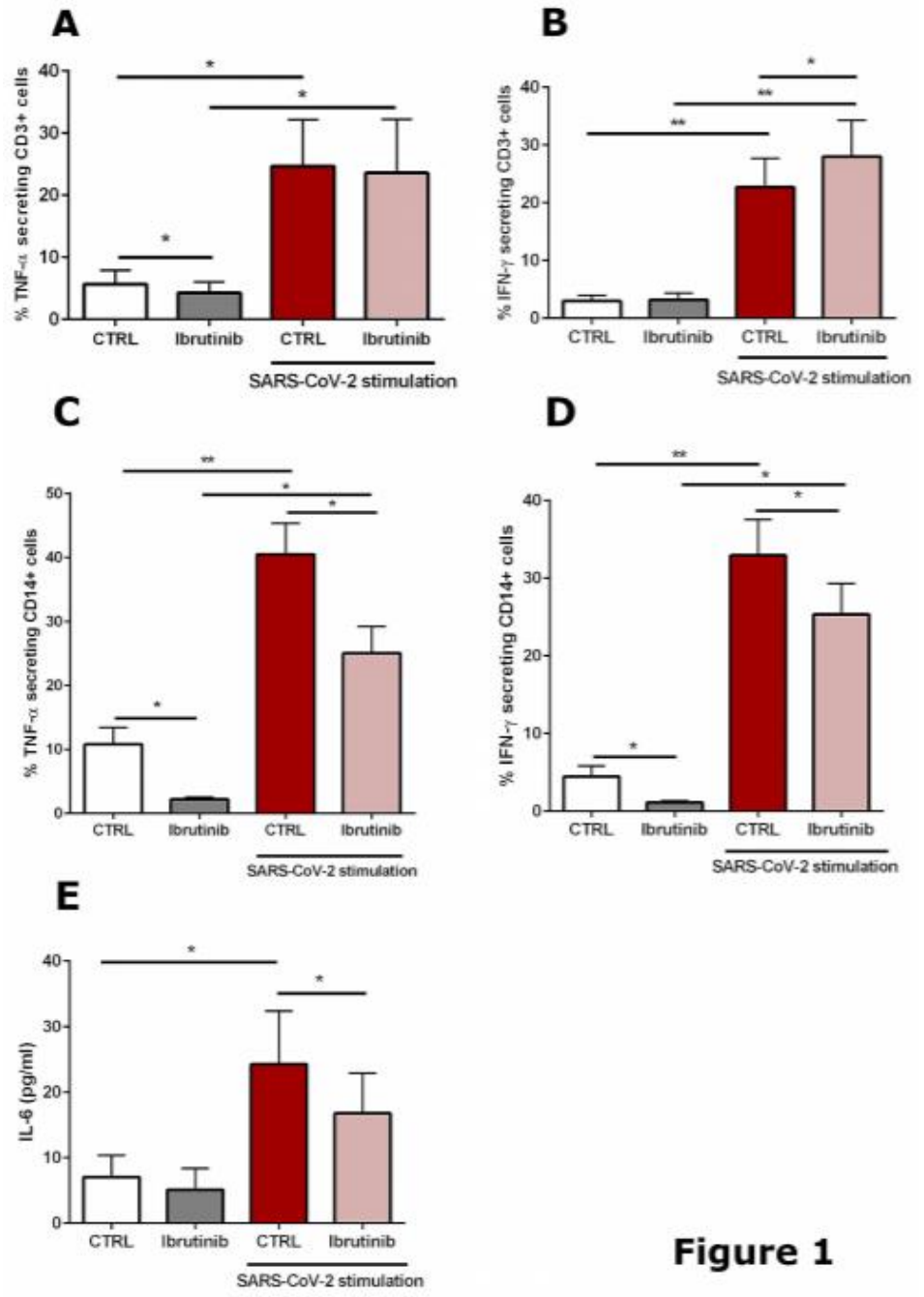


Figure 1. Immunomodulatory modifications induced by ibrutinib in CLL T cells and monocytes during infection by SARS-CoV-2. CLL PBMCs were isolated, treated with ibrutinib 1µM for 90 minutes and then stimulated with SARS-CoV-2 peptides (1 µg/ml) for additional 6 hours. TNF-α and IFN-γ secretion levels have been determined by cytokine secretion assay kit gating CD3+ and CD14+ populations by flow cytometry. A-B) Bar diagrams show the percentage of TNF-α and IFN-γ secretion by T cells either in presence or absence of stimulation by SARS-CoV-2 (n=7; *p<0.05,**p<0.01). C-D) Bar diagrams show the percentage of TNF-α and IFN-γ secretion by monocytes either in presence or absence of stimulation by SARS-CoV-2 (n=7; *p<0.05; **p<0.01). E) Conditioned media were collected for ELISA determination of IL-6. Bar diagrams represent the mean protein concentration measured in 11 separated experiments. Values presented are in pg/ml (n=11, *p<0.05).

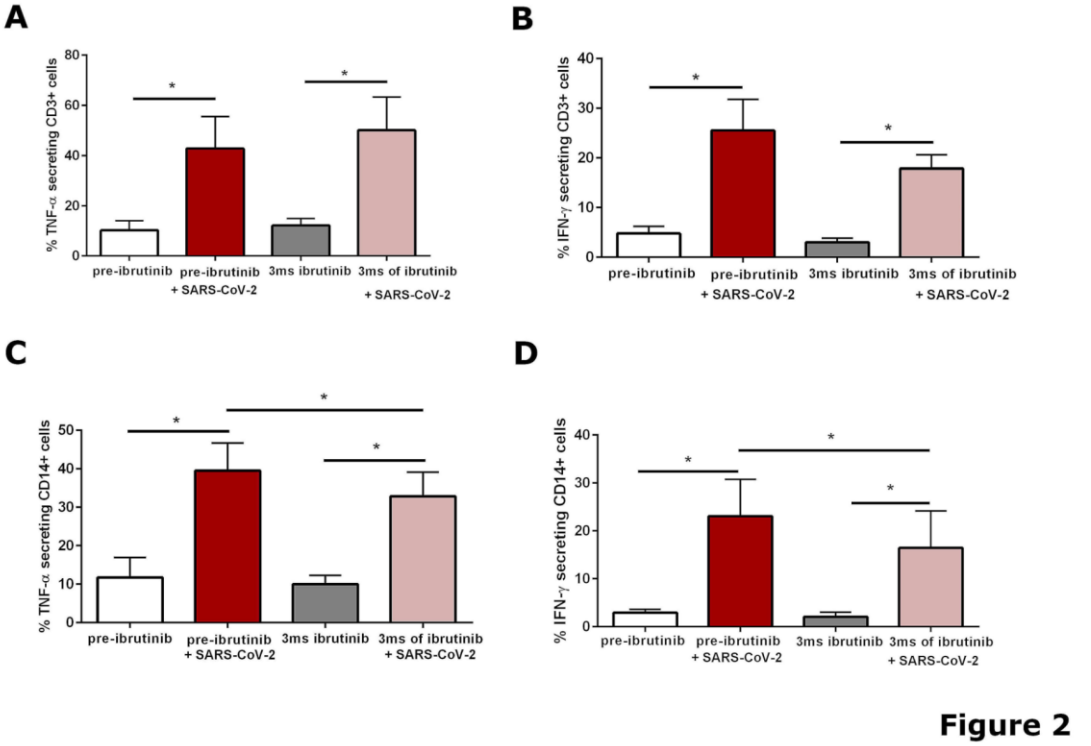


Figure 2

Figure 2. Immunological alterations in CLL patients under ibrutinib therapy during infection by SARS-CoV-2. CLL PBMCs were isolated from CLL patients before and after 3 months of treatment with ibrutinib and stimulated with SARS-CoV-2 peptides (1 µg/ml) for 6 hours. TNF-α and IFN-γ secretion levels have been determined by cytokine secretion assay kit gating CD3+ and CD14+ populations by flow cytometry. A-B) Bar diagrams show the percentage of TNF-α and IFN-γ secretion by T cells either in presence or absence of stimulation by SARS-CoV-2 (n=7; *p<0.05). C-D) Bar diagrams show the percentage of TNF-α and IFN-γ secretion by monocytes either in presence or absence of stimulation by SARS-CoV-2 (n=7; *p<0.05).

CARE FOR CHILDREN WITH HAEMOPHILIA DURING COVID-19: DATA OF THE PEDNET STUDY GROUP

Álvarez-Román MT, Kurnik K; PedNet Study Group.. Haemophilia. 2021 Mar 8. doi: 10.1111/hae.14286. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

The Departments of Hematology from La Paz University Hospital-IdiPaz in Madrid, Spain and University of Munich in Germany conducted a survey of 21 hemophilia treatment centers (HTCs) from Europe, Canada and Israel which all specialize in pediatric treatment and are part of the established PedNet network, detailing how they have adapted care during the COVID-19 pandemic with data from March 11, 2020 through July 20, 2020. Most of these specialized centers had to rapidly adapt while continuing to be accessible in some way with 65% switching to mainly telemedicine and only 25% remaining open as usual (Table 1). In addition, there was a decrease in supportive care such as social workers (45% of normal), physiotherapy (15% of normal), and homecare nurses (40% of normal), highlighting the toll of treatment changes in light of an unprecedented and uncontrollable setting, especially in pediatric patients with disease not well managed yet and no access to home therapies.

FIGURES

		%
Limited access to HTC	All outpatient clinics resumed as usual	25
	All outpatient clinics were cancelled	0
	For outpatients, emergency visits were allowed	55
	Other	20
Use of telemedicine programme	Yes	65
	No	35
Supportive care available as usual	Homecare by nurses	40
	Physiotherapy	15
	Social workers	45
	Summer camp	5
Informed about changes	By sending letters	15
	Via website	15
	Via phone individually	65
	Via webinar	10
	Other	30
Treatment	Continuation prophylaxis in severe patients	100
Clinical trials	Affected	35
	Continuation of recruitment	15
Change in external monitoring schedule	Cancelled by HTC	40
	Cancelled by CRO company	15
	Cancelled by HTC and CRO company	25
	Continued as usual	10
	Not applicable	10

Note: All the centres answered all the questions, but they did not add up to 20 (100%) since any of them were a multiple choice question.

Table 1. Results of the survey in percentages.

TOCILIZUMAB IN PATIENTS WITH MODERATE OR SEVERE COVID-19: A RANDOMIZED, CONTROLLED, OPEN-LABEL, MULTICENTER TRIAL

Wang D, Fu B, Peng Z, Yang D, Han M, Li M, Yang Y, Yang T, Sun L, Li W, Shi W, Yao X, Ma Y, Xu F, Wang X, Chen J, Xia D, Sun Y, Dong L, Wang J, Zhu X, Zhang M, Zhou Y, Pan A, Hu X, Mei X, Wei H, Xu X.. Front Med. 2021 Mar 9. doi: 10.1007/s11684-020-0824-3. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

A randomized, controlled open-label trial conducted by physicians at First Affiliated Hospital of University of Science and Technology of China assessed the effectiveness of tocilizumab therapy to attenuate the cytokine storm in COVID-19 patients (Table 1). The tocilizumab group (n=34) had no statistically meaningful cure rate versus the control group (n=31) (p = 0.4133; Table 2), but did have statistically significant improvement of hypoxia from day 12 versus the control group (p = 0.0359) (Fig. 2) The implication being that tocilizumab could potentially be effective in improving hypoxia and oxygenation in COVID-19 patients.

ABSTRACT

Tocilizumab has been reported to attenuate the "cytokine storm" in COVID-19 patients. We attempted to verify the effectiveness and safety of tocilizumab therapy in COVID-19 and identify patients most likely to benefit from this treatment. We conducted a randomized, controlled, open-label multicenter trial among COVID-19 patients. The patients were randomly assigned in a 1:1 ratio to receive either tocilizumab in addition to standard care or standard care alone. The cure rate, changes of oxygen saturation and interference, and inflammation biomarkers were observed. Thirty-three patients were randomized to the tocilizumab group, and 32 patients to the control group. The cure rate in the tocilizumab group was higher than that in the control group, but the difference was not statistically significant (94.12% vs. 87.10%, rate difference 95% CI-7.19%-21.23%, P = 0.4133). The improvement in hypoxia for the tocilizumab group was higher from day 4 onward and statistically significant from day 12 (P = 0.0359). In moderate disease patients with bilateral pulmonary lesions, the hypoxia ameliorated earlier after tocilizumab treatment, and less patients (1/12, 8.33%) needed an increase of inhaled oxygen concentration compared with the controls (4/6, 66.67%; rate difference 95% CI-99.17% to-17.50%, P = 0.0217). No severe adverse events occurred. More mild temporary adverse events were recorded in tocilizumab recipients (20/34, 58.82%) than the controls (4/31, 12.90%). Tocilizumab can improve hypoxia without unacceptable side effect profile and significant influences on the time virus load becomes negative. For patients with bilateral pulmonary lesions and elevated IL-6 levels, tocilizumab could be recommended to improve outcome.

FIGURES

Table 1 Baseline patient characteristics

Characteristics	Tocilizumab group ($N = 34$)	Control group ($N = 31$)	All
Age (year, median (IQR))	63.5 (58–71)	63 (54–69)	63 (55–71)
Sex (n (%))			
Male	18 (52.94)	15 (48.39)	33 (50.77)
Female	16 (47.06)	16 (51.61)	32 (49.23)
Symptom onset to randomization (median (IQR))	20 (9–29)	24 (19–33)	23 (12–30)
Coexisting condition (n (%))			
Hypertension	10 (29.41)	10 (32.26)	20 (30.77)
Diabetes	4 (11.76)	6 (19.35)	10 (15.38)
Others	8 (23.53)	9 (29.03)	17 (26.15)
Symptoms (n (%))			
Cough	13 (38.24)	15 (48.39)	28 (43.08)
Shortness of breath	12 (35.29)	11 (35.48)	23 (35.38)
Fever	8 (23.53)	5 (16.13)	13 (20.00)
Phlegm	6 (17.65)	6 (19.35)	12 (18.46)
Fatigue	3 (8.82)	5 (16.13)	8 (12.31)
Vital signs (median (IQR))			
Body temperature (°C)	36.6 (36.4–36.9)	36.6 (36.3–36.9)	36.6 (36.4–36.9)
Heart rate (beat/min)	80.5 (76–86)	82 (74–88)	82 (76–87)
Respiratory rate (breath/min)	20 (18–20)	20 (19–20)	20 (19–20)
Laboratory parameters (median (IQR))			
White cell count ($\times 10^9$/L)	6.265 (5.56–8.15)	5.77 (4.2–7.35)	6.15 (4.56–7.47)
Lymphocyte count ($\times 10^9$/L)	1.085 (0.895–1.645)	1.32 (0.92–1.58)	1.185 (0.91–1.6)
C-reactive protein (mg/L)	9.95 (3.3–23.6)	6.28 (1.15–33.7)	7.58 (3–32.04)
IL-6 (pg/mL)	26.03 (12.76–58.04)	24.35 (9.895–85.325)	25.13 (10.4–77.44)
ALT (U/L)	34 (18–69)	23 (15–43)	27 (16–59)
AST (U/L)	24 (20–32)	23 (20–31)	24 (20–32)
Creatine kinase (U/L)	66 (52.1–74)	70 (60–78)	68 (55–76)
Blood urea nitrogen (mmol/L)	4.55 (3.845–5.43)	4.22 (3.5–5.1)	4.36 (3.62–5.4)
Oxygen support mode (n (%))			
Nasal cannula	21 (61.76)	17 (54.84)	38 (58.46)
Mask	2 (5.88)	2 (6.45)	4 (6.15)
High flow	3 (8.82)	3 (9.68)	6 (9.23)
Air	8 (23.53)	9 (29.03)	17 (26.15)
Disease severity (n (%))			
Moderate	20 (58.82)	17 (54.84)	37 (56.92)
Severe	14 (41.18)	14 (45.16)	28 (43.08)
Fingertip oxygen saturation (median (IQR))	97 (96–98)	98 (96–99)	97 (96–98.5)
Drug combination (n (%))			
Glucocorticoid	5 (14.71)	2 (6.45)	7 (10.77)

Table 1 Baseline patient characteristics

Table 2 Comparison of the primary and secondary outcomes

Variables	Tocilizumab group	Control group	Rate or median difference 95% CI
Cure rate (n (%))	32 (94.12) ($N = 34$)	27 (87.10) ($N = 31$)	−7.19, 21.23
Rate of hypoxia recovery at day 14 (n (%))	22 (91.67) ($N = 24$)	12 (60.00) ($N = 20$)	7.52, 55.82
Length of hospitalization (median (IQR))	26 (17–27)	24 (15–28)	−4, 2
Time to negative virus (median (IQR))	17 (12–20)	16 (12–21.5)	−4, 5

Table 2 Comparison of the primary and secondary outcomes

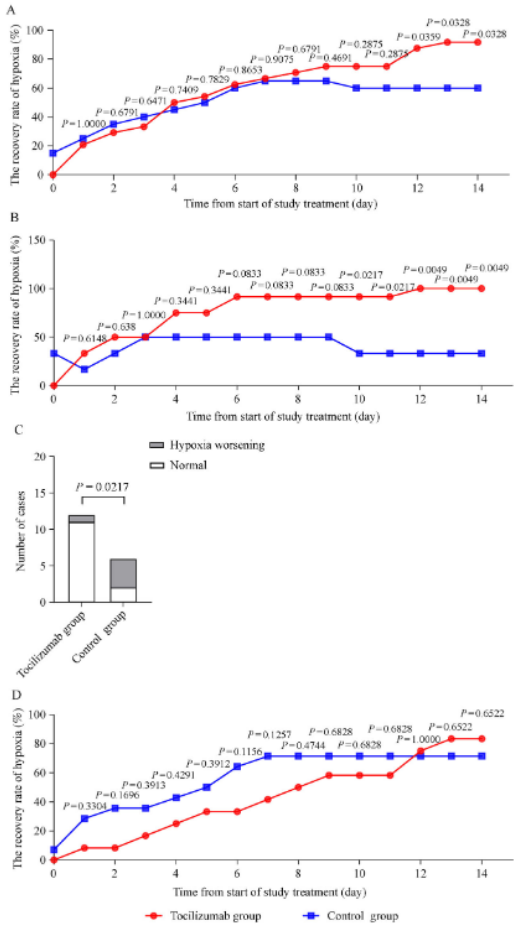


Fig. 2 Changes in hypoxia over 14 days. (A) The difference became significant ($P < 0.05$) on day 12 between the tocilizumab-treated group (●) and the controls (■). (B) Recovery rate of hypoxia in moderate patients over 14 days. The difference became significant ($P < 0.05$) on day 10 between the two groups. (C) Worsening rate of hypoxia during hospitalization in moderate patients. Less patients worsened in the tocilizumab-treated group (1/12, 8.33%) than in the controls (4/6, 66.67%) who needed an increase of inhaled oxygen concentration. (D) Recovery rate of hypoxia in severe patients over 14 days. No statistical differences were observed between patients treated with or without tocilizumab.

Fig. 2Changes in hypoxia over 14 days. (A) The difference became significant (P<0.05) on day 12 between the tocilizumab-treated group () andthe controls (). (B) Recovery rate of hypoxia in moderate patients over 14 days. The difference became significant (P<0.05) on day 10 between thetwo groups. (C) Worsening rate of hypoxia during hospitalization in moderate patients. Less patients worsened in the tocilizumab-treated group (1/12,8.33%) than in the controls (4/6, 66.67%) who needed an increase of inhaled oxygen concentration. (D) Recovery rate of hypoxia in severe patients over 14 days. No statistical differences were observed between patients treated with or without tocilizumab

DEVELOPMENTS IN DIAGNOSTICS

SARS-COV-2-DIRECTED ANTIBODIES PERSIST FOR MORE THAN SIX MONTHS IN A COHORT WITH MILD TO MODERATE COVID-19

Glück V, Grobecker S, Tydykov L, Salzberger B, Glück T, Weidlich T, Bertok M, Gottwald C, Wenzel JJ, Gessner A, Schmidt B, Peterhoff D.. Infection. 2021 Mar 10. doi: 10.1007/s15010-021-01598-6. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or “poor or non-independent reference standard

BLUF

Researchers of the department of microbiology at Regensburg University in Germany conducted a cohort study of 123 SARS-CoV-2 PCR-positive health-care workers to assess anti-SARS-CoV-2 Immunoglobin (IgG, IgM, IgA) levels for 30 weeks. They found that both levels of IgA and IgM decreased during follow up, but IgG levels remained elevated in 90% of participants for the duration of the study. They also found a correlation between IgG levels and increased age (p = 0.042, Figure.3) and severity of disease (p = 0.04, Table.2).

ABSTRACT

OBJECTIVE: To follow serological immune responses of front-line healthcare workers after PCR-confirmed COVID-19 for a mean of 30 weeks, describe the time-course of SARS-CoV-2 spike protein-specific IgG, IgA and IgM levels and to identify associations of the immune response with symptoms, demographic parameters and severity of disease. METHODS: Anti-SARS-CoV-2 S protein-specific IgG, IgA and IgM antibodies were measured at three time points during the 30-week follow-up. COVID-19-specific symptoms were assessed with standardized questionnaires. RESULTS: 95% of the participants mounted an IgG response with only modest decline after week 12. IgG-type antibodies were still detectable in almost 90% of the subjects at 30 weeks. IgA and IgM responses were less robust and antibody titers decreased more rapidly. At 30 weeks, only 25% still had detectable IgA-type and none had IgM-type antibodies. Higher age and higher disease severity were independently associated with higher IgG antibody levels, albeit with wide variations. CONCLUSION: Serological immune responses after COVID-19 show considerable inter-individual variability, but show an association with increasing age and higher severity of disease. IgG-type anti-SARS-CoV-2 antibodies remain positive in 90% of the individuals 30 weeks after onset of symptoms.

FIGURES

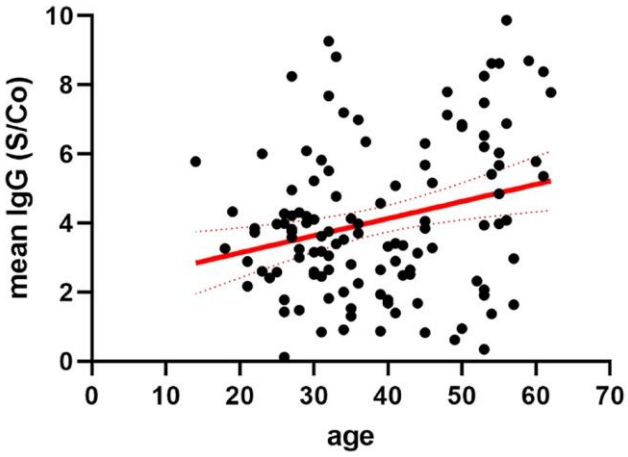


Figure.3

Table 2

Results of a generalized linear model with IgG levels (mean and 95% confidence intervals) as dependent variable over three time points as rep measurements

		Time point of serum sampling					
		First (3 weeks)		Second (12 weeks)		Third (30 weeks)	
Disease severity	Mild	4.34 (3.54-5.14)	↔ $p<0.05$	4.00 (3.32-4.67)	↔ $p<0.05$	2.98 (2.29 -3.67)	
		↕ n.s.	↕ n.s.	↕ $p<0.05$	↕ n.s.	↕ $p<0.05$	↕ n.s.
	Moderate	5.02 (4.03-5.62)	↔ n.s.	5.43 (4.59-6.36)	↔ $p<0.05$	4.14 (3.29-5.00)	
	Severe	6.17 (3.97-8.38)	↔ n.s.	5.42 (3.56-7.28)	↔ $p<0.05$	3.31 (1.41-5.22)	

n.s. not significant

MONOCLONAL ANTIBODIES FOR COVID-19

Lloyd EC, Gandhi TN, Petty LA.. JAMA. 2021 Mar 9;325(10):1015. doi: 10.1001/jama.2021.1225.
Level of Evidence: 5 - Review / Literature Review

BLUF

This review article authored by Physicians at University of Michigan Health System, Ann Arbor, provides information regarding the use of monoclonal antibodies, which target the spike protein on the surface of SARS-CoV-2, for treatment of COVID-19 in patients who do not require hospitalization, but have factors that place them at an increased risk of severe infection. Adverse effects of monoclonal antibody use include allergic and non-allergic infusion-related reactions presenting as flushing, itching, shortness of breath or low blood pressure. This review suggests that the use of monoclonal antibodies could be particularly beneficial for the prevention of severe COVID-19 development in patients who are considered high risk, >65 years old, or patients with certain medical conditions, such as obesity.

NEUTRALIZING APTAMERS BLOCK S/RBD-ACE2 INTERACTIONS AND PREVENT HOST CELL INFECTION

Liu X, Wang YL, Wu J, Qi J, Zeng Z, Wan Q, Chen Z, Manandhar P, Fu X, Zhang X, Salazar E, Umetani M, Sen M, Willson RC, Chen SH, Zu Y, Cavener VS, Boyle NR, Kuchipudi SV, Kapur V.. Angew Chem Int Ed Engl. 2021 Mar 8. doi: 10.1002/anie.202100345. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A recent in vitro experiment conducted by doctoral researchers associated with Houston Methodist Hospital and University of Houston utilized synthetic oligonucleotide aptamers to target the receptor-binding domain (RBD) of SARS-CoV-2 spike (S) proteins. The study found that synthetic aptamers blocked S/RBD and ACE2 receptor interactions with an IC50 = 5.2 nM and 4.4 nM (Fig. 3) and prevented host cell infection via neutralization of S-proteins with a neutralization IC50 = 76.9 nM and 53.0 nM (Fig. 3f). This data suggests that neutralizing aptamers could be a promising avenue to create novel COVID-19 therapies.

ABSTRACT

The receptor-binding domain (RBD) of the severe acute respiratory syndrome coronavirus 2 spike (S) protein plays a central role in mediating the first step of virus infection to cause disease: virus binding to angiotensin-converting enzyme 2 (ACE2) receptors on human host cells. Therefore, S/RBD is an ideal target for blocking and neutralization therapies to prevent and treat coronavirus disease 2019 (COVID-19). Using a target-based selection approach, we developed oligonucleotide aptamers containing a conserved sequence motif that specifically targets S/RBD. Synthetic aptamers had high binding affinity for S/RBD-coated virus mimics (K D ~7 nM) and also blocked interaction of S/RBD with ACE2 receptors (IC 50 ~5 nM). Importantly, aptamers were able to neutralize S protein-expressing viral particles and prevent host cell infection, suggesting a promising COVID-19 therapy strategy.

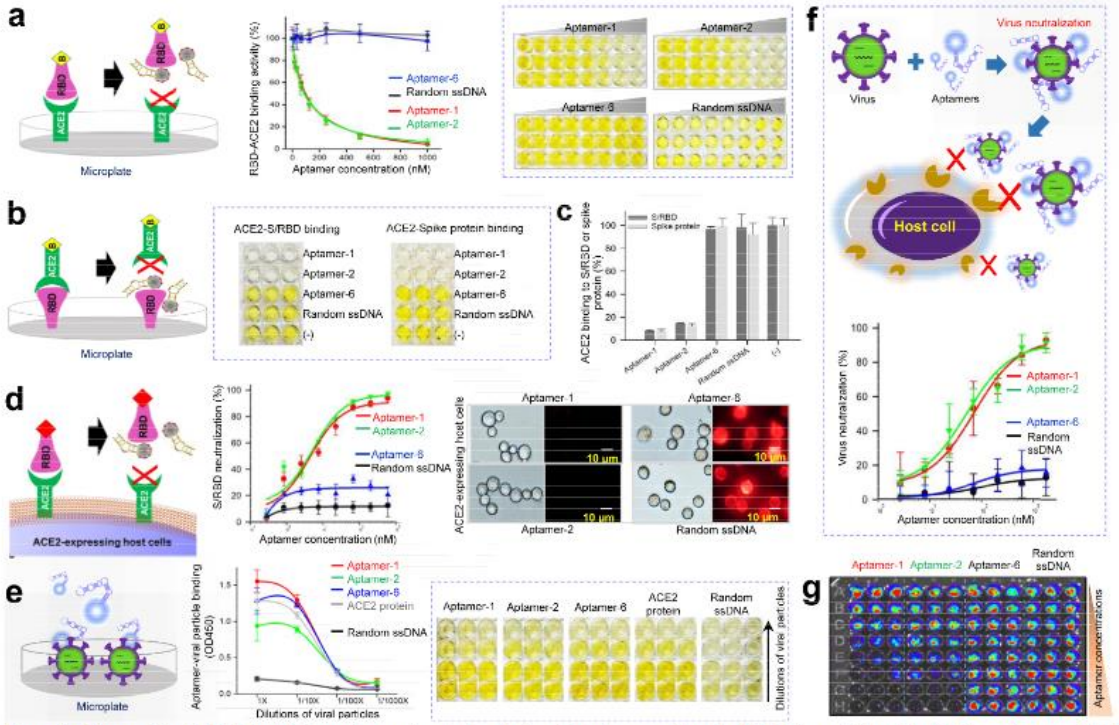


Figure 3. Aptamers block S/RBD-ACE2 interaction and neutralize viral particles to prevent host cell infection. a, Schematic depicting aptamer-mediated blockade of S/RBD-ACE2 interaction. ELISA reveals that aptamers-1 and -2 block S/RBD binding to ACE2 receptor proteins pre-coated on microplates (mimicking host cell surface). In contrast, aptamer-6 and random ssDNA sequences have no blocking effects under the same conditions. **b**, Aptamers-1 and -2 prevent ACE2 binding to S/RBD and **c**, S proteins pre-coated on microplates (mimicking virus surface). **d**, Flow cytometry and fluorescent microscopy demonstrate that aptamers-1 and -2 interrupt S/RBD binding to ACE2-expressing host cells. Aptamer-6 shows minimal blocking effects and random ssDNA sequences have no effect. **e**, Aptamers specifically target S protein-expressing viral particles in a virus dose-dependent manner, similar to the pattern observed with ACE2 protein. **f**, Virus neutralization assays. Aptamers-1 and -2 effectively neutralize viral particles and prevent host cell infection, while aptamer-6 and control random ssDNA sequences do not. **g**, Aptamer virus neutralization effects were also confirmed post-treatment using bioluminescent imaging of microplates, which contained intact host cells in the presence of luciferin for signal development.

Figure 3. Aptamers block S/RBD-ACE2 interaction and neutralize viral particles to prevent host cell infection.a, Schematic depicting aptamer-mediated blockade of S/RBD-ACE2 interaction. ELISA reveals that aptamers-1 and -2 block S/RBD binding to ACE2 receptor proteins pre-coated on microplates (mimicking host cell surface). In contrast, aptamer-6 and random ssDNA sequences have no blocking effects under the same conditions. b, Aptamers-1 and -2 prevent ACE2 binding to S/RBD and c, S proteins pre-coated on microplates (mimicking virus surface). d, Flow cytometry and fluorescent microscopy demonstrate that aptamers-1 and -2 interrupt S/RBD binding to ACE2-expressing host cells. Aptamer-6 shows minimal blocking effects and random ssDNA sequences have no effect. e, Aptamers specifically target S protein-expressing viral particles in a virus dose-dependent manner, similar to the pattern observed with ACE2 protein. f, Virus neutralization assays. Aptamers-1 and -2 effectively neutralize viral particles and prevent host cell infection, while aptamer-6 and control random ssDNA sequences do not. g, Aptamer virus neutralization effects were also confirmed post-treatment using bioluminescent imaging of microplates, which contained intact host cells in the presence of luciferin for signal development

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