The Daily COVID-19 Literature Surveillance Team Report

June 16, 2020

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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

Climate

- Public health experts discuss the difficulties in obtaining personal protective equipment and other supplies for South American countries during the pandemic due to their reliance on imported supplies and emphasize the importance of global support during these times.
- A study of 217 frontline healthcare professionals in Germany found that individuals estimated their personal likelihood of infection at a mean of 21% with a relative increase in perceived infection risk in female and younger participants. However, weekly SARS-CoV-2 IgG serology revealed only a 1-2% prevalence of infection, leading the authors to suggest a gap in perceived versus actual SARS-CoV-2 infection risk in the healthcare setting.

Epidemiology

- A systematic review and meta-analysis consisting of a total of 17,794 patients found that high cardiac troponin I and aspartate aminotransferase levels as well as advanced age were predictors of poor COVID-19 prognosis.
- A study of EEGs of 26 patients diagnosed with severe COVID-19 in various intensive care units throughout Paris found that five patients demonstrated a delta wave pattern concerning for brain injury as a direct or indirect result of COVID-19 leading the authors to encourage the use of EEGs to assess COVID-19 patients that present with unexplained changes in mental status.
- A retrospective study of 182 children, 43 of whom had history of allergic disease, found no difference between rate or severity of disease between the two populations suggesting that having a history of allergic disease does not place children at a higher risk for developing COVID-19

Understanding the Pathology

- A molecular and genetic analysis of SARS-CoV-1, SARS-CoV-2, and MERS-CoV conducted at the National Institutes of Health found that key changes in the nuclear localization sequence and distinct insertions in the spike glycoprotein of the virus may be responsible for the high pathogenicity of SARS-CoV-2 compared to SARS-CoV-1 and MERS-CoV.
- A study of cardiac tissue found SARS-CoV-2 gene sequences - specifically low amounts (100-500 copies/reaction) of the SARS-CoV-2 E-gene - in endomyocardial tissue biopsies of five out of 104 patients with suspected myocarditis or unexplained heart failure showing a possible link between COVID-19 infection and cardiac involvement.

Management

- Guidelines and recommendations include proper management of infected neonates or neonates born to parents with COVID-19
- A retrospective cohort study of patients admitted to Tongji Hospital in Wuhan, China found that patients with Interstitial Lung Disease (ILD) exhibited increased severity of COVID-19 compared to non-ILD patients (39.29% vs 15.38%, P = 0.004).
- A modeling study conducted by Certara utilizing the "Simcyp (V19.1) population-based physiologically based pharmacokinetic (PBPK) simulator", found that when lung pH decreased from 6.7 to 6.0, the lung to plasma partition coefficient increased and the lung exposure of azithromycin, hydroxychloroquine, and chloroquine increased 2.7, 4.0, and 20 times, respectively, suggesting that therapeutic doses for these drugs may need to be adjusted in the treatment of patients with COVID-19 to avoid overexposure.
    - Additionally, renal impairment, which is a common comorbidity with COVID-19, increased the exposure of azithromycin, hydroxychloroquine, and chloroquine in the lungs by 3.4, 8.0, and 30 times, respectively, suggesting that renal functioning must also be considered when determining therapeutic drug dosages.
- A matched cohort study in multiple surgical units of Spedali Civil Hospital found that 30-day mortality rates and post-op complications, especially pulmonary and thrombotic, were significantly higher in 41 surgical patients with COVID-19 than 82 controls without COVID-19 (mortality OR: 9.5, 95% CI: 1.77-96.53; complications OR: 4.98, 95% CI: 1.81-16.07), suggesting that COVID-19 disease is an important consideration for postponing surgery when possible.

Adjusting Practice During COVID-19

- Guidelines and recommendations for adjusting practice during the pandemic include:
    - Strategies to address factors that may worsen cardiometabolic risk factors monitoring
- A retrospective cohort study involving 307 COVID-19 patients found significant co-infection rates with Influenza A (49.8%) and Influenza B (7.5%) and patients co-infected with Influenza B and SARS-CoV-2 exhibited worse prognosis as they were more likely to have chest CT abnormalities, fatigue, decreased lymphocyte count, and decreased eosinophil counts. Thus, authors recommend testing for Influenza A and B in any COVID-19 patients as early detection and treatment could potentially improve patient outcomes.

R&D: Diagnosis and Treatment

- A study of 16 COVID-19 patients in Greece received hydroxychloroquine and azithromycin and were then classified into two groups (Group A, with persistent fever and "severe radiological findings", received lopinavir/ritonavir as a third agent with n=8 while Group B did not). Findings suggest that lopinavir/ritonavir may be effective at reducing the viral load in patients with severe SARS-CoV-2 infections.
- A newly developed rapid (30-45 minute) screening diagnostic test for SARS-CoV-2 using a reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay was both sensitive (95%) and specific (90%) in detecting SARS-CoV-2 infection in patients by quantitative RT-PCR in vitro and thus warrants investigation outside of the laboratory.

Mental Health & Resilience Needs

- An online survey of 996 participants from 22 countries, using HEXACO (Honesty-Humility, Emotionality, Extraversion, Agreeableness, Conscientiousness, and Openness to Experience) inventory to determine personality dimensions, found that 'Emotionality' predicted perceived threat of COVID-19 ($p<0.01$), which may have indirectly affected stockpiling behavior, and individuals high in 'Conscientiousness' engaged in more toilet paper stockpiling ($p=0.048$). Thus, it was suggested that effective communication by public authorities may lead to decreased anxiety levels and reduce commodity stockpiling during a pandemic.

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CLIMATE

ABDOMINAL PREGNANCY DURING THE COVID-19 PANDEMIC

Damiani GR, Biffi A, Del Boca G, Arezzo F.. Int J Gynaecol Obstet. 2020 Jun 10. doi: 10.1002/ijgo.13271. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

A case study by Italian authors describes a 33-year-old who presented with abdominal pain for 15 days and delayed seeking care due to fear of contracting COVID-19. The patient was found to be at 14 weeks gestation with a fetus posterior to the uterus along with 2 liters of blood in the pouch of Douglas. After hemodynamic resuscitation, the fetus and decidual tissue were removed laparoscopically, and the patient recovered well after treatment with methotrexate. While the patient tested negative for COVID-19, this case highlights the potentially deleterious effects of delaying care during the pandemic for acute non-COVID-19-related medical problems due to fear of disease contraction.

ABSTRACT

Abdominal pregnancy is a rare type of ectopic pregnancy with an incidence of 1:10 000 to 1:30 000 women. Several different locations have been reported, including the pouch of Douglas, pelvic sidewall, bowel, broad ligament, omentum, and spleen. Most abdominal pregnancies are diagnosed after presenting with various complications; however, in a few cases it may remain asymptomatic and is rarely established before surgery. Institutional Review Board approval was not required for this case report; written informed consent was obtained.

GLOBAL

LATIN AMERICA AND ITS GLOBAL PARTNERS TOIL TO PROCURE MEDICAL SUPPLIES AS COVID-19 PUSHES THE REGION TO ITS LIMIT

Rubin R, Abbasi J, Voelker R.. JAMA. 2020 Jun 12. doi: 10.1001/jama.2020.11182. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

This article describes the difficulties in obtaining personal protective equipment (PPE) and other medical supplies that South American countries face during the COVID-19 pandemic due to their reliance on imported supplies and lack of manufacturing resources. The authors also describe how many of these countries have tried to compensate by equipping more hospitals with beds, workers, and other supplies.

AFFECTING THE HEALTHCARE WORKFORCE

PERCEIVED VERSUS PROVEN SARS-COV-2-SPECIFIC IMMUNE RESPONSES IN HEALTH-CARE PROFESSIONALS

Behrens GMN, Cossmann A, Stankov MV, Witte T, Ernst D, Happle C, Jablonka A.. Infection. 2020 Jun 10. doi: 10.1007/s15010-020-01461-0. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers in Northern Germany conducted a prospective cohort study regarding perception of risk versus actual SARS-CoV-2 infection in 217 frontline healthcare professionals from March through April 2020. Participants estimated their personal likelihood of infection at a mean of 21% (median 15%, interquartile range 5-30%), with a relative increase in perceived infection risk in female and younger participants. However, weekly SARS-CoV-2 IgG serology revealed only a 1-2% prevalence of infection, suggesting a gap in perceived versus actual SARS-CoV-2 infection risk in the healthcare setting (Figure 1).

ABSTRACT

There have been concerns about high rates of thus far undiagnosed SARS-CoV-2 infections in the health-care system. The COVID-19 Contact (CoCo) Study follows 217 frontline health-care professionals at a university hospital with weekly SARS-CoV-2-specific serology (IgA/IgG). Study participants estimated their personal likelihood of having had a SARS-CoV-2 infection with a mean of 21% [median 15%, interquartile range (IQR) 5-30%]. In contrast, anti-SARS-CoV-2 IgG prevalence was about 1-2% at baseline. Regular anti-SARS-CoV-2 IgG testing of health-care professionals may aid in directing resources for protective measures and care of COVID-19 patients in the long run.

FIGURES

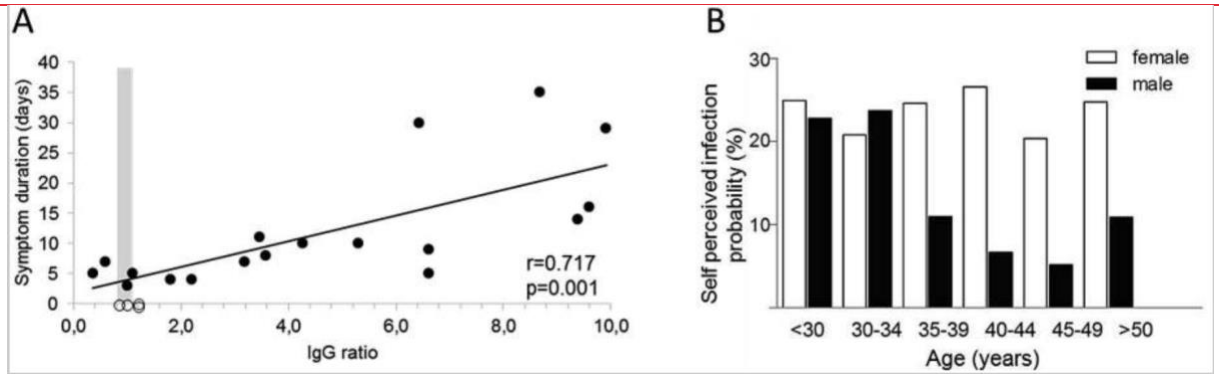


Figure 1: a. Anti-SARS-CoV-2 IgG ELISA results. PCR-confirmed COVID-19 cases are depicted as black dots, and health-care professionals depicted as open dots (for which symptoms were not considered). The gray zone (0.8–1.1 ratio) represents the range with equivocal ELISA results. b. Differences in mean self-perceived probability for SARS-CoV-2 infection in relation to sex and age

DISPARITIES

STRUCTURAL BARRIERS TO ADHERING TO HEALTH BEHAVIOURS IN THE CONTEXT OF THE COVID-19 CRISIS: CONSIDERATIONS FOR LOW- AND MIDDLE-INCOME COUNTRIES

Coetzee BJ, Kagee A.. Glob Public Health. 2020 Jun 11:1-10. doi: 10.1080/17441692.2020.1779331. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

The authors describe the importance of national lockdowns on fighting the COVID-19 pandemic and also highlight the effects of the lockdowns on low- and middle-income families in countries around the world by conceptualizing structural barriers and utilizing the Theoretical Domains Framework to explain how they influence adherence to lockdown rules. The authors recommend that to counter these problems (summarized below) governments need to make sure health and resource information is both easily accessible and effectively disseminated to their populations. They will need to provide resources such as e-banking, water, food, and sanitation, and they will need to engage with traditional leaders in the community to partner in their efforts.

SUMMARY

The authors describe how

- Social isolation disproportionately impacts those who live in overcrowded homes possibly without sanitation and running water
- Employment status is affected by the adaptability of occupations to be transferred onto an online format, people employed in industries that cannot support that shift are excessively impacted
- The risk of COVID-19 must be considered against prevailing conditions such as war, crime, political strife, threat of domestic violence, and endemic diseases
- Health literacy of populations and capacity to disseminate information through the availability of internet and other messaging modalities affects population compliance with physical distancing and isolation practices.
- Demographic challenges with health policy compliance, which has historically been seen in youth and younger adults, will affect compliance
- Traditional and cultural beliefs such as religious congregating are often at odds with public health advice

ABSTRACT

ABSTRACT In seeking to limit the number of new infections of COVID-19, governments around the world have implemented national lockdowns and guidelines about safe behaviours. Lockdown requires people to stay home and only leave when essential such as to purchase groceries and medication. In low- and middle-income countries, many of which have large proportions of the population living in precarity, lockdown forces millions of people to spend prolonged periods of time together in close proximity to one another and with limited resources. In many ways, efforts to contain the spread of COVID-19 in densely populated communities with limited access to food, water and sanitation may seem counter-intuitive and even impossible under conditions of precarity. In this paper, we explore the barriers to implementation of lockdown rules in conditions of precarity. We conceptualise the structural barriers by drawing on the Theoretical Domains Framework to explain how these barriers influence adherence to lockdown rules. We argue that without sufficient support or intervention to help poor communities mitigate these structural barriers, adhering to lockdown rules is difficult, resulting in continued COVID-19 infections.

EPIDEMIOLOGY

MODELING

THE IMPACT OF COVID-19 AND STRATEGIES FOR MITIGATION AND SUPPRESSION IN LOW- AND MIDDLE-INCOME COUNTRIES

Walker PGT, Whittaker C, Watson OJ, Baguelin M, Winskill P, Hamlet A, Djafaara BA, Cucunubá Z, Olivera Mesa D, Green W, Thompson H, Nayagam S, Ainslie KEC, Bhatia S, Bhatt S, Boonyasiri A, Boyd O, Brazeau NF, Cattarino L, Cuomo-Dannenburg G, Dighe A, Donnelly CA, Dorigatti I, van Elsland SL, FitzJohn R, Fu H, Gaythorpe KAM, Geidelberg L, Grassly N, Haw D, Hayes S, Hinsley W, Imai N, Jorgensen D, Knock E, Laydon D, Mishra S, Nedjati-Gilani G, Okell LC, Unwin HJ, Verity R, Vollmer M, Walters CE, Wang H, Wang Y, Xi X, Lalloo DG, Ferguson NM, Ghani AC.. Science. 2020 Jun 12:eabc0035. doi: 10.1126/science.abc0035. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

Epidemiologists in the United Kingdom used a SIR (susceptible–infected–removed) framework to model potential impact and theoretical mitigation strategies for COVID-19 infections in low- and middle-income countries. Taking into account demographics, social contact patterns, health care availability and quality, co-morbidities, and mitigation strategies; this model gives insight into how these variables may affect the number of cases in these countries and the ultimate health impact of COVID-19. Additional discussion on the variables included below.

SUMMARY

1. Using a simple SIR (susceptible–infected–removed) model, researchers estimated the theoretical burden of COVID-19 on low- and middle-income countries. This model assumes that there are no pharmaceutical interventions, such as a vaccine or effective treatment discovered. Additionally, other parameters taken into account are demographics, social contact patterns, healthcare availability and quality, co-morbidities, and mitigation and suppression strategies. The authors explain that these factors are important to take into account and may vary dramatically between high-income countries and low- to middle-income countries.
2. In terms of demographics and social contact patterns, low- and middle-income countries generally have younger populations and a smaller proportion of adults over the age of 65, which is a major risk factor of mortality with COVID-19 infections (Figure 1). The number of individuals living in a household was another key difference, with low- and middle-income countries, on average, have a higher persons per household.
3. Low- and middle-income countries also have fewer high-quality healthcare resources. For example, low-income countries have on average 1.28 ICU beds per 1,000 while high-income countries have 4.68 ICU beds per 1,000 (Figure 2). This may cause hospitals to become more easily overwhelmed and interfere with proper care for COVID-19 patients.
4. Co-morbidity prevalence is another difference, with current risk factors such as hypertension, diabetes, and chronic obstructive pulmonary disorder (COPD) having a higher prevalence in high-income countries. However, the incidence of diseases such as Tuberculosis and HIV is higher in low- and middle-income countries and it is unknown if these are a risk factor (Figure 3).
5. Ultimately, researchers used this model to predict the amount of social distancing that results in the highest mitigation of cases. Assuming "optimal" mitigation strategies are followed (e.g. social distancing), the model predicts a reduction in infections between 30-38% and a decrease in mortality between 19-55%.

ABSTRACT

The ongoing COVID-19 pandemic poses a severe threat to public health worldwide. We combine data on demography, contact patterns, disease severity, and health care capacity and quality to understand its impact and inform strategies for its control. Younger populations in lower income countries may reduce overall risk but limited health system capacity coupled with closer inter-generational contact largely negates this benefit. Mitigation strategies that slow but do not interrupt transmission will still lead to COVID-19 epidemics rapidly overwhelming health systems, with substantial excess deaths in lower income countries due to the poorer health care available. Of countries that have undertaken suppression to date, lower income countries have acted earlier. However, this will need to be maintained or triggered more frequently in these settings to keep below available health capacity, with associated detrimental consequences for the wider health, well-being and economies of these countries.

FIGURES

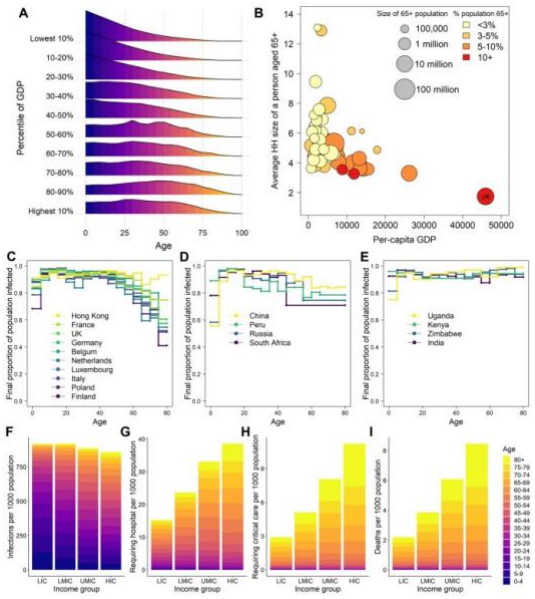


Figure 1. Demographic, societal and mixing patterns relevant to SARS-CoV-2 transmission and burden. (A) Aggregated demographic patterns within 2020 World Population Prospects (WPP) projections across countries within each 2018 World Bank (WB) GDP per-capita decile. (B) Average household size within Demographic Health Surveys (DHS) of individuals aged 65 and over by 2018 WB GDP per-capita. For reference, the average household size of contacts in the UK is also provided as an example for a HIC. (C) Final proportion of population infected in an unmitigated epidemic for an age-structured SIR model with R0 = 3.0 and age-specific social mixing based upon contact surveys identified in HICs. (D) and (E) equivalent figure for surveys identified in UMICs and LMIC/LICs respectively. F-I output from simulations across countries of an unmitigated pandemic with R0 = 3.0. (F) shows the attack rate in terms of number of individuals infected per 1000 population, (G) the equivalent rates of infection leading to illness requiring hospitalization, (H) illness requiring critical care and (I) mortality assuming a health system functioning at the level of China throughout the pandemic. LIC=low income country, LMIC=low-middle income country, UMIC=upper-middle income country, HIC=high income country

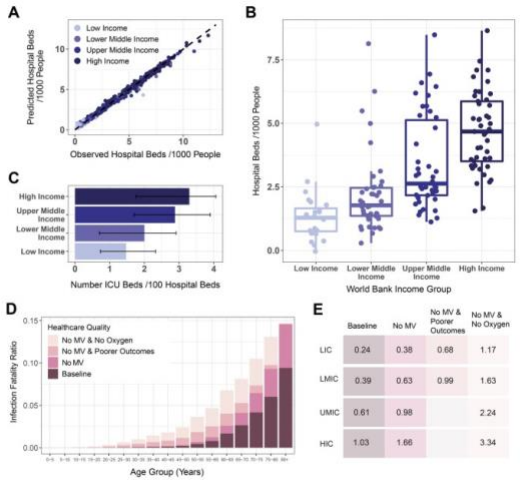


Figure 2. Estimates of hospital bed and ICU capacity, and the potential impact of health care quality on the infection fatality ratio. (A) Comparison of BRT model prediction and empirically observed numbers of hospital beds per 1000 population. Each point represents a country, with the x-axis indicating the observed number of hospital beds per 1000 population for that country, and the y-axis indicating the model predicted number of hospital beds per 1000 population. Coloring of the points indicates which World Bank income strata the country belongs to. (B) Boxplots of the number of hospital beds per 1000 population, stratified by World Bank income group. Points are modeled estimates of hospital beds per 1,000 population obtained from the model. (C) Results from a systematic review describing the percentage of all hospital beds that are in ICUs, stratified by World Bank income group. Error bars indicate the interquartile range of the median. (D) Age-stratified scenarios for the infection fatality ratio under different health care quality. The baseline are estimates based on data for highincome settings. “No MV” denotes not being able to access an ICU unit with mechanical ventilation available. “Poorer outcomes”

represents a higher risk of mortality from severe pneumonia in an LMIC setting if only limited or poor-quality oxygen support is available. "No Oxygen" represents the outcomes if hospitalized patients do not receive oxygen support. The stacked bars represent the cumulative increase in IFR at each stage. Note that the final stage "No MV and No Oxygen" represents the additional IFR due to increasing mortality rates from 20% in the presence of limited/poor-quality oxygen support to 60% in the absence of any oxygen support. (E) Estimated representative IFR averaged across age-groups in different settings under a range of health care quality assumptions. The differences between LIC, LMIC, UMIC and HIC at baseline reflect the demography and social contact patterns but otherwise assume the same health care quality. Lower health care quality is not shown for UMIC and HIC as these settings are likely to have the quality of health care incorporated in the baseline estimates.

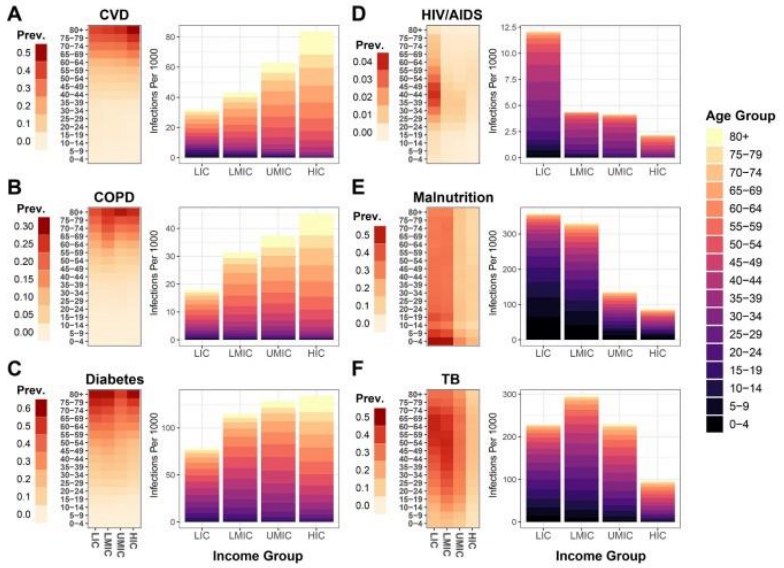


Fig. 3. The prevalence of different co-morbidities across income settings and the proportion of SARS-CoV-2 infections co-occurring with them. The age-distribution of co-morbidities relevant as modifiers of COVID-19 disease severity was extracted from Global Burden of Disease 2017 estimates (12) and integrated with estimates of the predicted age-distribution of infection in an unmitigated pandemic scenario. For (**A**) Cardiovascular Disease, (**B**) Chronic Obstructive Pulmonary Disease, (**C**) Diabetes, (**D**) HIV/AIDS, (**E**) Malnutrition and (**F**) Tuberculosis, the left heatmap shows the age-distribution of these co-morbidities across different income-settings, expressed as the proportion of the population in that income setting that have the comorbidity. The bar charts (colored according to age-group) shown the number of infections per 1,000 population that co-occur with the respective co-morbidity.

Figure 2. Estimates of hospital bed and ICU capacity, and the potential impact of health care quality on the infection fatality ratio. (A) Comparison of BRT model prediction and empirically observed numbers of hospital beds per 1000 population. Each point represents a country, with the x-axis indicating the observed number of hospital beds per 1000 population for that country, and the y-axis indicating the model predicted number of hospital beds per 1000 population. Coloring of the points indicates which World Bank income strata the country belongs to. (B) Boxplots of the number of hospital beds per 1000 population, stratified by World Bank income group. Points are modeled estimates of hospital beds per 1,000 population obtained from the model. (C) Results from a systematic review describing the percentage of all hospital beds that are in ICUs, stratified by World Bank income group. Error bars indicate the interquartile range of the median. (D) Age-stratified scenarios for the infection fatality ratio under different health care quality. The baseline are estimates based on data for highincome settings. "No MV" denotes not being able to access an ICU unit with mechanical ventilation available. "Poorer outcomes" represents a higher risk of mortality from severe pneumonia in an LMIC setting if only limited or poor-quality oxygen support is available. "No Oxygen" represents the outcomes if hospitalized patients do not receive oxygen support. The stacked bars represent the cumulative increase in IFR at each stage. Note that the final stage "No MV and No Oxygen" represents the additional IFR due to increasing mortality rates from 20% in the presence of limited/poor-quality oxygen support to 60% in the absence of any oxygen support. (E) Estimated representative IFR averaged across age-groups in different settings under a range of health care quality assumptions. The differences between LIC, LMIC, UMIC and HIC at baseline reflect the demography and social contact patterns but otherwise assume the same health care quality. Lower health care quality is not shown for UMIC and HIC as these settings are likely to have the quality of health care incorporated in the baseline estimates.

SYMPTOMS AND CLINICAL PRESENTATION

DOES CORONAVIRUS AFFECT THE AUDIO-VESTIBULAR SYSTEM? A RAPID SYSTEMATIC REVIEW

Almufarrij I, Uus K, Munro KJ.. Int J Audiol. 2020 Jun 12:1-5. doi: 10.1080/14992027.2020.1776406. Online ahead of print.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A rapid systematic review conducted by the University of Manchester in the United Kingdom, found that in two cross sectional studies and five case reports (Table 1), there were reports of hearing loss, tinnitus, vertigo, and otalgia associated with SARS-CoV-2. However, the reported incidence of such audio-vestibular symptoms was less than 1%, suggesting that either audio-vestibular symptoms are not reported as frequently as life-threatening symptoms or they are not common among patients diagnosed with COVID-19. Given the fair to poor quality of the studies reported, more high quality studies regarding the effects of SARS-CoV-2 on the audio-vestibular system are needed. The selection process for studies is demonstrated in Figure 1.

ABSTRACT

Objective: This rapid systematic review investigated audio-vestibular symptoms associated with coronavirus.Design: The protocol for the rapid review was registered in the International Prospective Register of Systematic Reviews and the review methods were developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Risk of bias was assessed using the National Institute of Heath quality assessment tools.Study sample: After rejecting more than 2300 records, there were five case reports and two cross-sectional studies that met the inclusion criteria.Results: No records of audio-vestibular symptoms were reported with the earlier types of coronavirus (i.e. severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]). Reports of hearing loss, tinnitus, and vertigo have rarely been reported in individuals who tested positive for the SARS-CoV-2.Conclusion: Reports of audio-vestibular symptoms in confirmed COVID-19 cases are few, with mostly minor symptoms, and the studies are of poor quality. Emphasis over time is likely to shift from life-threatening concerns to longer-term health-related consequences such as audio-vestibular dysfunction. High-quality studies are needed to investigate the acute effects of COVID-19, as well as for understanding long-term risks, on the audio-vestibular system. Review registration: Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020184932).

FIGURES

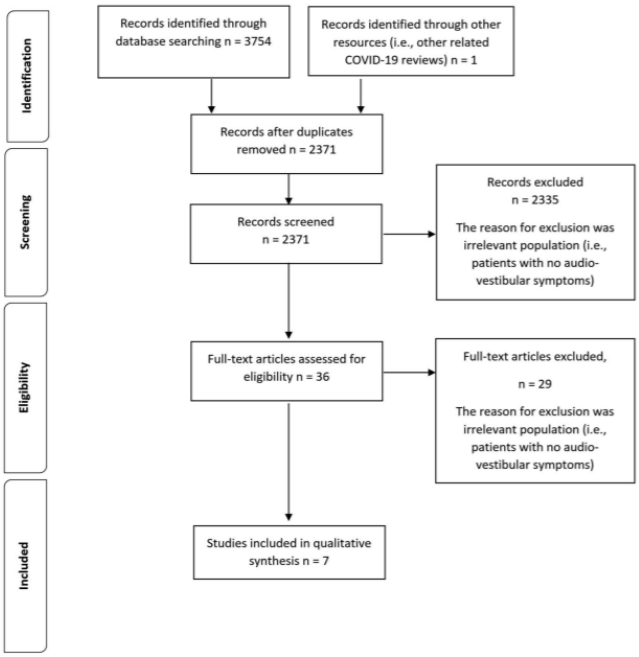


Figure 1. A flow diagram of the selection process based on preferred reporting items for systematic reviews and meta-analyses (PRISMA-P).

Table 1. The characteristics and main findings of the included studies.

Authors, publication year and setting	Study design	Participants	Audio-vestibular symptoms	Results	Overall quality rating* consensus
Cui et al. (2020) China	Case report	$N = 20$ (11M; 9F) Confirmed Covid-19 cases Median age = 63 years	Tinnitus ($N = 1$; 5%) Otitis externa ($N = 1$; 5%)	–	Fair
Fidan (2020) Turkey	Case report	$N = 1$ (F) Confirmed Covid-19 case Age = 35 years	Previously undefined ear-pain and tinnitus Acute otitis media and conductive hearing loss	• Unilateral mild to moderate conductive hearing loss.	Fair
Han et al. (2020) China	Case report	$N = 1$ (M) Confirmed Covid-19 case Age = 47 years	Vertigo		Fair
Lechien et al. (2020) Europe	Cross-sectionnal	$N = 1420$ (458M; 962F) Confirmed Covid-19 cases Mean age = 39.17 (SD 12) years	Ear pain ($N = 358$; 25%), Rotatory vertigo ($N = 6$; 0.4%) and tinnitus ($N = 5$; 0.3%),	–	Fair
Mustafa (2020) Egypt	Cross-sectionnal	SARS-CoV-2 group: $N = 20$ (age range 20 to 50 years) PTA = 17 dB HL Average TEOAE amplitude = 7.9 Control group: $N = 20$ PTA ≤ 15 dB HL Average TEOAE amplitude = 9.2	Hearing loss	• The SARS-CoV-2 group have a significantly lower TEOAE amplitudes ($p < 0.001$). • The SARS-CoV-2 group have a significantly higher hearing threshoulds at 4 kHz and above ($p < 0.05$).	Poor
Sriwijitalai and Wiwanitkitb (2020) Thailand.	Case report	$N = 82$ Confirmed Covid-19 cases Age = unreported	Sensorineural hearing loss ($N = 1$; 1.2%)	–	Poor
Sun, Liu, and Wang (2020) China	Case report	$N = 1$ (M) Confirmed Covid-19 case Age = 38 years	Binaural hearing loss and tinnitus	–	Poor

N: number of participants; M: male; F: female; SD: standard deviation; PTA: pure-tone average; HL: hearing level; TEOAE: Transient otoacoustic emission; SD: standard deviation; *using National Institutes of Health's quality assessment tools.

ORAL LESIONS OF HERPES ZOSTER IN COVID-19 PATIENTS OR TRULY ASSOCIATED TO THE DISEASE?

das Chagas E Silva de Carvalho LF, Kitakawa D, Cabral LAG.. Oral Dis. 2020 Jun 10. doi: 10.1111/odi.13472. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Researchers in Brazil wrote a letter to the editor responding to case series from Carreras-Presas et. al. (2020) in which three patients with COVID-19 (two presumptive positives and one confirmed positive) presented with oral vesico-bullous lesions. The authors argue it is unclear whether the lesions are truly a manifestation of SARS-CoV-2 infection or possibly the result of herpes-zoster or a reaction to stress. They advocate for careful and accurate evaluation of new clinical features of COVID-19, including oral lesions.

ABSTRACT

In response to the report of Carreras-Presas et al. (2020) in which they present 3 cases with vesico-bullous oral lesions associated with SARS-Cov-2 infection and with very interesting findings, however we cannot consider the possibility that findings be intrinsic related to COVID-19 disease. The first two cases presented did not have laboratory confirmation of COVID-19 infection, but the authors reported that these patients had compatible signs and symptoms.

ADULTS

ASSOCIATION OF CARDIAC BIOMARKERS AND COMORBIDITIES WITH INCREASED MORTALITY, SEVERITY, AND CARDIAC INJURY IN COVID-19 PATIENTS: A META-REGRESSION AND DECISION TREE ANALYSIS

Toraih EA, Elshazli RM, Hussein MH, Elgaml A, Amin MN, El-Mowafy M, El-Mesery M, Ellythy A, Duchesne J, Killackey MT, Ferdinand KC, Kandil E, Fawzy MS.. J Med Virol. 2020 Jun 12. doi: 10.1002/jmv.26166. Online ahead of print.
Level of Evidence: 1 - Systematic review of inception cohort studies

BLUF

This systematic review and meta-analysis pooled 56 studies published up to May 8, 2020 consisting of a total of 17,794 patients to assess the association between the history of cardiovascular diseases and their specific biological marker levels with COVID-19 severity and mortality. The authors found that high cardiac troponin I ($p<0.001$) and aspartate aminotransferase (AST) levels ($p<0.001$) as well as advanced age (>60 years; $p<0.01$) were predictors of poor COVID-19 prognosis (Figure 2). These results suggest that elevated cardiac injury biomarkers may be used to identify COVID-19 patients who are at a higher risk of severe disease.

ABSTRACT

BACKGROUND: Coronavirus disease-2019 (COVID-19) has a deleterious effect on several systems, including the cardiovascular system. We aim to systematically explore the association of COVID-19 severity and mortality rate with the history of cardiovascular diseases and/or other comorbidities and cardiac injury laboratory markers.
METHODS: The standardized mean difference (SMD) or odds ratio (OR) and 95% confidence intervals (CI) were applied to estimate pooled results from the 56 studies. The prognostic performance of cardiac markers for predicting adverse outcomes and to select the best cutoff threshold was estimated by ROC curve analysis. Decision tree analysis by combining cardiac markers with demographic and clinical features was applied to predict mortality and severity in COVID-19 patients.
RESULTS: A meta-analysis of 17,794 patients showed patients with high cardiac troponin I (OR=5.22, 95%CI=3.73-7.31, p<0.001) and AST levels (OR=3.64, 95%CI=2.84-4.66, p<0.001) were more likely to develop adverse outcomes. High troponin I >13.75 ng/L combined with either advanced age >60 years or elevated AST level >27.72 U/L was the best model to predict poor outcomes.
CONCLUSIONS: COVID-19 severity and mortality are complicated by myocardial injury. Assessment of cardiac injury biomarkers may improve the identification of those patients at the highest risk and potentially lead to improved therapeutic approaches. This article is protected by copyright. All rights reserved.

FIGURES

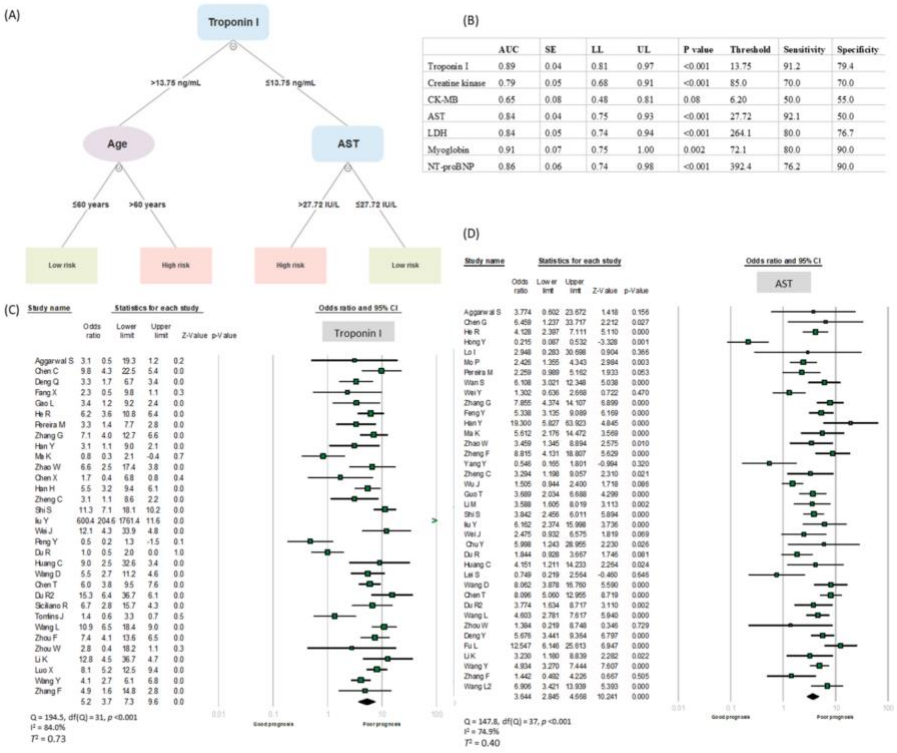


FIGURE 2. (A) Decision tree model analysis for clinical and cardiac biomarkers. Based on several inputs (clinical parameters and biomarkers), a model was created by a multi-level split. Each interior node corresponds to one of the input variables, each leaf represents a value of the target variable given the values of the input variables represented by the path from the root to the leaf. (B) Receiver Operating Characteristics for cardiac biomarkers. AUC: area under the curve, SE: standard error, LL: lower limit, UL: upper limit, CK-MB: creatine kinase myocardial band, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, NT-proBNP: N-terminal-pro hormone B-type Natriuretic peptide. (C) Forest plot of high-sensitivity cardiac troponin I in critical/expired patients compared to non-critical cases. Each horizontal bar represents a study, with lines extending from the symbols representing 95% confidence intervals. The size of the data marker indicates relative weight. Pooled estimates are represented by the black diamond. (D) Forest plot for AST in critical/expired patients compared to non-critical cases.

TIME SCALE FOR RESOLUTION OF OLFACTORY DYSFUNCTION IN COVID-19

Speth MM, Singer-Cornelius T, Oberle M, Gengler I, Brockmeier SJ, Sedaghat AR.. Rhinology. 2020 Jun 13. doi: 10.4193/Rhin20.227. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

This letter is from researchers in Switzerland who followed a cohort of 112 patients from a Swiss hospital to evaluate the prevalence of olfactory dysfunction (OD) in COVID-19 patients. 66 patients experienced OD at a mean of 4 days after the onset of COVID-19 symptoms, and OD symptoms progressively improved with at least one third of patients requiring three weeks for resolution of OD (Figure 1), suggesting that the overall prognosis for resolution of OD is excellent and that this symptom should be approached with patience and conservative treatment.

SUMMARY

New discoveries about the presentation and symptoms of COVID-19 are continually being discovered and olfactory dysfunction (OD) has been noted to be a symptom with high prevalence in the disease course. This letter describes the prevalence and prognosis for OD in a population of 112 COVID-19 positive patients from a Swiss hospital of which 66 developed OD as a symptom at a mean time of 4 days after the onset of COVID-19 symptoms. The majority (81.5%) reported severe OD, and 78.8% of patients with OD reported complete resolution of symptoms in a mean time of 11 days,19.7% had partial resolution of OD, and 1.5% had no noticeable improvement of OD symptoms. This suggests that the overall prognosis for resolution of OD is excellent, but that some patients required greater than one month to see resolution of symptoms, leading the authors to suggest patience when approaching patients with OD.

ABSTRACT

By now, the 2019 novel coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, is widely recognized around the world as a pandemic that has infected millions and claimed the lives of hundreds of thousands (1). Despite months of mitigation strategies, COVID-19 continues to spread and ascertainment of new knowledge about the disease process continues to be a priority of the medical community. Originally described by characteristic symptoms of fever, cough and/or shortness of breath that can rapidly progress to acute respiratory distress syndrome, it has become clear that COVID-19 has manifold clinical presentations (2-4). Notably, olfactory dysfunction (OD)-decreased sense of smell-has been reported to occur in up to 85.6% of COVID-19 patients (2,5).

FIGURES

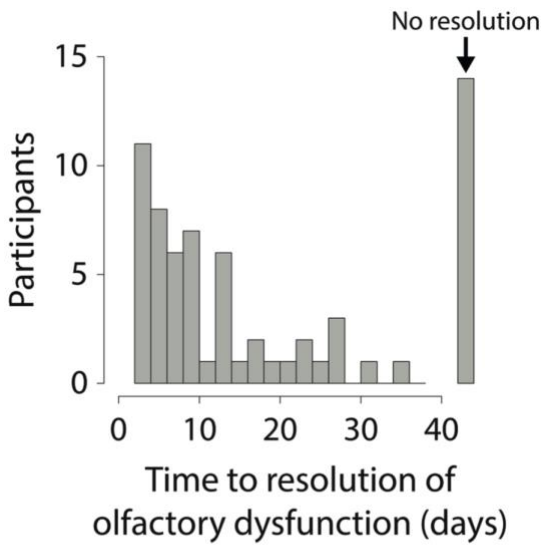


Figure 1. Histogram plot of duration of olfactory dysfunction in COVID-19 patients who experienced olfactory dysfunction as a symptom.

DYSPNEA: THE VANISHED WARNING SYMPTOM OF COVID-19 PNEUMONIA

Allali G, Marti C, Grosgurin O, Morélot-Panzini C, Similowski T, Adler D.. J Med Virol. 2020 Jun 12. doi: 10.1002/jmv.26172. Online ahead of print.
Level of Evidence: 3 - Expert Opinion

BLUF

The authors hypothesize that the the low prevalence of dyspnea (less than 50%) seen in COVID-19 patients with acute respiratory distress syndrome (ARDS) may result from the neuroinvasiveness of SARS-CoV-2 blunting the perception of

labored breathing. This could contribute to the high mortality of COVID-19 due to late admission to the ICU and suggests that surrogate markers of respiratory distress (use of neck muscles, inspiratory abdominal paradox, and appearance of fear) should be relied upon rather than patient self-reporting of dyspnea.

SUMMARY

It has been observed that many COVID-19 patients presenting with respiratory distress do not self-report dyspnea, which could be due to SARS-CoV-2 interfering with their own perception of troubled breathing and is problematic as it contributes to late presentation to ICU. Because of the low value of dyspnea as a warning sign for respiratory distress, the Geneva University Hospital in Switzerland has an intermediate care unit (ICMU) dedicated to patients with an FiO2>50%, SpO2<90%, and absence of surrogate markers of respiratory distress (use of accessory neck muscles, inspiratory abdominal paradox, and expression of fear), while patients who present with these values plus one of the surrogate markers are admitted to the ICU. 60 patients were admitted to the ICMU at Geneva University Hospital with worsening hypoxemia based on this criteria, of which only 20 required eventual transfer to the ICU for mechanical ventilation. This suggests that dyspnea as self-reported by the patient cannot be relied upon to predict a poor respiratory prognosis in COVID-19, and that surrogate markers of respiratory distress should be observed to predict which patients will have severe respiratory distress.

ABSTRACT

Since December 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has rapidly spread worldwide, challenging the clinician and focusing the entire globe on critical illness high mortality. This article is protected by copyright. All rights reserved.

REPORT OF EEG FINDING ON CRITICALLY ILL PATIENTS WITH COVID-19

Vespignani H, Colas D, Lavin BS, Soufflet C, Maillard L, Pourcher V, Paccoud O, Medjebar S, Frouin PY.. Ann Neurol. 2020 Jun 13. doi: 10.1002/ana.25814. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

This retrospective study reviewed the EEGs of 26 patients diagnosed with severe COVID-19 in various intensive care units throughout Paris between 18 March and 31 March, 2020. Five patients (four men, mean age 67) demonstrated a delta wave pattern concerning for brain injury as a direct or indirect result of COVID-19 (Table 1). The authors encourage the use of EEGs to assess COVID-19 patients that present with unexplained changes in mental status in order to identify treatable disorders.

ABSTRACT

In March 2020, we treated a cohort of 26 critically ill hospitalized SARS-CoV-2 infected patients who received EEGs to assess unexplained altered mental status, loss of consciousness, or poor arousal and responsiveness. Of the 26 patients studied, 5 patients had EEGs that showed Periodic Discharges (PD) consisting of high amplitude frontal monomorphic delta waves with absence of epileptic activity. These findings may suggest CNS injury potentially related to COVID-19 in these patients. This article is protected by copyright. All rights reserved.

FIGURES

Patient	Age	Gender	Medical History	Intervention	*Days Intubated at time of EEG*	EEG Interpretation	Clinical Outcome
1	58	M	Coma, Face and Eye myoclonus	Ventilator Deep Sedation (propofol,fentanyl) ECMO Lumbar Puncture	4	Generalized Bilateral Frontal intermittent Symmetric Biphasic delta Theta activity	Died 8 days after EEG performed
2	70	M	Delayed Awakening, Cardiac Arrest	Ventilator Not Sedated	8	Generalized Bilateral Frontal high amplitude Symmetric Biphasic delta theta activity	Died 3 days after EEG performed
3	70	M	Poor Arousal Epilepsy?	Ventilator Mild Sedation (Midazolam) CT Scan	6	Lateralized Right Focal Frontal high amplitude Symmetric Biphasic delta Symmetric	Remains Hospitalized in ICU
4	70	M	Coma, Face Myoclonus	Ventilator Deep Sedation (propofol, fentanyl) Renal Dialysis	12	Generalized Biphasic delta Asymmetric Frontal predominance	Died 9 days after EEG performed
5	67	F	Confusion, Lethargy	MRI Lumbar Puncture	N/A	Generalized Frontal slowing Symmetric Biphasic delta theta activity	Remains Hospitalized on Ward Significant cognitive deficit

Table 1. Clinical Profile of Patients With Evidence of EEG Periodic Discharge

GUILLAIN-BARRÉ SYNDROME IN A PATIENT WITH ANTIBODIES AGAINST SARS-COV-2

Helbok R, Beer R, Löscher W, Boesch S, Reindl M, Hornung R, Schiefecker AJ, Deisenhammer F, Pfausler B.. Eur J Neurol. 2020 Jun 12. doi: 10.1111/ene.14388. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

The authors present the case of a previously healthy 68-year-old male who developed Guillain-Barré syndrome (GBS) two weeks after developing dry cough, headache, fatigue, mylagia, fever, anosmia and ageusia. Although he had multiple negative RT-PCR tests for SARS-CoV-2, the patient had CT findings consistent with COVID-19 and highly positive antibody testing, suggesting he had fully recovered from COVID-19 prior to his GBS symptoms. This is the first documented case of COVID-19-associated GBS.

ABSTRACT

There are now several reports on neurologic features of SARS-CoV-2 infection.1 2 In a recent study of 214 patients with COVID-19, 78 (36.4%) patients had neurological manifestations, including headache, dizziness, acute cerebrovascular diseases, and impaired consciousness.2.

PEDIATRICS

CLINICAL CHARACTERISTICS OF 182 PEDIATRIC COVID-19 PATIENTS WITH DIFFERENT SEVERITIES AND ALLERGIC STATUS

Du H, Dong X, Zhang JJ, Cao YY, Akdis M, Huang PQ, Chen HW, Li Y, Liu GH, Akdis CA, Lu XX, Gao YD.. Allergy. 2020 Jun 10. doi: 10.1111/all.14452. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A retrospective study of pediatric patients admitted to Wuhan Children's hospital from January 28 to February 28, 2020 found that of 182 children with confirmed COVID-19, 43 had a history of allergic disease (Table 2), yet no difference between the rate or severity of disease occurred between those with allergy and those without (Figure 1). This suggests that having a history of allergic disease does not place children at a higher risk for developing COVID-19. Additional findings included:
- Fever (43.4%) and dry cough (44.5%) were the most common symptoms, but 30.2% were asymptomatic
- Older children (10+ years) experienced more fatigue and more CT ground glass opacity findings ($p<0.05$)
- Eosinophil counts, aspartate aminotransferase (AST), D-dimer, and procalcitonin (PCT) were lower ($p<0.05$), while IgE was higher ($p=0.048$) in the allergic disease group

- Allergic rhinitis (36/43, 83.7%) was the most common disease among those with a history of allergic disease
- 130 patients (71.4%) had abnormal CT results, with ground glass opacities (28%) being the most common
- Inhalation of interferon-alpha was the most utilized treatment
- All children but 1 eventually recovered from the disease (Figure 1)

ABSTRACT

BACKGROUND: The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has made widespread impact recently. We aim to investigate the clinical characteristics of COVID-19 children with different severities and allergic status.
METHODS: Data extracted from the electronical medical records, including demographics, clinical manifestations, comorbidities, laboratory and immunological results and radiological images of 182 hospitalized COVID-19 children were summarized and analyzed.
RESULTS: The median age was 6 years old, ranging from 3 days to 15 years, and there were more boys (male-female ratio about 2:1) within the studied 182 patients. Most of the children were infected by family members. Fever (43.4%) and dry cough (44.5%) were common symptoms, and gastrointestinal manifestations accounted for 11.0%, including diarrhea, abdominal discomfort and vomiting. 71.4% had abnormal chest computed tomography (CT) scan images, and typical signs of pneumonia were ground-glass opacity and local patchy shadowing on admission. Laboratory results were mostly within normal ranges, and only a small ratio of lymphopenia (3.9%) and eosinopenia (29.5%) were observed. The majority (97.8%) of infected children were not severe, and 24 (13.2%) of them had asymptomatic infections. Compared to children without pneumonia(manifested as asymptomatic and acute upper respiratory infection), children with pneumonia were associated with higher percentages of the comorbidity history, symptoms of fever and cough, and increased levels of serum procalcitonin, alkaline phosphatase and serum interleukins (IL)-2, IL-4, IL-6, IL-10 and TNF-alpha. There were no differences of treatments, duration of hospitalization, time from first positive to first negative nucleic acid testing and outcomes between children with mild pneumonia and without pneumonia. All the hospitalized COVID-19 children had recovered except one death due to intussusception and sepsis. In 43 allergic children with COVID-19, allergic rhinitis (83.7%) was the major disease, followed by drug allergy, atopic dermatitis, food allergy and asthma. Demographics and clinical features were not significantly different between allergic and non-allergic groups. Allergic patients showed less increase in acute phase reactants, procalcitonin, D-dimer and aspartate aminotransferase levels compared to all patients. Immunological profiles including circulating T, B and NK lymphocyte subsets, total immunoglobulin and complement levels and serum cytokines did not show any difference in allergic and pneumonia groups. Neither eosinophil counts nor serum total immunoglobulin E (IgE) levels showed a significant correlation with other immunological measures, such as other immunoglobulins, complements, lymphocyte subsets numbers and serum cytokine levels.
CONCLUSION: Pediatric COVID-19 patients tended to have a mild clinical course. Patients with pneumonia had higher proportion of fever and cough and increased inflammatory biomarkers than those without pneumonia. There was no difference between allergic and non-allergic COVID-19 children in disease incidence, clinical features, laboratory and immunological findings. Allergy was not a risk factor for developing and severity of SARS-CoV-2 infection and hardly influenced the disease course of COVID-19 in children.

FIGURES

Table 2: Comorbidities and medical history of pediatric patients with COVID-19 in detail.

Allergic patients (n = 43)		Non-allergic patients (n = 139)	
Allergic diseases - No. (%)		**Medical history - No. (%)**	24 (17.3)
Allergic rhinitis (AR)	28 (65.1)	Pneumonia	2 (1.4)
Atopic dermatitis (AD)	3 (7.0)	Wheezing	2 (1.4)
Drug allergy	3 (7.0)	Acute lymphocytic leukemia	2 (1.4)
AR + Drug allergy	5 (11.6)	Fatty liver	2 (1.4)
AR + AD	1 (2.3)	Pneumonia, wheezing	1 (0.7)
AR + Food allergy	1 (2.3)	Frequent upper respiratory infections, wheezing	1 (0.7)
AR + Food allergy + Drug allergy	1 (2.3)	Tonsillitis	1 (0.7)
Asthma + Urticaria + Drug allergy	1 (2.3)	Adenoid hypertrophy and adenoidectomy; otitis media	1 (0.7)
		Tonsillectomy and adenoidectomy	1 (0.7)
Reported allergen - No. (%)		Appendicitis and appendectomy	1 (0.7)
Dust mite	1 (2.3)	Palatoschisis	1 (0.7)
Egg	1 (2.3)	Kidney disease	1 (0.7)
Mango	1 (2.3)	Cerebral palsy	1 (0.7)
Penicillin	10 (23.3)	Febrile convulsion	1 (0.7)
		Febrile convulsion, wheezing	1 (0.7)
Other medical history - No. (%)	8 (18.6)	Nodal tachycardia	1 (0.7)
Repetitive or annual pneumonia	4 (9.3)	Atrial septal defect cured by intervention	1 (0.7)
Frequent upper respiratory infections	2 (4.7)	Traumatic brain injury	1 (0.7)
Adenoid hypertrophy	1 (2.3)	Intestinal pneumatosis and effusion	1 (0.7)
Adenoid hypertrophy, otitis media	1 (2.3)	Herpesviral encephalitis and secondary epilepsy	1 (0.7)

COVID-19, coronavirus disease 2019.

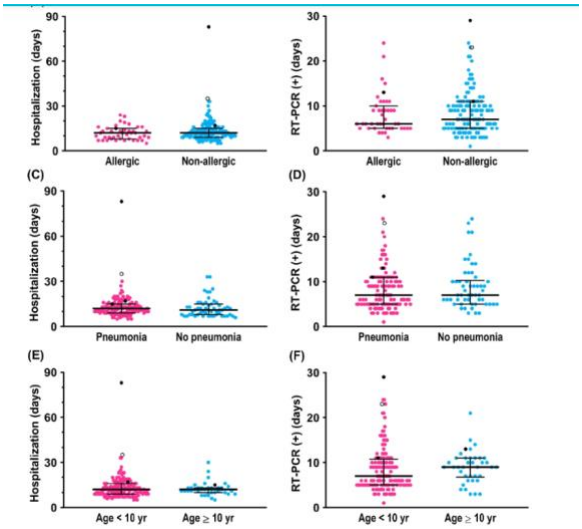


Figure 1: The comparisons in the duration of hospitalization and the time of negative conversion of RT-PCR assays for SARS-CoV-2 nucleic acid, respectively, between the following COVID-19 subgroups: (A, B), allergic and non-allergic patients; (C, D), no pneumonia and mild 496 pneumonia patients; (E, F), patients aged < 10 years and 10 years. In each graph, the dots denote each 497 of numerical values, the middle long lines denote medians, and bilateral short lines denote interquartile ranges. In particular, the black dots denote the numerical values of three severe/critical cases, and the hollow black dot denotes that of one dead case. Details of these four severe or critically ill patients were presented in 500 Table 7. All of the comparisons were not significantly different ($p > 0.05$). RT-PCR, real-time reverse 501 transcription polymerase chain reaction. (+),positive

EARLY CT FINDINGS OF CORONAVIRUS DISEASE 2019 (COVID-19) IN ASYMPTOMATIC CHILDREN: A SINGLE-CENTER EXPERIENCE

Lan L, Xu D, Xia C, Wang S, Yu M, Xu H.. Korean J Radiol. 2020 Jul;21(7):919-924. doi: 10.3348/kjr.2020.0231.
Level of Evidence: 4 - Case-series

BLUF

A cohort study conducted at Zhongnan Hospital of Wuhan University in China analyzed radiologic data from four pediatric cases of asymptomatic COVID-19 (ages 7 to 13) diagnosed via reverse transcriptase (RT)-PCR between 20 January 2020 and 28 February 2020. While one patient had no significant abnormalities on lung CT, three patients had ground glass opacities with small peripheral lesions in the lower lobe (two patients with unilateral involvement and one with bilateral involvement; Figures 1, 2, 3). One of these patients had a left lower lobe consolidation (Figure 1). Though limited by sample size, these findings suggest that pediatric patients with asymptomatic COVID-19 may have lung involvement characterized by unilateral and peripheral ground glass opacities. The authors also suggest more evidence is needed to determine the role of CT scans in pediatric COVID-19 cases.

ABSTRACT

OBJECTIVE: The current study reported a case series to illustrate the early computed tomography (CT) findings of coronavirus disease 2019 (COVID-19) in pediatric patients.
MATERIALS AND METHODS: All pediatric patients who were diagnosed with COVID-19 and who underwent CT scan in Zhongnan Hospital of Wuhan University from January 20, 2020 to February 28, 2020 were included in the current study. Data on clinical and CT features were collected and analyzed.
RESULTS: Four children were included in the current study. All of them were asymptomatic throughout the disease course (ranging from 7 days to 15 days), and none of them showed abnormalities in blood cell counts. Familial cluster was the main transmission pattern. Thin-section CT revealed abnormalities in three patients, and one patient did not present with any abnormal CT findings. Unilateral lung involvement was observed in two patients, and one patient showed bilateral lung involvement. In total, five small lesions were identified, including ground-glass opacity (n = 4) and consolidation (n = 1). All lesions had ill-defined margins with peripheral distribution and predilection of lower lobe.
CONCLUSION: Small patches of ground-glass opacity with subpleural distribution and unilateral lung involvement were common findings on CT scans of pediatric patients in the early stage of the disease.

FIGURES

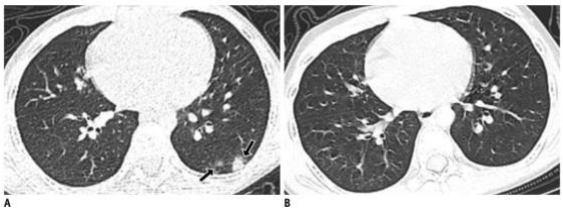


Figure 1: 7-year-old twin girl diagnosed with COVID-19. A. CT scan on admission (day 1) showed subpleural ground-glass opacity and consolidation in left lower lobe (arrows). B. On discharge (day 13), acute exudative lesions were substantially resolved after treatment. COVID-19 = coronavirus disease 2019, CT = computed tomography

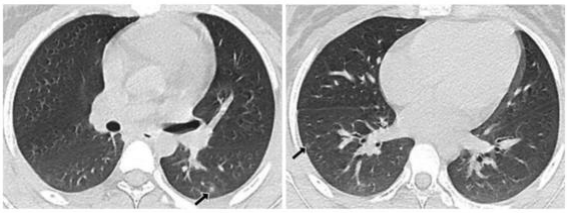


Figure 2: 12-year-old girl diagnosed with COVID-19. Small patches of ground-glass opacity were observed on CT scan, with subpleural distribution and bilateral lung involvement (arrows).

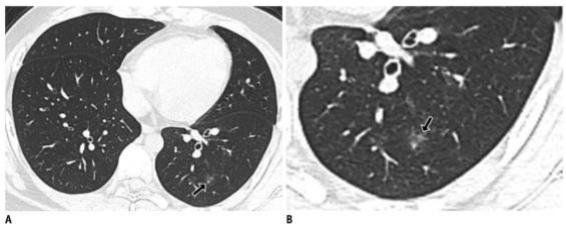


Figure 2: 12-year-old girl diagnosed with COVID-19. Small patches of ground-glass opacity were observed on CT scan, with subpleural distribution and bilateral lung involvement (arrows).

CYTOKINE STORM AND LEUKOCYTE CHANGES IN MILD VERSUS SEVERE SARS-COV-2 INFECTION: REVIEW OF 3939 COVID-19 PATIENTS IN CHINA AND EMERGING PATHOGENESIS AND THERAPY CONCEPTS

Wang J, Jiang M, Chen X, Montaner LJ.. J Leukoc Biol. 2020 Jun 13. doi: 10.1002/JLB.3COVR0520-272R. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Researchers in China and the USA present a review of the cytokine storm seen in COVID-19 patients in China. They found an increase in cytokine release in both mild and severe SARS-CoV-2 infection, as well as decreased B and T lymphocytes in more severe infections, suggesting treatment studies should be targeted at dampening the inflammatory response and lowering the risk of cytokine storm. Further details on these pathways given below.

SUMMARY

This review found an increase in cytokine release (particularly IL-6, IL-10, and TNF) in both mild and severe disease, with an increased risk of cytokine storm as the disease progresses. Additionally, SARS-CoV-2 is found to infect ACE2 in macrophages, which suggests macrophage involvement in systemic spread of infection. Neutrophil count is increased as disease progresses, whereas the lymphocyte count is decreased; characterized primarily with a decrease in B and T lymphocytes in severe disease (Figure 2). The authors suggest this pattern of cytokine release could dysregulate the host's inflammatory response, allowing the virus to evade the initial innate immune response. Finally, they suggest a method for predicting severity of disease, primarily by a neutrophil to lymphocyte ratio; a more severe infection with SARS-CoV-2 would have an increased ratio.

ABSTRACT

Clinical evidence indicates that the fatal outcome observed with severe acute respiratory syndrome-coronavirus-2 infection often results from alveolar injury that impedes airway capacity and multi-organ failure-both of which are associated with the hyperproduction of cytokines, also known as a cytokine storm or cytokine release syndrome. Clinical reports show that both mild and severe forms of disease result in changes in circulating leukocyte subsets and cytokine secretion, particularly IL-6, IL-1beta, IL-10, TNF, GM-CSF, IP-10 (IFN-induced protein 10), IL-17, MCP-3, and IL-1ra. Not surprising, therapies that target the immune response and curtail the cytokine storm in coronavirus 2019 (COVID-19) patients have become a focus of recent clinical trials. Here we review reports on leukocyte and cytokine data associated with COVID-19 disease in 3939 patients in China and describe emerging data on immunopathology. With an emphasis on immune modulation, we also look at ongoing clinical studies aimed at blocking proinflammatory cytokines; transfer of immunosuppressive mesenchymal stem cells; use of convalescent plasma transfusion; as well as immunoregulatory therapy and traditional Chinese medicine regimes. In examining leukocyte and cytokine activity in COVID-19, we focus in particular on how these levels are altered as the disease progresses (neutrophil NETosis, macrophage, T cell response, etc.) and proposed consequences to organ pathology (coagulopathy, etc.). Viral and host interactions are described to gain further insight into leukocyte biology and how dysregulated cytokine responses lead to disease and/or organ damage. By better understanding the mechanisms that drive the intensity of a cytokine storm, we can tailor treatment strategies at specific disease stages and improve our response to this worldwide public health threat.

FIGURES

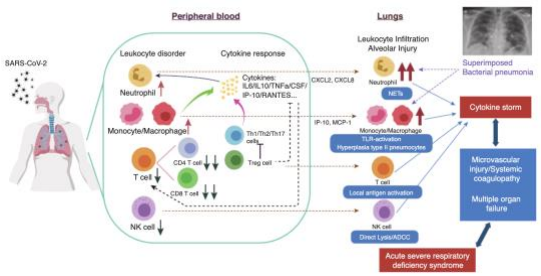


Figure 2. Severe SARS-CoV-2 infection: summary of aberrant activation of leukocytes and cytokine production contributing to a cytokinestorm and pathology. Conceptual model of observations associated with severe SARS-CoV-2 infection. The activation of monocytes/macrophagesand lymphocyte subsets in blood are likely to be major sources of cytokine release, together with the infiltration of leukocytes into lung tissue.Alveolar injury is shown to be associated with cell infiltrates, the release of neutrophil extracellular traps (NETs), hyperplasia of type II pneumocytes,among others, all of which could result in ARDS, lung

insufficiency and a cytokine storm (exacerbated if combined with a superimposed bacterialinfection). COVID-19/bacterial pneumonia image provided by: Dr. Ana S. Kolansky, University of Pennsylvania.

DETECTION OF VIRAL SARS-COV-2 GENOMES AND HISTOPATHOLOGICAL CHANGES IN ENDOMYOCARDIAL BIOPSIES

Escher F, Pietsch H, Aleshcheva G, Bock T, Baumeier C, Elsaesser A, Wenzel P, Hamm C, Westenfeld R, Schultheiss M, Gross U, Morawietz L, Schultheiss HP.. ESC Heart Fail. 2020 Jun 12. doi: 10.1002/ehf2.12805. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A study conducted by German physicians between February 3rd, 2020 and March 26th, 2020 found SARS-CoV-2 gene sequences - specifically low amounts (100-500 copies/reaction) of the SARS-CoV-2 E-gene - in endomyocardial tissue biopsies of five out of 104 patients with suspected myocarditis or unexplained heart failure (Table 1, Table 2). This study builds upon existing literature showing a possible link between COVID-19 infection and cardiac involvement, and suggests that there may be a direct mechanism of action in heart tissue that warrants further study.

ABSTRACT

AIMS: Since December 2019, the novel coronavirus SARS-CoV-2 has spread rapidly throughout China and keeps the world in suspense. Cardiovascular complications with myocarditis and embolism due to COVID-19 have been reported. SARS-CoV-2 genome detection in the heart muscle has not been demonstrated so far, and the underlying pathophysiological mechanisms remain to be investigated.
METHODS AND RESULTS: Endomyocardial biopsies (EMBs) of 104 patients (mean age: 57.90 +- 16.37 years; left ventricular ejection fraction: 33.7 +- 14.6%, sex: n = 79 male/25 female) with suspected myocarditis or unexplained heart failure were analysed. EMB analysis included histology, immunohistochemistry, and detection of SARS-CoV-2 genomes by real-time reverse transcription polymerase chain reaction in the IKDT Berlin, Germany. Among 104 EMBs investigated, five were confirmed with SARS-CoV-2 infected by reverse real-time transcriptase polymerase chain reaction. We describe patients of different history of symptoms and time duration. Additionally, we investigated histopathological changes in myocardial tissue showing that the inflammatory process in EMBs seemed to permeate vascular wall leading to small arterial obliteration and damage.
CONCLUSIONS: This is the first report that established the evidence of SARS-CoV-2 genomes detection in EMBs. In these patients, myocardial injury ischaemia may play a role, which could explain the ubiquitous troponin increases. EMB-based identification of the cause of myocardial injury may contribute to explain the different evolution of complicated SARS-CoV-2-infection and to design future specific and personalized treatment strategies.

FIGURES

Group	All patients
Number of patients, *n* (%)	104 (100)
Men, *n* (%)	79 (76)
Age at diagnosis, mean ± SD (years)	57.9 ± 16.4
LVEF at diagnosis, mean ± SD (%)	33.7 ± 14.6
Diagnosis, *n* (%)	
• Active myocarditis	14 (13.4)
• Inflammatory cardiomyopathy	34 (32.6)
• Borderline myocarditis	3 (2.9)
• Dilated cardiomyopathy	43 (41.3)
• Amyloidosis	10 (9.6)
EMB results	
CD3+ count in EMB Mean ± SD (cells/mm^2)	24.1 ± 54.0
CD45R0+ count in EMB Mean ± SD (cells/mm^2)	87.9 ± 96.4
LFA-1+ count in EMB Mean ± SD (cells/mm^2)	29.9 ± 48.3
Mac-1+ count in EMB Mean ± SD (cells/mm^2)	70.3 ± 106.7
Perforin+ count in EMB Mean ± SD (cells/mm^2)	1.3 ± 3.8
CD54+ count in EMB Mean ± SD (%Area fraction)	2.7 ± 1.5
HLADR+ count in EMB Mean ± SD ((%Area fraction)	4.6 ± 2.0
SARS-CoV-2, *n* (%)	5 (4.8)
B19V, *n* (%)	70 (67.3)
HHV6, *n* (%)	8 (7.7)
ADV, *n* (%)	0 (0.0)
EBV, *n* (%)	4 (3.8)
COX, *n* (%)	1 (1.0)

Table 1. Clinical Characteristics and Biopsy Findings. EMB, endomyocardial biopsy; LVEF, left ventricular ejection fraction. Immunohistological marker: CD3, T-lymphocytes; LFA-1, leukocyte function antigen-1; Mac-1, macrophage-1 antigen; CD45R0 (UCHL1), leucocyte common antigen; perforin, cytotoxiccells; CD54/ICAM-1, intercellular adhesion molecule-1; HLADR, MHC class II cell surface receptor; B19V, Parvovirus B19; HHV6, Human Herpesvirus 6; ADV, Adenovirus; EBV, Epstein–Barr-Virus; COX, Coxsackivirus. The data are presented as mean ± standard deviation.

Patient	1	2	3	4	5
Age at diagnosis (years)	48	62	60	36	39
Clinical suspected diagnosis	Acute myocarditis	Unexplained heart failure	Unexplained heart failure	Inflammatory cardiomyopathy	Acute myocarditis
Diagnosis	Active myocarditis	Inflammatory cardiomyopathy	Inflammatory cardiomyopathy	Inflammatory cardiomyopathy	Borderline-myocarditis
Sex	M	M	F	M	M
LVEF at diagnosis (%)	22	40	60	25	55
Laboratory parameters:					
High sensitive Troponin (pg/mL)	3264	-	83	56	379
BNP (pg/mL)	12 232	-	113	258	109
EMB analysis:					
Myocyte diameter (μm)	18	18	32	22	19
CD3+ count in EMB (cells/mm^2)	106.98	7.0	20.54	4.97	18.74
CD45R0+ count in EMB (cells/mm^2)	156.23	14.0	96.15	61.47	162.38
LFA-1+ count in EMB (cells/mm^2)	83.15	-	24.36	16.95	102.6
Mac-1+ count in EMB (cells/mm^2)	155.34	39,5	91.56	49.09	154.35
Perforin+ count in EMB (cells/mm^2)	1.79	-	1.74	0.00	4.01
CD54+ count in EMB (%Area Fraction)	6.42	-	1.91	1.90	4.05
HLADR+ count in biopsy (%Area Fraction)	7.25	0,5	3.78		7.14

Table 2. Characteristics of Patients. EMB, endomyocardial biopsy; LVEF, left ventricular ejection fraction. Immunohistological marker: CD3, T-lymphocytes; LFA-1, leukocyte function antigen-1; Mac-1, macrophage-1 antigen; CD45R0 (UCHL1), leucocyte common antigen; perforin, cytotoxic cells; CD54/ICAM-1, intercellular adhesion molecule-1; HLADR, MHC class II cell surface receptor.

THE PATHOLOGIC AUTOPSY OF CORONAVIRUS DISEASE 2019 (COVID-2019) IN CHINA: A REVIEW

Zhou B, Zhao W, Feng R, Zhang X, Li X, Zhou Y, Peng L, Li Y, Zhang J, Luo J, Li L, Wu J, Yang C, Wang M, Zhao Y, Wang K, Yu H, Peng Q, Jiang N.. Pathog Dis. 2020 Jun 13:ftaa026. doi: 10.1093/femspd/ftaa026. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A group of researchers from Chongqing Medical University in China conducted a retrospective review of 39 autopsy reports to identify changes associated with SARS-CoV-2 infection. Authors discuss histopathological findings from lung, liver, kidney, spleen, and heart tissues positive for SARS-CoV-2 antigen via immunohistochemistry (IHC) staining and virion identification using transmission electron microscopy (TEM). They identify their current limitations due to a small sample size and call for regularly performed autopsies of deceased COVID-19 patients to further understand the pathology of the disease.

SUMMARY

Particular pathologic findings include:

-infected lung tissue displays hyaline membrane formation, fibrin exudates, epithelial damage, and diffuse type II pneumocyte hyperplasia consistent with diffuse alveolar damage (Figure 3).

-infected liver tissue displays moderate microvesicular steatosis and mild lobular and portal activity.

-infected spleen tissue is congested and hemorrhagic, lacks lymphoid follicles. Splenic corpuscles are atrophied, and fibrous tissue accumulated in the splenic sinus.

-infected lymph nodes (Figure 5) demonstrate virion presence marginal sinus of lymph nodules, capillaries, germinal centers. Additionally macrophages that overexpress ACE 2, CD68, and CD169 show much higher rate of virion inclusion (Figure 6).

-infected kidney tissue shows that the virions were only present in renal tubular cells and that infection led to acute renal tubular damage that spares the glomerulus. Accumulation of SARS-CoV-2 in the renal tubule also provides a route of urinary transmission of the virus.

ABSTRACT

The coronavirus disease 2019 (COVID-2019) emerged in Wuhan, China, has rapidly spread to many countries across all six WHO regions. However, its pathobiology remains incompletely understood and many efforts are underway to study it worldwide. To clarify its pathogenesis to some extent, it will inevitably require lots of COVID-2019-associated deaths at pathologic autopsy. Pathologists from all over the world have raised concern with pathologic autopsy relating to COVID-2019. The issue of whether a person dies from COVID-2019 infection or not always is an ambiguous problem in some cases, and ongoing epidemiology from China may shed light on it. This review retrospectively summarizes the research status of pathologic autopsy in COVID-2019 in China, which will be important for the cause of death, prevention, control and clinical strategies of COVID-2019. Moreover, it points out several challenges at autopsy. We believe pathological studies from China enable to correlate clinical symptoms and pathological features of COVID-2019 for doctors and provide an insight into COVID-2019 disease.

FIGURES

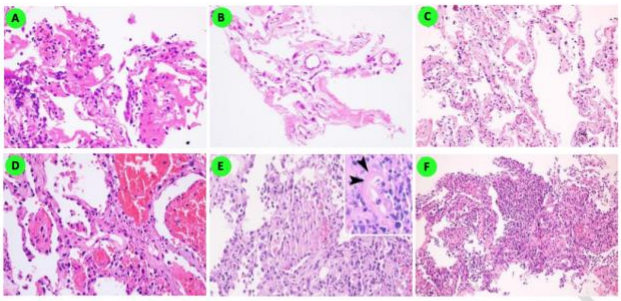


Figure 3. Microscopic features in the lung tissues from victims who died of COVID-2019 pneumonia in Zhongnan Hospital, Wuhan. (A) Case 1: Thick hyaline membrane together with desquamative pneumocytes and mononuclear inflammatory cells. (B) Case 2: More delicate hyaline membranes in absence of evident inflammatory infiltration. (C) Case 3: Focal hyaline membrane, type II pneumocyte hyperplasia and mild interstitial thickening. (D) Case 4: Alveolar spaces are filled with red blood cell exudation, and small fibrin plugs are present in adjacent alveoli. (E) Case 4: Organization with intra-alveolar fibroblasts along with fibrin and inflammatory cellular infiltration. Diffuse type II pneumocyte hyperplasia in the background (inset: fibrinoid vascular necrosis indicated by black arrow). (F) Case 4: Changes of bronchopneumonia with prominent neutrophilic infiltration filling up alveolar spaces. Images adapted from reference 27, with Creative Commons Attribution License

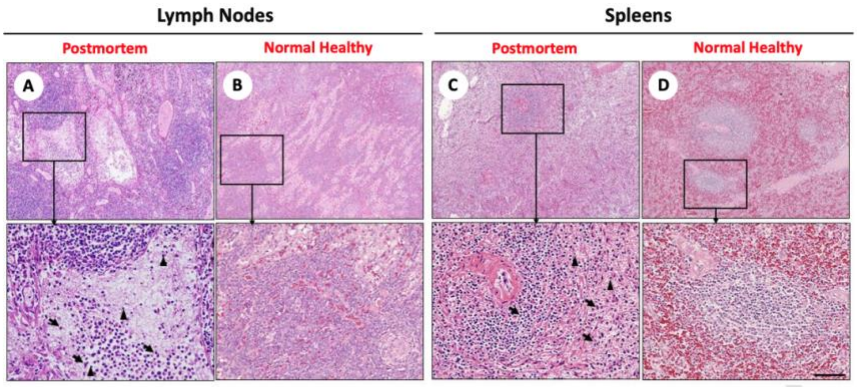


Figure 5. Representative H&E staining comparison of lymph nodes (A and B) and spleen (C and D) tissues between one patient, who confirmed with SARS-CoV-2 infection in Jinyintan Hospital, Wuhan, and normal healthy control.[31] In these images, arrow indicated apoptotic lymphocytes, which emphasizes a significant reduction of total lymphocytes when one suffers from SARS-CoV-2 infection. Scale bar: 100 μM. Images are obtained under a CC BY-NC-ND 4.0 International License

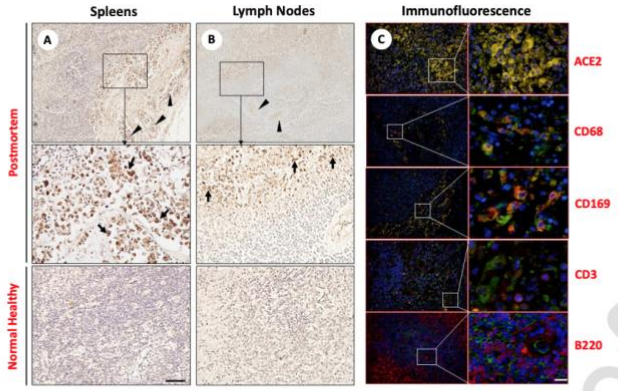


Figure 6. Distribution of SARS-CoV-2 in spleen and LN tissues by immunohistochemistry (IHC) assay from one patient who confirmed with SARS-CoV-2 infection in Jinyintan Hospital, Wuhan.[31] IHC comparison of SARS-CoV-2 distribution in spleen (A) and LN (B) tissues between one patient, who confirmed with SARS-CoV-2 infection in Jinyintan Hospital, Wuhan, and normal healthy control. (C) Immunofluorescent double staining analyzed viral NP antigen expression. Arrow indicated viral NP positive cells. Scale bar: 100 μm. Images are obtained under a CC BY-NC-ND 4.0 International License.

HAPPY HYPOXEMIA IN COVID-19-A NEURAL HYPOTHESIS

U R A, Verma K.. ACS Chem Neurosci. 2020 Jun 12. doi: 10.1021/acschemneuro.0c00318. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Authors from a research group of a private drug company in Pondicherry, India hypothesize that atypical symptoms of COVID-19, such as hypoxemia with normal breathing, anosmia, and ageusia may be due to impaired afferent signaling from the cranial nerves VII, IX, and X secondary to inflammation of the nucleus tractus solitarius (Figures 1 & 2). If confirmed in autopsy samples, this hypothesis may provide a pathologic mechanism for these symptoms.

ABSTRACT

Many COVID-19 patients are presenting with atypical clinical features. Happy hypoxemia with almost normal breathing, anosmia in the absence of rhinitis or nasal obstruction, and ageusia are some of the reported atypical clinical findings. Based

on the clinical manifestations of the disease, we are proposing a new hypothesis that SARS-CoV-2 mediated inflammation of the nucleus tractus solitarius may be the reason for happy hypoxemia in COVID-19 patients.

FIGURES

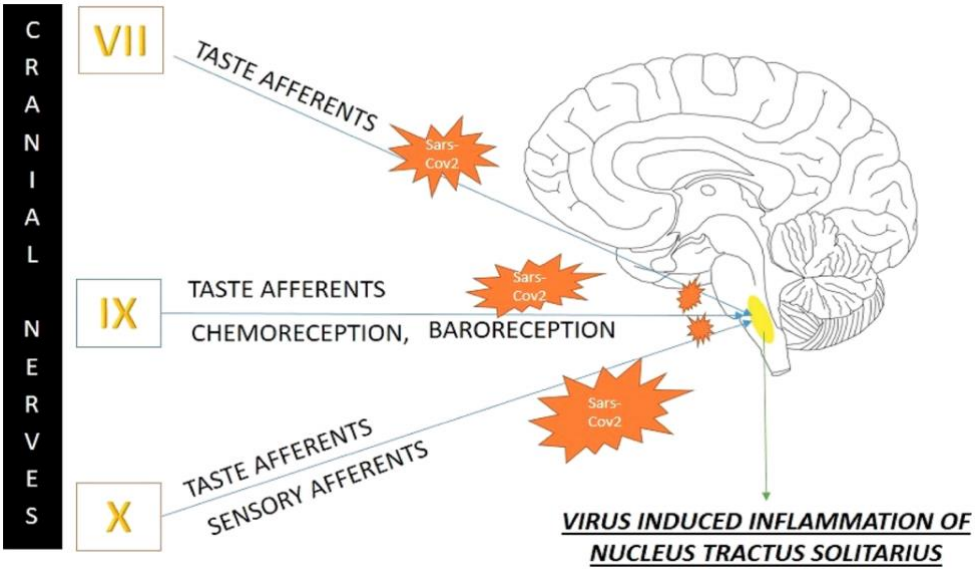


Figure 1.

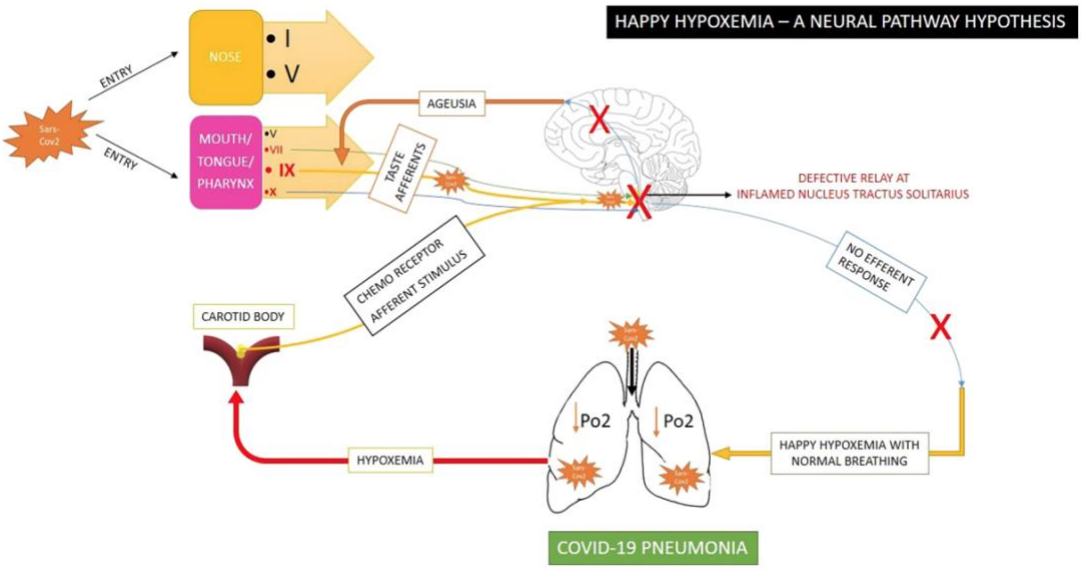


Figure 2.

IN SILICO

GENOMIC DETERMINANTS OF PATHOGENICITY IN SARS-COV-2 AND OTHER HUMAN CORONAVIRUSES

Gussow AB, Auslander N, Faure G, Wolf YI, Zhang F, Koonin EV.. Proc Natl Acad Sci U S A. 2020 Jun 10:202008176. doi: 10.1073/pnas.2008176117. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A molecular and genetic analysis of SARS-CoV-1, SARS-CoV-2, and MERS-CoV conducted by an interdisciplinary group of researchers from the National Institutes of Health (NIH) in Bethesda, Maryland found that key changes in the nuclear localization sequence (NLS) and distinct insertions in the spike glycoprotein of the virus may be responsible for the high pathogenicity of SARS-CoV-2 compared to SARS-CoV-1 and MERS-CoV (Figure 1). These features are thought to correlate with

animal switching and the high fatality of these infections and may be crucial targets for drug development and medical interventions.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses an immediate, major threat to public health across the globe. Here we report an in-depth molecular analysis to reconstruct the evolutionary origins of the enhanced pathogenicity of SARS-CoV-2 and other coronaviruses that are severe human pathogens. Using integrated comparative genomics and machine learning techniques, we identify key genomic features that differentiate SARS-CoV-2 and the viruses behind the two previous deadly coronavirus outbreaks, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), from less pathogenic coronaviruses. These features include enhancement of the nuclear localization signals in the nucleocapsid protein and distinct inserts in the spike glycoprotein that appear to be associated with high case fatality rate of these coronaviruses as well as the host switch from animals to humans. The identified features could be crucial contributors to coronavirus pathogenicity and possible targets for diagnostics, prognostication, and interventions.

FIGURES

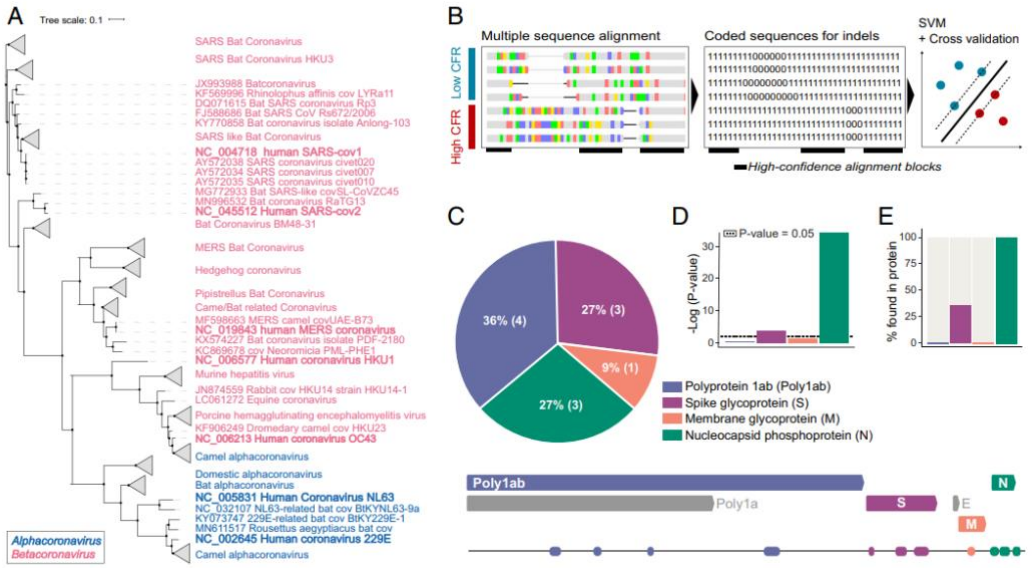


Figure 1: Searching coronavirus genomes for determinants of pathogenicity. (A) Phylogenetic tree of coronavirus species, based on the alignment of complete nucleotide sequences of virus genomes. Blue font corresponds to alphacoronaviruses, and magenta font corresponds to betacoronaviruses. (B) A schematic illustration of the pipeline applied for detection of genomic regions predictive of high-CFR strains. (C) (Top) Pie chart showing the percentage of identified genomic determinants in each protein. (Bottom) Map of SARS-CoV-2 genome with detected regions. (D) Bar plot showing the significance of the distribution of detected regions across each protein. (E) Percentage of detected predictive regions in each protein

PERSISTENT VIRAL RNA SHEDDING AFTER COVID-19 SYMPTOM RESOLUTION IN OLDER CONVALESCENT PLASMA DONORS

Hartman WR, Hess AS, Connor J.. Transfusion. 2020 Jun 13. doi: 10.1111/trf.15927. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

In this study at the University of Wisconsin-Madison School of Medicine, 86 previously positive SARS-CoV-2 subjects were re-tested using reverse transcriptase (RT)-PCR of nasopharyngeal swab samples less than 28 days after self-reported resolution of symptoms in order to determine if viral shedding was still occurring. The results revealed no significant difference in gender or duration of symptoms between the positive subjects (13%) and negative subjects (87%), however there was a significant difference in age, with mean of 54 years-old verses 42 years-old, respectively (Table 1). These results highlight the necessity of testing COVID-19 convalescent plasma donors, especially less than 28 days since resolution of symptoms and in the older population.

ABSTRACT

INTRODUCTION: The novel coronavirus, SARS-CoV-2, is responsible for a world-wide pandemic. While the medical community understands the mode of viral transmission, less is known about how long viral shedding occurs once viral symptoms have resolved. Our objective was to determine how long the SARS-CoV-2 remains detectable following self-reporting of viral symptom resolution.
METHODS: This study was approved by the University of Wisconsin Institutional Review Board. A cohort of previously SARS-CoV-2 positive patients less than 28 days after self-reported symptom resolution were re-tested for proof of viral recovery by nasal swab rtPCR for SARS-CoV-2 RNA.
RESULTS: 152 potential participants were screened, of which 5 declined, 54 were ineligible, and 93 were recruited; 86 of 93 completed testing. 11/86 (13%) were still positive at a median of 19 days (range 12-24 days) after symptom resolution. Positive participants were significantly older than negative participants (mean 54 years; 95% CI 44, 63 vs. 42 years; 95% CI 38, 46; p = 0.024). CT values were significantly, inversely associated with age (beta = -0.04, r2 = 0.389, p=0.04). The number of days since symptom recovery was not apparently different between positive and negative participants.
CONCLUSION: We found evidence of persistent viral shedding in nasopharyngeal secretions more than two weeks after resolution of symptoms from confirmed COVID-19 infection. Persistent shedding was more common in older participants, and viral load was higher in among older positive participants. These results underscore the necessity of testing COVID-19 convalescent plasma donors less than 28 days after symptom resolution.

FIGURES

Table 1: Screening results for previously COVID-19 positive patients recruited to a convalescent plasma program (n=86).

	SARS-CoV-2 Viral RNA PCR Result		
	Positive (N = 11)	Negative (N = 75)	p
Days since last symptoms *median (interquartile range)*	19 (14, 22)	18 (15, 21)	0.771*
Age *mean ± SD*	53 ± 15	43 ± 16	0.024†

*Wilcoxon-Mann-Whitney test

†T-test

DEVELOPMENTS IN TRANSMISSION & PREVENTION

ENVIRONMENTAL AND DECONTAMINATION ISSUES FOR HUMAN CORONAVIRUSES AND THEIR POTENTIAL SURROGATES

Cimolai N.. J Med Virol. 2020 Jun 12. doi: 10.1002/jmv.26170. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

This review from the University of British Columbia presents methods and limitations for decontamination of SARS-CoV-2 and other viruses in the coronavirus family. The author considers the transmission and stability of coronaviruses, taking into account its survival in different setting/surface types, initial viral load, and susceptibility to different temperatures, solvents, and pH environments. The authors utilize the findings from their review to formulate guidelines for effective and safe decontamination and urge scientists to use SARS-CoV-2-related viruses only as a screening vector rather than a diagnostic means (summarized below).

SUMMARY

Guidelines for effective decontamination are as follows:

- Coronaviruses different from SARS-CoV-2 should be used only for screening purposes and not as the final vector in experimentation. SARS-CoV-2 should be used directly in understanding broader application for decontamination.
- Initial cleaning via detergents and other solvents before attempted decontamination can improve efficacy of the described protocols.
- Use of active agents with rapid onset of action is preferred.
- Users must consider the surface being decontaminated as well as temperature and pH to guide disinfectant choice.
- Clinicians are urged to utilize personal protective equipment and use negative pressure ventilation in patient rooms.
- Minimize exposure of nearby items in patient rooms to possible sources of SARS-CoV-2 by physical covering. Remove all unnecessary items to minimize decontamination efforts.

Guidelines for safe use of decontaminants are as follows:

- Consider all pathogens that must be eradicated when choosing a decontamination procedure.
- Users are urged to consider less obvious sources of viral RNA, such as the floor, during decontamination.
- Consider the corrosive, hazardous, caustic, and flammable qualities of any decontaminant used.
- Consider patient response to choice of decontaminant, such as allergic reactions, and thus avoid direct skin contact.

ABSTRACT

Pandemic COVID-19 gives ample reason to generally review coronavirus (CoV) containment. For establishing some preliminary views on decontamination and disinfection, surrogate CoVs have commonly been assessed. This review serves to examine the existing science in regards to CoV containment generically and then to translate these findings into timely applications for COVID-19. There is widespread dissemination of CoVs in the immediate patient environment, and CoVs can potentially be spread via respiratory secretions, urine, and stool. Interpretations of the spread however must consider whether studies examine for viral RNA, virus viability by culture, or both. Pre-symptomatic, asymptomatic, and post-fourteen day virus excretion from patients may complicate the epidemiology. Whereas droplet spread is accepted, there continues to be controversy over the extent of possible airborne spread and especially now for SARS-CoV-2. CoVs are stable in body secretions and sewage at reduced temperatures. In addition to temperature, dryness or relative humidity, initial viral burden, concomitant presence of bioburden, and the type of surface can all affect stability. Generalizing, CoVs can be susceptible to radiation, temperature extremes, pH extremes, peroxides, halogens, aldehydes, many solvents, and several alcohols. Whereas detergent surfactants can have some direct activity, these agents are better used as complements to a complex disinfectant solution. Disinfectants with multiple agents and adverse pH are more likely to be best active at higher water temperatures. Real-life assessments should be encouraged with working dilutions. The use of decontamination and disinfection should be balanced with considerations of patient and caregiver safety. Processes should also be balanced with considerations for other potential pathogens that must be targeted. Given some CoV differences and given that surrogate testing provides experimental correlates at best, direct assessments with SARS-CoV, MERS-CoV, and SARS-CoV-2 are required. This article is protected by copyright. All rights reserved.

PREVENTION IN THE COMMUNITY

LARGE-SCALE NATIONAL SCREENING FOR COVID-19 IN CHINA

Fang Y.. J Med Virol. 2020 Jun 13. doi: 10.1002/jmv.26173. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

In this commentary from the Department of Public Health in Hangzhou, China, Fang outlines necessary actions in order to achieve the "Four early" measures for controlling COVID-19 spread in China: "early detection, early report, early isolation, early treatment." Fang emphasizes that the first early measure is achievable through large-scale national screening, suggestions for which are summarized below.

SUMMARY

Important populations to screen with nucleic acid testing:

- "Confirmed COVID-19 cases and close contacts
- Imported cases and close contacts
- Asymptomatic cases and close contacts
- Patients with fever
- Patients in need of hospitalization
- Personnel returning from business trip, especially from regions of high risks
- Personnel returning to school or work
- Staff of medical institutions, port quarantine inspection, public security and judicial supervision, social welfare and pension institutions, maternal and child service institutions and other key places."

Steps required for government-facilitated large-scale screening:

- Sustained and steady production of testing kits to meet the demand of increased testing
- Continue monitoring imported cases and asymptomatic patients

ABSTRACT

Faced with the new challenges in the pandemic control, imported COVID-19 infections and asymptomatic infection, Chinese authorities have implemented new intervention measures---- national large-scale nucleic acid testing. This article summarizes the population who needs the nucleic acid testing, analyzes the current data of daily COVID-19 tests per thousand people, concludes the timeline of coronavirus testing and suggests what needs to be done to facilitate the government large-scale screening measures.

CLINICAL CHARACTERISTICS OF COVID-19 IN PATIENTS WITH PRE-EXISTING ILD: A RETROSPECTIVE STUDY IN A SINGLE CENTER IN WUHAN, CHINA

Huang H, Zhang M, Chen C, Zhang H, Wei Y, Tian J, Shang J, Deng Y, Du A, Dai H.. J Med Virol. 2020 Jun 13. doi: 10.1002/jmv.26174. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A retrospective prognostic cohort study of patients admitted to Tongji Hospital in Wuhan, China from February 7th to March 27th, 2020 found that patients with Interstitial Lung Disease (ILD) were associated with increased severity of COVID-19 compared to non-ILD patients (39.29% vs 15.38%, P = 0.004). Thus, the authors advocate for a large scale clinical study in order to establish specific guidelines for COVID-19 management in ILD patients.

ABSTRACT

BACKGROUND: Since the outbreak of 2019 novel coronavirus (SARS-CoV-2) pneumonia, many patients with underlying disease, such as interstitial lung disease (ILD), were admitted to Tongji hospital in Wuhan, China. To date, no data have ever been reported to reflect the clinical features of Corona Virus Disease 2019 (COVID-19) among these patients with pre-existing ILD.
METHODS: We analyzed the incidence and severity of COVID-19 patients with ILD among 3201 COVID-19 inpatients, and compared two independent cohorts of COVID-19 patients with pre-existing ILD (n=28) and non-ILD COVID-19 patients (n=130).
RESULTS: Among those 3201 COVID-19 inpatients, 28 of whom were COVID-19 with ILD (0.88%). Fever was the predominant symptom both in COVID-19 with ILD (81.54%) and non-ILD COVID-19 patients (72.22%). However, COVID-19 patients with ILD were more likely to have cough, sputum, fatigue, dyspnea, and diarrhea. Very significantly higher number of neutrophils, monocytes, IL-8, IL-10, IL-1beta and D-Dimer was characterized in COVID-19 with ILD as compared to those of non-ILD COVID-19 patients. Furthermore, logistic regression models showed neutrophils counts, pro-inflammatory cytokines (TNF-alpha, IL6, IL1beta, IL2R), and coagulation dysfunction biomarkers (D-Dimer, PT, Fbg) were significantly associated with the poor clinical outcomes of COVID-19.
CONCLUSION: ILD patients could be less vulnerable to SARS-CoV-2. However, ILD patients tend to severity condition after being infected with SARS-CoV-2. The prognosis of COVID-19 patients with per-existing ILD is significantly worse than that of non-ILD patients. And more, aggravated inflammatory responses and coagulation dysfunction appear to be the critical mechanisms in the COVID-19 patients with ILD. This article is protected by copyright. All rights reserved.

FIGURES

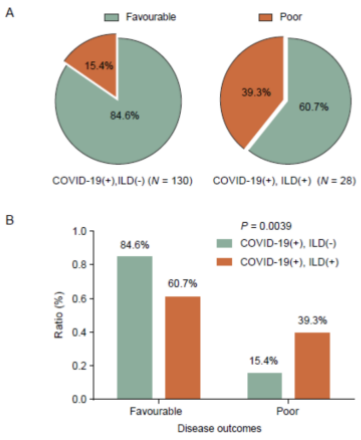


Figure 1. COVID-19 patients with pre-existing ILD were more likely to have poor outcome (39.29%), a percentage much higher than COVID-19 without pre-existing ILD patients (15.38%), P = 0.004.

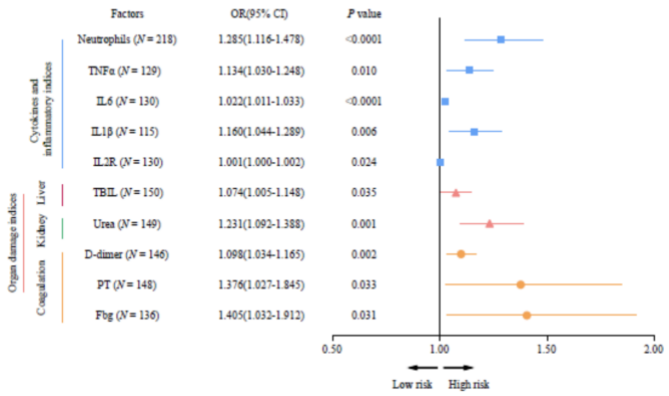


Figure 2. Logistic regression models showed several factors related to the clinical outcomes of COVID-19.

CAN STEROIDS REVERSE THE SEVERE COVID-19 INDUCED 'CYTOKINE STORM'?

Kolilekas L, Loverdos K, Giannakaki S, Vlassi L, Levounets A, Zervas E, Gaga M.. J Med Virol. 2020 Jun 12. doi: 10.1002/jmv.26165. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

A case series of 6 consecutive COVID-19 patients with symptoms of COVID-19 associated hyperinflammatory syndrome admitted from 19 March to 24 April 2020 to the Sotiria Chest Hospital in Athens, Greece were treated with IV methylprednisolone 125mg once daily and were able to avoid intubation. These patients were middle-aged, mostly male, and were either never smokers or ex-smokers with otherwise insignificant medical history. Noticeable symptomatic improvement and significant reductions in most inflammatory markers suggest that corticosteroids may have some efficacy in improving symptoms in severely ill COVID-19 patients, especially when this intervention is applied prior to descent into full classical ARDS (Figure 1).

ABSTRACT

Severe COVID-19 is characterized by an excessive pro-inflammatory cytokine storm, resulting in acute lung injury and development of ARDS. The role of corticosteroids is controversial in severe COVID-19 pneumonia and associated hyper-inflammatory syndrome. We reported a case series of six consecutive COVID-19 patients with severe pneumonia, ARDS and laboratory indices of hyper-inflammatory syndrome. All patients were treated early with a short course of corticosteroids, and clinical outcomes were compared before and after corticosteroids administration. All patients evaded intubation and intensive care admission, ARDS resolved within 11.8 days (median), viral clearance was achieved in 4 patients within 17.2 days (median), and all patients were discharged from the hospital in 16.8 days (median). Early administration of short course corticosteroids improves clinical outcome of patients with severe COVID-19 pneumonia and evidence of immune hyper-reactivity.

FIGURES

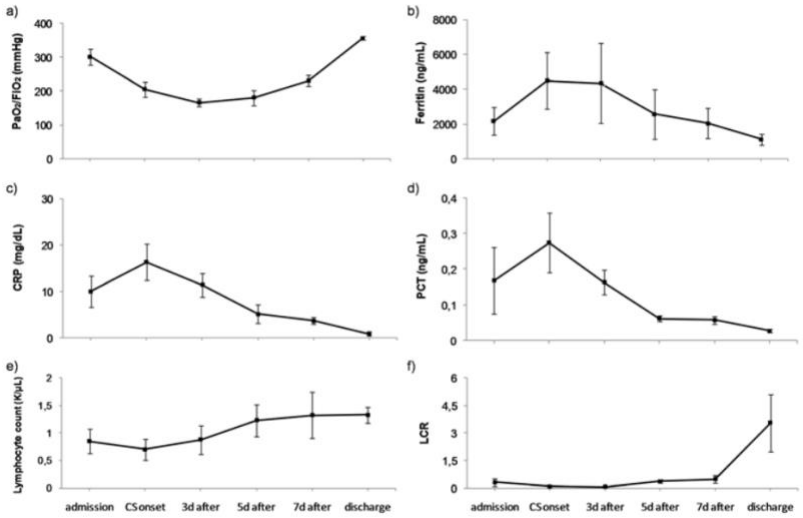


Figure 1: Comparative trend of inflammatory markers and oxygenation from hospital admission to CS treatment onset and on days 3, 5, 7 post CS initiation and on discharge. Data are presented as mean ± standard error of the mean. CRP: Creactive protein, normal range < 0.70 mg/dL. Lymphocyte absolute number: normal range 1.2-4.0 K/µl. PCT: procalcitonin, normal range < 0.25 ng/mL. Ferritin: normal range 21.81-274.6 ng/mL. LCR: lymphocyte-to-CRP ratio, CS: corticosteroids.

IMPACT OF DISEASE ON PLASMA AND LUNG EXPOSURE OF CHLOROQUINE, HYDROXY-CHLOROQUINE AND AZITHROMYCIN: APPLICATION OF PBPK MODELLING

Rowland Yeo K, Zhang M, Pan X, Ban Ke A, Jones HM, Wesche D, Almond LM.. Clin Pharmacol Ther. 2020 Jun 12. doi: 10.1002/cpt.1955. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

A modeling study conducted by Certara utilizing the "Simcyp (V19.1) population-based physiologically based pharmacokinetic (PBPK) simulator", found that when lung pH decreased from 6.7 to 6.0, as has been seen in patients with respiratory disease, the lung to plasma partition coefficient increased (Figure 1) and the lung exposure of azithromycin, hydroxychloroquine, and chloroquine increased 2.7, 4.0, and 20 times respectively (Table 2), suggesting that therapeutic doses for these drugs may need to be adjusted in the treatment of patients with COVID-19 to avoid overexposure. Additionally, renal impairment, which is a common comorbidity with COVID-19, increased the exposure of azithromycin, hydroxychloroquine, and chloroquine in the lungs by 3.4, 8.0, and 30 times respectively, suggesting that renal functioning must also be considered when determining therapeutic drug dosages.

ABSTRACT

We use a mechanistic lung model to demonstrate that accumulation of chloroquine (CQ), hydroxychloroquine (HCQ) and azithromycin (AZ) in the lungs is sensitive to changes in lung pH, a parameter that can be affected in patients with COVID-19. A reduction in pH from 6.7 to 6 in the lung, as observed in respiratory disease, led to 20-, 4.0- and 2.7-fold increases in lung exposure of CQ, HCQ and AZ, respectively. Simulations indicated that the relatively high concentrations of CQ and HCQ in lung tissue were sustained long after administration of the drugs had stopped. Patients with COVID-19 often present with kidney failure. Our simulations indicate that renal impairment (plus lung pH reduction) caused 30-, 8.0- and 3.4-fold increases in lung exposures for CQ, HCQ and AZ, respectively, with relatively small accompanying increases (20 to 30%) in systemic exposure. Although a number of different dosage regimens were assessed, the purpose of our study was not to provide recommendations for a dosing strategy, but to demonstrate the utility of a PBPK modelling approach to estimate lung concentrations. This, used in conjunction with robust in vitro and clinical data, can help in the assessment of COVID-19 therapeutics going forward.

FIGURES

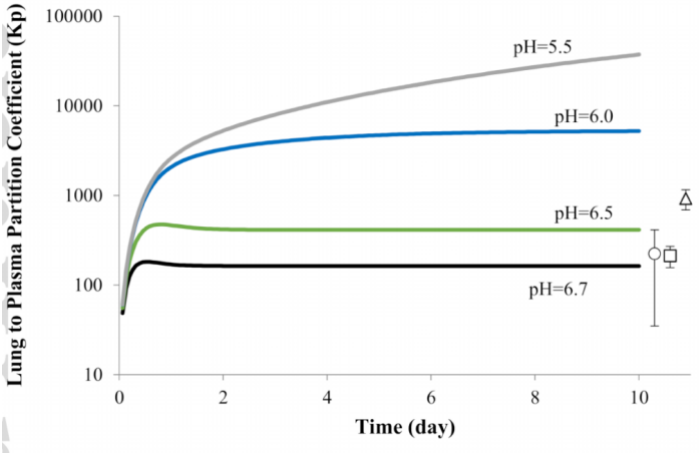


Figure 1. Effect of lung pH on the lung to plasma partition coefficient (Kp) over time after a single oral dose of 300 mg CQ base. The data points and error bars represent the mean and standard deviation of the reported Kp values in rats (circle: Adelusi and Salako (1982a) (36); square: Adelusi and Salako (1982b) (37); triangle: McChesney (1967) (31))

Table 2. Impact of lung pH and renal impairment on the lung CQ levels relative to *in vitro* efficacy (EC_{90}) for different dosage regimens

No	Study	Lung mass pH	R_{EC50}, R_{EC90} Days after the first dose			
			1	3	10	25
1	WHO regimen	6.7	2.4, 0.4	4.4, 0.7	1.9, 0.3	0.3, 0.1
2	FDA regimen	6.7	3.9, 0.6	4.3, 0.7	1.9, 0.3	0.3, 0.1
3	NCT04328493	6.7	4.8, 0.8	5.0, 0.8	6.8, 1.1	1.3, 0.2
4	NCT04323527	6.7	6.1, 1.0	5.0, 2.1	6.8, 4.1	1.3, 0.7
		6.0	54, 9	187, 31	494, 81	152, 25
		6.0	101, 16	334, 55	927, 152	529, 87
5	NCT04333732	6.7	1.2, 0.2	2.8, 0.5	2.3, 0.4	1.0, 0.2
6	NCT04333732	6.7	1.3, 0.2	2.8, 0.5	3.7, 0.6	4.3, 0.7
		6.0	16, 2.5	49, 8.0	85, 14	108, 18
		6.0	29, 4.7	87, 14	163, 27	261, 43

R_{EC50}: Ratio of the simulated lung mass unbound concentration to the reported lowest EC_{50} value (1.13 μM) against SARS-CoV-2 virus in Vero E6 cells with 48-hour incubation time.

R_{EC90}: Ratio of the simulated lung mass unbound concentration to EC_{90} value (6.9 μM) against SARS-CoV-2 virus in Vero E6 cells .

Bold values indicate when renal impairment is also being accounted for.

COVID-19 CARRIER OR PNEUMONIA: POSITIVE REAL-TIME REVERSE-TRANSCRIPTASE POLYMERASE CHAIN REACTION BUT NEGATIVE OR POSITIVE CHEST CT RESULTS

Lei P, Fan B, Sun Y.. Korean J Radiol. 2020 Jul;21(7):925-928. doi: 10.3348/kjr.2020.0360.
Level of Evidence: Other - Expert Opinion

BLUF

A group of Chinese physicians respond to a case series detailing false-negative results using real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) to detect the SARS-CoV-2 virus. While both they and the original authors of the case series agree on the definition of an asymptomatic carrier, they differ in their treatment options. The critics suggest no treatment for asymptomatic carriers and isolation alone, while the original authors respond to the critique and advocate for medical management for treatment, as well as for further research on the impact of an imperfect screening method.

SUMMARY

This publication includes a critique of a case series from China describing false-negative results using rRT-PCR to detect SARS-CoV-2 and the original case series authors' response to the critique. The authors of the critique propose patients with a positive rRT-PCR result and negative chest computed tomography (CT) findings should be classified as carriers and isolated only, whereas patients with both a positive rRT-PCR result and CT findings should be diagnosed with COVID-19 and subsequently isolated and treated. The original authors of the case series respond that while asymptomatic carriers with positive rRT-PCR results and normal imaging exist, they propose treatment with anti-viral medicine despite negative CT findings. This is based on their conclusion that the infectivity of these patients is currently unknown. The original authors

conclude their response with a suggestion to further study asymptomatic carriers, as well as the impact of false-negative rRT-PCR results to aid in containment of the pandemic.

CRITICAL CARE

A PLEA FOR AVOIDING SYSTEMATIC INTUBATION IN SEVERELY HYPOXEMIC PATIENTS WITH COVID-19-ASSOCIATED RESPIRATORY FAILURE

Villarreal-Fernandez E, Patel R, Golamari R, Khalid M, DeWaters A, Haouzi P.. Crit Care. 2020 Jun 12;24(1):337. doi: 10.1186/s13054-020-03063-6.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

A case series by Pennsylvania State University reports on 10 severely hypoxemic patients with COVID-19, 4 of whom were immediately intubated (within the first 2 days) while the other 6 utilized self-prone positioning and only used a nasal cannula (NC) or high-flow nasal cannula (HFNC) when a higher FiO2 was required. Although 2 of these 6 patients eventually needed intubation, these patients collectively had a shorter length of stay than the early-intubated patients (Figure 1), suggesting that avoiding early intubation is possible in patients with COVID-19 and severe hypoxemia.

FIGURES

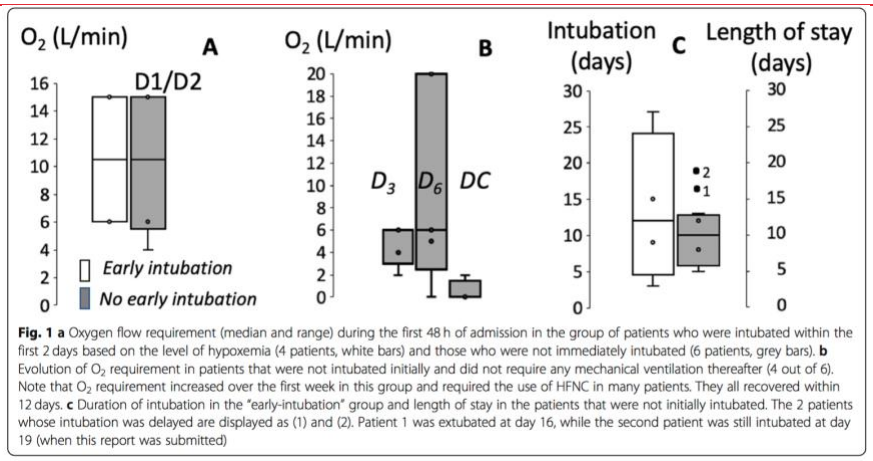


Fig. 1 a Oxygen flow requirement (median and range) during the first 48 h of admission in the group of patients who were intubated within the first 2 days based on the level of hypoxemia (4 patients, white bars) and those who were not immediately intubated (6 patients, grey bars). **b** Evolution of O_2 requirement in patients that were not intubated initially and did not require any mechanical ventilation thereafter (4 out of 6). Note that O_2 requirement increased over the first week in this group and required the use of HFNC in many patients. They all recovered within 12 days. **c** Duration of intubation in the "early-intubation" group and length of stay in the patients that were not initially intubated. The 2 patients whose intubation was delayed are displayed as (1) and (2). Patient 1 was extubated at day 16, while the second patient was still intubated at day 19 (when this report was submitted)

A COMPLICATION OF CORONAVIRUS DISEASE 2019: DELIRIUM

Cipriani G, Danti S, Nuti A, Carlesi C, Lucetti C, Di Fiorino M.. Acta Neurol Belg. 2020 Jun 10. doi: 10.1007/s13760-020-01401-7. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Physicians from Italy conducted a literature review analyzing the relationship between COVID-19 and delirium, noting that COVID-19 in critically-ill and elderly patients may precipitate delirium. These findings suggest an increased need for delirium prevention management programs in these high risk patient populations, including both non-pharmacological (table 5) and pharmacological treatments.

ABSTRACT

COVID-19 is predominantly a respiratory disease. However, some cases exhibit other features including Central Nervous System symptoms. In the older adult, COVID-19 may present with atypical symptoms, including delirium and its complications. The objective of this study is to describe the relationship between the new type of coronavirus infection and delirium. Systematic research (Cochrane Library and PubMed) was carried out (only upper time limit: April 2020). Publications found through this indexed search were reviewed and manually screened to identify relevant studies. Search terms used included "COVID-19, Delirium, Dementia, Intensive Care Unit". We manually added articles identified through other sources (i.e., key journals). Older people are at the greatest risk from COVID-19. If infected, they may present delirium. Moreover, it is not exclusive to older people. Delirium is not inevitable; rather, it is preventable. Delirium prevention programs are even more

crucial in the era of COVID-19 and cannot be allowed to wither despite the challenges of integrating delirium prevention with COVID-19 care. An acute change in condition, behaviour, or mental status should prompt a delirium screen. As regards the treatment, it is advisable to use non-pharmacological interventions first where possible. Medication may be needed for patients with agitation where there is intractable distress or high risk to self/others.

FIGURES

Minimize indwelling catheters and other "tethers," such as intravenous lines, electrocardiography leads
Eliminate physical restraints and mobilize the patient as soon as possible
Monitor urinary and bowel output; avoid urine retention and fecal impaction, which can contribute to delirium
Address nutritional needs, including assistance with meals and possible hand-feeding—delirious patients may have difficulty attending to food and are at risk for acute malnutrition
Provide adequate sensory input, including use of glasses and hearing aids, provision of clocks, calendars, and adequate lighting
Provide frequent orientation and structured interpersonal contact to facilitate cognitive "reconditioning"
Adopt healthy sleep–wake cycles, encouraging night sleeping by reducing environmental stimuli, including minimizing staff noise, using vibrating (silent) pagers, eliminating waking for vital signs except if essential, reducing hospital ward lighting, and turning off televisions and radios

Table 5. Key steps in the supportive care of delirious patients (according to the American College of Physicians).

NEONATAL/PEDIATRIC INTENSIVE CARE

WHAT CAN WE LEARN FROM NEONATES WITH COVID-19?

Xiao TT, Yan K, Wang LS, Zhou WH.. World J Pediatr. 2020 Jun 10. doi: 10.1007/s12519-020-00376-y. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

Researchers in Shanghai, China review how COVID-19 infections affect neonates based on six confirmed cases. More specifically, they discuss:

1. Mechanism of infection - likely family cluster with the possibility of vertical transmission
2. Clinical characteristics - most commonly fever, shortness of breath, vomiting, absence of cough and rarely neonatal respiratory distress syndrome or pneumonia
3. Proper management of infected neonates or neonates born to parents with COVID-19 - depends on severity of illness but includes delayed cord clamping, isolation, and formula feeding neonates.

MEDICAL SUBSPECIALTIES

NEPHROLOGY

ACUTE KIDNEY INJURY IN CRITICALLY ILL PATIENTS WITH COVID-19

Gabarre P, Dumas G, Dupont T, Darmon M, Azoulay E, Zafrani L.. Intensive Care Med. 2020 Jun 12. doi: 10.1007/s00134-020-06153-9. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Parisian researchers present a literature review on the epidemiology, pathophysiology, and treatment for acute kidney injury (AKI) associated with COVID-19 (see below). The research suggests AKI may have a higher prevalence in critically ill patients such as those with COVID-19. However, there are no specific treatments for SARS-CoV-2 induced AKI and the authors conclude early detection of AKI and use of established renal therapies is the best strategy to improve patients' outcome.

- Epidemiology in Wuhan China reports an average incidence for AKI is 11% overall and 23% for critically ill patients (Figure 1).
- Pathophysiologic mechanisms of AKI include direct renal injury, increased RAAS activation, and elevation of inflammatory cytokines (Figure 3).
- Proteinuria, hematuria and increased kaliuresis on urinalysis with SARS-CoV-2 infection are associated with higher mortality rates and admission to the ICU.

- SARS-CoV-2 can gain entry to kidney cells via attachment to angiotensin converting enzyme 2 (ACE2) which may also lead to imbalanced RAAS (Figure 4).

ABSTRACT

Acute kidney injury (AKI) has been reported in up to 25% of critically-ill patients with SARS-CoV-2 infection, especially in those with underlying comorbidities. AKI is associated with high mortality rates in this setting, especially when renal replacement therapy is required. Several studies have highlighted changes in urinary sediment, including proteinuria and hematuria, and evidence of urinary SARS-CoV-2 excretion, suggesting the presence of a renal reservoir for the virus. The pathophysiology of COVID-19 associated AKI could be related to unspecific mechanisms but also to COVID-specific mechanisms such as direct cellular injury resulting from viral entry through the receptor (ACE2) which is highly expressed in the kidney, an imbalanced renin-angotensin-aldosteron system, pro-inflammatory cytokines elicited by the viral infection and thrombotic events. Non-specific mechanisms include haemodynamic alterations, right heart failure, high levels of PEEP in patients requiring mechanical ventilation, hypovolemia, administration of nephrotoxic drugs and nosocomial sepsis. To date, there is no specific treatment for COVID-19 induced AKI. A number of investigational agents are being explored for antiviral/immunomodulatory treatment of COVID-19 and their impact on AKI is still unknown. Indications, timing and modalities of renal replacement therapy currently rely on non-specific data focusing on patients with sepsis. Further studies focusing on AKI in COVID-19 patients are urgently warranted in order to predict the risk of AKI, to identify the exact mechanisms of renal injury and to suggest targeted interventions.

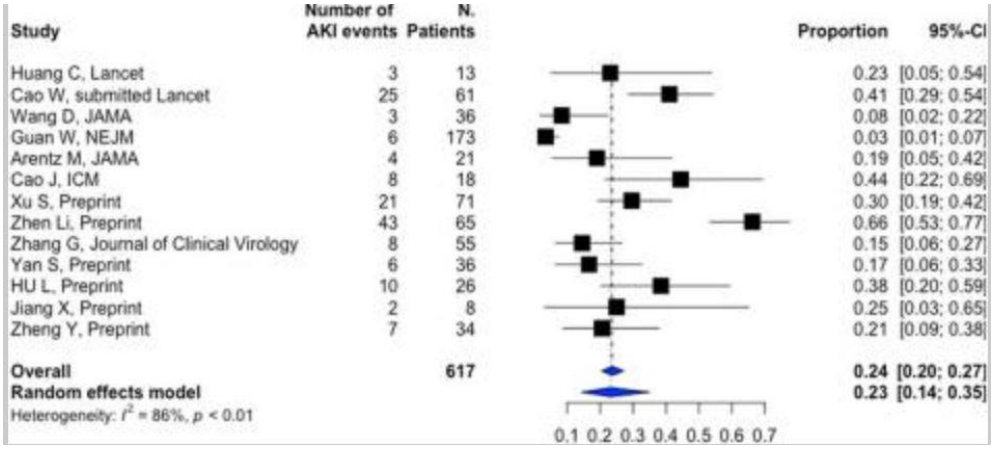


Figure 4. Role of ACE2 and renin–angiotensin–aldosterone system (RAAS) during SARS-CoV-2 infection. Angiotensinogen is converted into angiotensin I by renin and then into angiotensin II (also known as angiotensin (1–8)) by ACE. Angiotensin II, through its binding to AT1R, is responsible for the deleterious effects of RAAS activation (i.e., fibrosis, inflammation, vasoconstriction). ACE2 counteracts deleterious effects of RAAS activation by converting angiotensin I into angiotensin (1–9) and angiotensin II into angiotensin 1–7 that binds to Mas receptor and exerts anti-inflammatory and vasodilatory effects. SARS-CoV-2 binds to membrane-bound ACE2 and invades the cell membrane by endocytosis thus reducing levels of membrane-bound ACE2. Cell invasion depends on ACE2 expression and also on the presence of the protease TMPRSS2, that is able to cleave the viral spike. Diminution of ACE2 results in an accumulation of angiotensin II that is responsible for overactivation of RAAS, leading to increased inflammation, fibrosis, vasoconstriction. Circulating ACE2 could act as a decoy and bind to SARS-CoV-2, thereby preventing internalization of membrane-bound ACE2 by SARS-CoV-2. Under physiological conditions, ACE2 is linked to AT1R, forming a complex that prevents degradation of membrane-bound ACE2 through lysozome internalization. Angiotensin II links to AT1R and decreases the interaction between ACE2 and AT1R, inducing ubiquitination and internalization of ACE2. ARB may increase membrane-bound ACE2 availability by preventing its internalization. However, as the virus requires membrane-bound ACE2 internalization to penetrate the cell, ARB may also decrease the susceptibility to the virus by preventing from virus-ACE2 internalization. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RAAS, renin–angiotensin–aldosterone system; ACE, angiotensin-converting enzyme; ATII, angiotensin II; AT1R, angiotensin receptor type I; ACE2, angiotensin-converting enzyme 2; Mas-R, Mas receptor; ARB, angiotensin receptor blocker; TMPRSS2, transmembrane protease, serine 2

SURGICAL SUBSPECIALTIES

FACTORS ASSOCIATED WITH SURGICAL MORTALITY AND COMPLICATIONS AMONG PATIENTS WITH AND WITHOUT CORONAVIRUS DISEASE 2019 (COVID-19) IN ITALY

Doglietto F, Vezzoli M, Gheza F, Lussardi GL, Domenicucci M, Vecchiarelli L, Zanin L, Saraceno G, Signorini L, Panciani PP, Castelli F, Maroldi R, Rasulo FA, Benvenuti MR, Portolani N, Bonardelli S, Milano G, Casiraghi A, Calza S, Fontanella MM.. JAMA Surg. 2020 Jun 12. doi: 10.1001/jamasurg.2020.2713. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A matched cohort study in multiple surgical units of Spedali Civil Hospital from February 23 to April 1, 2020 found that 30-day mortality rates and post-op complications, especially pulmonary and thrombotic, were significantly higher in 41 surgical patients with COVID-19 than 82 controls without COVID-19 (mortality OR: 9.5, 95% CI: 1.77-96.53; complications OR: 4.98, 95% CI: 1.81-16.07). The authors also used two different models, the classification tree and the cumulative link model, to identify COVID-19 as a main contributing factor to complications (Figure 1; Table 4). These findings suggest that COVID-19 disease is an important consideration for postponing surgery when possible.

ABSTRACT

Importance: There are limited data on mortality and complications rates in patients with coronavirus disease 2019 (COVID-19) who undergo surgery. Objective: To evaluate early surgical outcomes of patients with COVID-19 in different subspecialties. Design, Setting, and Participants: This matched cohort study conducted in the general, vascular and thoracic surgery, orthopedic, and neurosurgery units of Spedali Civili Hospital (Brescia, Italy) included patients who underwent surgical treatment from February 23 to April 1, 2020, and had positive test results for COVID-19 either before or within 1 week after surgery. Gynecological and minor surgical procedures were excluded. Patients with COVID-19 were matched with patients without COVID-19 with a 1:2 ratio for sex, age group, American Society of Anesthesiologists score, and comorbidities recorded in the surgical risk calculator of the American College of Surgeons National Surgical Quality Improvement Program. Patients older than 65 years were also matched for the Clinical Frailty Scale score. Exposures: Patients with positive results for COVID-19 and undergoing surgery vs matched surgical patients without infection. Screening for COVID-19 was performed with reverse transcriptase-polymerase chain reaction assay in nasopharyngeal swabs, chest radiography, and/or computed tomography. Diagnosis of COVID-19 was based on positivity of at least 1 of these investigations. Main Outcomes and Measures: The primary end point was early surgical mortality and complications in patients with COVID-19; secondary end points were the modeling of complications to determine the importance of COVID-19 compared with other surgical risk factors. Results: Of 41 patients (of 333 who underwent operation during the same period) who underwent mainly urgent surgery, 33 (80.5%) had positive results for COVID-19 preoperatively and 8 (19.5%) had positive results within 5 days from surgery. Of the 123 patients of the combined cohorts (78 women [63.4%]; mean [SD] age, 76.6 [14.4] years), 30-day mortality was significantly higher for those with COVID-19 compared with control patients without COVID-19 (odds ratio [OR], 9.5; 95% CI, 1.77-96.53). Complications were also significantly higher (OR, 4.98; 95% CI, 1.81-16.07); pulmonary complications were the most common (OR, 35.62; 95% CI, 9.34-205.55), but thrombotic complications were also significantly associated with COVID-19 (OR, 13.2; 95% CI, 1.48-). Different models (cumulative link model and classification tree) identified COVID-19 as the main variable associated with complications. Conclusions and Relevance: In this matched cohort study, surgical mortality and complications were higher in patients with COVID-19 compared with patients without COVID-19. These data suggest that, whenever possible, surgery should be postponed in patients with COVID-19.

Variables	OR (95% CI)	*P* value
Outcome CCI_ord ~ group + age + respiratory function at admission		
Group (COVID-19)	13.29 (5.09-34.68)	<.001
Age	1.04 (1.01-1.07)	.01
Respiratory function at admission		
Poor	3.35 (0.36-31.62)	.29
Good	0.38 (0.16-0.94)	.04
R^2 Nagelkerke = 0.43	NA	

Abbreviations: CCI, comprehensive complication; COVID-19, coronavirus disease 2019; NA, not applicable; OR, odds ratio.

[a] Convergence of the model was achieved with only 3 covariates (group, age, and respiratory function at admission). The model identified COVID-19 as the strongest variable associated with complications (they are 13 times more likely in patients with COVID-19) while age retained its relevance but with less strength.

Table 4. Cumulative Link Model

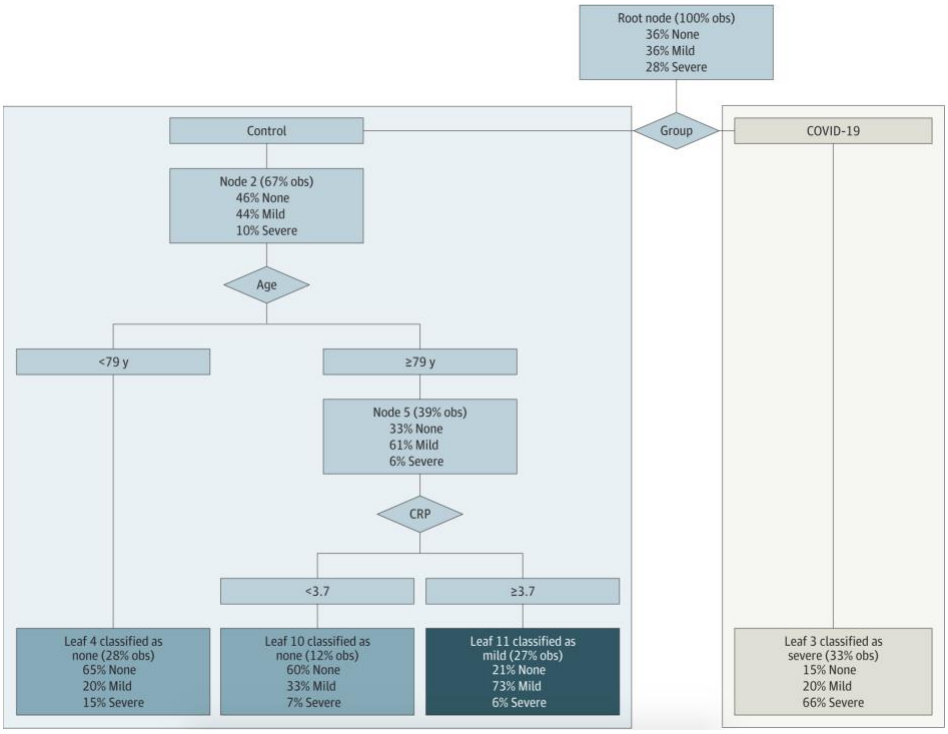


Figure 1. Classification Tree for Complications and Their Associated Variables. Each leaf of the tree (in color) is classified according to the most frequent class in it (majority vote rule); blue, dark blue, and gray are for none, mild, and severe complications, respectively. The root node (containing all observations) is automatically divided by the algorithm with respect to the group variable: control patients are positioned on the left of the tree and coronavirus disease 2019 (COVID-19) on the right. The control branches lead to blue or dark blue leaves. In contrast, the COVID-19 branch leads to a unique gray leaf classified as severe complications. CRP indicates C-reactive protein; obs, observed.

THE EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS OF CO-INFECTION OF SARS-COV-2 AND INFLUENZA VIRUSES IN PATIENTS DURING COVID-19 OUTBREAK

Yue H, Zhang M, Xing L, Wang K, Rao X, Liu H, Tian J, Zhou P, Deng Y, Shang J.. J Med Virol. 2020 Jun 12. doi: 10.1002/jmv.26163. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

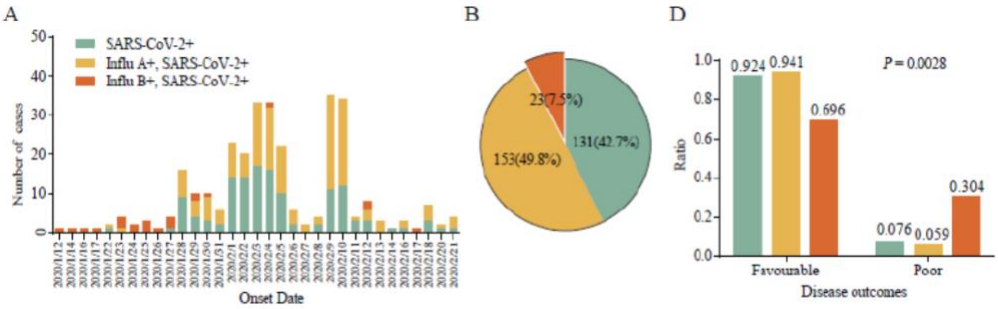
BLUF

This retrospective cohort study conducted in Wuhan, China involving 307 COVID-19 patients from 1/12/20 - 2/21/20 found significant co-infection rates with Influenza A (49.8%) and Influenza B (7.5%) (Figure 1B). Prevalence of Influenza B was far more prevalent in the first two weeks of the study (Figure 1A). Patients co-infected with Influenza B and SARS-CoV-2 exhibited worse prognosis (Figure 1D) as they were more likely to have chest CT abnormalities, fatigue, decreased lymphocyte count, and decreased eosinophil counts (p-values given in Figure 1C). Based on these findings, the authors recommend testing for Influenza A and B in any COVID-19 patients as early detection and treatment could potentially improve patient outcomes.

ABSTRACT

In this study, we performed a single-centred study of 307 SARS-CoV-2 infected patients. It was found that co-infection of SARS-CoV-2 and influenza virus was common during COVID-19 outbreak. And patients co-infected with SARS-CoV-2 and influenza B virus have a higher risk of developing poor outcomes so a detection of both viruses was recommended during COVID-19 outbreak.

FIGURES



C

Indicators	Influenza-, SARS-CoV-2+	Influenza A+, SARS-CoV-2+	Influenza B+, SARS-CoV-2+	*P* value
Character	n = 131	n = 153	n = 23	
Age (years)	64 (50.5-70)	61 (46-68)	56 (43-66.5)	0.158[b]
Male	69 (52.7%)	64 (41.8%)	11 (47.8%)	0.188[c]
Female	62 (47.3%)	89 (58.2%)	12 (52.2%)	
Symptoms				
Fever	104 (79.4%)	132 (86.3%)	16 (69.6%)	0.080[d]
Cough	40 (30.5%)	38 (24.8%)	6 (26.1%)	0.556[c]
Fatigue	13 (9.9%)	5 (3.3%)	3 (13.0%)	**0.026**[d]
diarrhea	11 (8.4%)	6 (3.9%)	0 (0.0%)	0.161[d]
Difficulty breathing	9 (6.9%)	11 (7.2%)	2 (8.7%)	0.886[d]
Abnormalities on chest CT	122 (97.6%), n=125	127 (94.8%), n=134	23 (100%)	**0.401**[d]
laboratory findings (median, IQR)				
Lymphocytes (×10⁹/L)	0.92 (0.68-1.19)	1.06 (0.73-1.41)	0.84 (0.68-1.27)	0.109[b]
Eosinophils (×10⁹/L)	0.01 (0.00-0.03)	0.01 (0.00-0.06)	0.00 (0.00-0.01)	**0.02**[b]
Eosinophils (×10⁹/L), mean (SD)	0.021±0.035	0.046±0.095	0.023±0.05	**0.049**[a]
IL-6 (pg/mL)	10.13 (3.03-25.94), n=104	9.95 (2.62-27.72), n=131	10.95 (4.69-24.15), n=20	0.981[b]
IL-8 (pg/L)	12.70 (7.25-21.73), n=102	9.95 (5.2-20.23), n=128	11.80 (7.70-18.50), n=21	0.186[b]
hs-CRP (mg/L)	36.10 (11.00-82.70), n=129	26.00 (6.20-76.45), n=152	33.50 (14.30-64.65), n=23	0.098[b]

Figure 1. Co-infection of SARS-CoV-2 and influenza viruses among patients. (A) Records of daily new cases in a single-centered study at Tongji hospital (Wuhan, China) from 12 January to 21 February 2020. Flu A: influenza type A virus; Flu B: influenza type B virus. Patients were grouped into SARS-CoV-2 single positive (green color), co-infection with influenza A virus (yellow color) or co-infection with influenza B virus (red color). (B) Number of cases and percentage of each group. (C) Character, clinical symptoms and laboratory comparison of patients among these three groups. Hs-CRP, Hypersensitive C-reactive protein. Continuous variables were described as median and interquartile range (IQR) or mean and standard deviation (SD) and differences were assessed using Analysis of Variance (ANOVA) or Kruskal-Wallis test. Categorical variables were expressed as number (%) and differences between groups were assessed using Pearson's [chi-squared] test or Fisher's exact test. a, ANOVA; b, Kruskal-Wallis test; c, Pearson's [chi-squared] test; d, Fisher's exact test. P < 0.05 was bold. n=131, 153, or 23

individually unless indicated. (D) Disease outcomes for patients among three groups. Favourable means disease alleviated or recovered; poor means disease aggravated with certain deaths. The differences between groups were assessed using Pearson's [chi-squared] test or Fisher's exact test.

REACTIVATION OF COVID-19 - 14 DAYS FROM THE ONSET OF SYMPTOMS MAY NOT BE ENOUGH TO ALLOW DENTAL TREATMENT

Tarakji B, Nassani MZ.. Oral Dis. 2020 Jun 10. doi: 10.1111/odi.13487. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Dental professionals in Saudi Arabia believe the current recommendation to perform dental treatment on COVID-19 positive patients 14 days after onset of symptoms is too short of a period. Their guidance is based on prior research from China, Japan and Korea which revealed several cases of COVID-19 reactivation well beyond 14 days. To mitigate the risk of transmission, the authors recommend extending the recommendation to 28 days of quarantine after onset of symptoms to ensure adequate time for recovery.

ABSTRACT

The pandemic of coronavirus disease 2019 (COVID-19) has become a global health disaster (Phelan et al., 2020). On the level of dental practice, the risk of cross infection between infected patients and dental professionals is quite alarming. The current recommendations suggest that dental treatment of patients with suspected/confirmed coronavirus disease should be postponed for at least 14 days from the onset of symptoms (Peng et al., 2020).

ACUTE CARE

DECREASE IN HOSPITAL ADMISSIONS FOR TRANSIENT ISCHEMIC ATTACK, MILD, AND MODERATE STROKE DURING THE COVID-19 ERA

Diegoli H, Magalhães PSC, Martins SCO, Moro CHC, França PHC, Safanelli J, Nagel V, Venancio VG, Liberato RB, Longo AL.. Stroke. 2020 Jun 12:STROKEAHA120030481. doi: 10.1161/STROKEAHA.120.030481. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers from Joinville, Brazil analyze the impact of COVID-19 on stroke admissions before the onset of COVID-19 restrictions (February 16 to March 17, 2020) and after the onset (March 17 to April 15, 2020). They found a reduction of 36.4% for inpatient admission of all causes of stroke (P=0.0126) when compared with the same period in 2019. Authors attribute the findings to fear of hospital presentation, thus advocating for public health agencies in Brazil to prioritize measures to ensure stroke management and improve patient outcomes.

SUMMARY

Specific findings include:
1. TIA - reduction from 2.28 cases per 100,000 inhabitants per month in 2019 (SD 0.8) to 0.51 after COVID-19 (P=0.0049)
2. Mild stroke (NIHSS score 0-4) - reduction from 7.72 (SD 1.08) to 5.25 (P=0.0425)
3. Moderate stroke (NIHSS score 5-8) - reduction from 1.95 (SD 0.85) to 0.51 (P=0.0103)
4. Severe stroke (NIHSS score 9-14) - reduction from 1.11 (SD 0.37) to 0.85 (P=0.1521)
5. Very severe stroke (NIHSS score >14) - reduction from 1.83 (SD 0.67) to 1.52 (P=0.6181).

ABSTRACT

BACKGROUND AND PURPOSE: Since the onset of the coronavirus 2019 (COVID-19) pandemic, doctors and public authorities have demonstrated concern about the reduction in quality of care for other health conditions due to social restrictions and lack of resources. Using a population-based stroke registry, we investigated the impact of the onset of the COVID-19 pandemic in stroke admissions in Joinville, Brazil. METHODS: Patients admitted after the onset of COVID-19 restrictions in the city (defined as March 17, 2020) were compared with those admitted in 2019. We analyzed differences between stroke incidence, types, severity, reperfusion therapies, and time from stroke onset to admission. Statistical tests were also performed to compare the 30 days before and after COVID-19 to the same period in 2019. RESULTS: We observed a decrease in total stroke admissions from an average of 12.9/100 000 per month in 2019 to 8.3 after COVID-19 (P=0.0029). When compared with the

same period in 2019, there was a 36.4% reduction in stroke admissions. There was no difference in admissions for severe stroke (National Institutes of Health Stroke Scale score >8), intraparenchymal hemorrhage, and subarachnoid hemorrhage. CONCLUSIONS: The onset of COVID-19 was correlated with a reduction in admissions for transient, mild, and moderate strokes. Given the need to prevent the worsening of symptoms and the occurrence of medical complications in these groups, a reorganization of the stroke-care networks is necessary to reduce collateral damage caused by COVID-19.

FIGURES

	Stroke Admissions/100 000 Inhabitants	*P* Value	Stroke Admissions With NIHSS 0–8/100 000 Inhabitants	*P* Value
February 15–March 16, 2019	11.7		8.5	
March 17–April 15, 2019	13		9.8	
February 16–March 16, 2020	12.7 (+8.7%)	0.6168	9.8 (+16%)	0.5005
March 17–April 15, 2020	8.3 (−36.4%)	0.0126*	5.8 (−41.4%)	0.016*

Table 1. Change in Stroke Admissions From 2019 to 2020
The percentual change and P value are related to the same period in the previous year. NIHSS indicates National Institutes of Health Stroke Scale.
*P values considered statistically significant.Figure 2. Stroke admissions by time period.
The admission rates per 100 000 inhabitants of ischemic stroke (IS), transient ischemic attack (TIA), intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH),
and strokes of unknown cause are demonstrated for each month in 2019 and the first quarter of 2020. COVID-19 indicates coronavirus 2019.

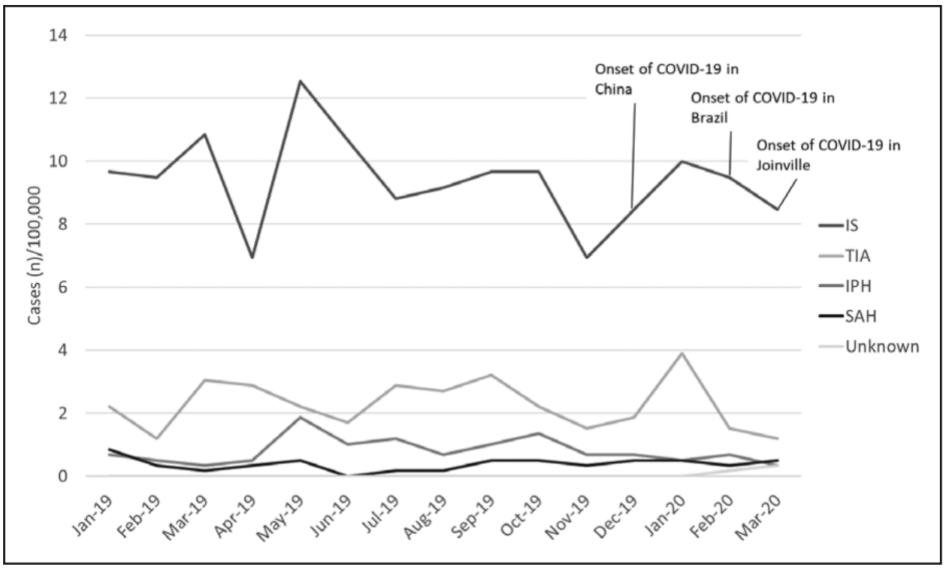


Figure 2. Stroke admissions by time period. The admission rates per 100 000 inhabitants of ischemic stroke (IS), transient ischemic attack (TIA), intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), and strokes of unknown cause are demonstrated for each month in 2019 and the first quarter of 2020. COVID-19 indicates coronavirus 2019.

MEDICAL SUBSPECIALTIES

CARDIOLOGY

CARDIOMETABOLIC RISK FACTOR CONTROL DURING TIMES OF CRISES AND BEYOND

Brook RD, Levy P, Rajagopalan S.. Circ Cardiovasc Qual Outcomes. 2020 Jun 11. doi: 10.1161/CIRCOUTCOMES.120.006815. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

The authors discuss "disastrous cardiometabolic risk factors (CMRFs)," a previously observed phenomenon in which CMRFs and their control rates worsen during and following a major disaster, leading to a second crisis. The authors anticipate disastrous CMRFs in the wake of the current COVID-19 pandemic and outline possible strategies to address factors that may worsen CMRF monitoring (Table).

ABSTRACT

The world is currently suffering through one the greatest crises of the last century. The coronavirus disease-19 (COVID-19) pandemic is taking an enormous toll on public health and stretching medical resources in an unprecedented fashion. Our priorities are rightly focusing on meeting this existential threat. Nonetheless, we wish to call to attention that during major catastrophes the health consequences of chronic diseases, in particular cardiometabolic risk factors (CMRFs), continue unabated. In fact, new and serious problems arise part-and-parcel with the catastrophe and conspire to hamper our already imperfect ability to control CMRFs1,2. Our objective is to raise awareness that we need to anticipate (and not just be reactive to) the possible coming of a second crisis we term "disastrous CMRFs". This refers to the worsening of CMRFs and their control rates during and following a major disaster. Health care providers, in particular cardiologists, need to recognize the potential for this serious problem as it could promote a burgeoning of cardiovascular morbidity and mortality if not addressed. The COVID-19 pandemic should also serve as a wake-up call to the antiquated flaws in our healthcare model that collude to undermine the successful management of CMRFs in general. This current crisis can be a catalyst for optimizing practices and creating critical new capacities that will be beneficial moving forward and serve as a bulwark against future crises.

FIGURES

Table. Causes of and potential remedies for "disastrous cardio-metabolic risk factors"

Categories	Issues That Could Worsen CMRF Control	Potential Strategies That Could Help Mitigate The Issues
Social factors	Financial hardships	
	Additional job responsibilities and insecurities	
	Reduced capacity for lifestyle management	Expand insurance coverage for remote consults to include non-physician-based health promotion and education (e.g. dietary and exercise therapies)
	Insurance coverage difficulties	Alternative insurance paradigms and expanded coverage systems (e.g., "medicare for all") that are part of a larger debate might be helpful.
	Restricted available time for clinic visits	Expand non-traditional healthcare settings (e.g., barber shops, salons) in communities to improve access and proximity to care[3]
	Transportation and travel difficulties	Improving access and reducing costs of medical transportation. Use of non-traditional care settings. Use of telehealth and a dedicated remote "CMRF-control program"
	Decreased medication and lifestyle compliance	Involve proven methods to enhance persistence (e.g., mobile health platforms, text/call reminders)[5]
	Medication loss	Free home medication delivery, secure medication vending-machines. Increase the pool of independent prescribers (e.g., pharmacists)
Biological responses	Endothelial dysfunction	Improve CMRF control
	Chronic post-traumatic stress disorder	Expand insurance coverage for remote consults to also include counselling for psychological disorders by physicians and other mental health professionals
	Reduced sleep duration/quality (circadian disruption)	Expand insurance coverage for remote consults to also include counselling and medication therapy for sleep disorders when appropriate
	SNS and HPAA activation	Use of anti-SNS medications (e.g., beta blockers or clonidine) when appropriate.
	Poor diet - alcohol abuse, increased dietary sodium	Expand insurance coverage for remote consults to also include dieticians
	Weight gain, inactivity	Expand insurance coverage for remote consults to also include dieticians and exercise therapists
Healthcare system failures	Reduced medication availability	Adequate stock-pile of "essential" cardiovascular medications (e.g., statins, BP medications)
	Reduced clinic space and time availability	Telemedicine and non-traditional settings of care Use a dedicated remote "CMRF-control program"
	Fewer health care providers and reduced availability	Telemedicine and non-traditional settings of care Use a dedicated remote "CMRF-control program"
	Decrease in medical resources and equipment	Telemedicine and non-traditional settings of care Use a dedicated remote "CMRF-control program"
	Prioritization of care to urgent health issues	Education of the importance of "disastrous CMRFs" to healthcare providers and patients. Use a dedicated remote "CMRF-control program"
	Down-playing continued importance of CMRF control by providers	Education of the importance of "disastrous CMRFs" to healthcare providers and patients. Use a dedicated remote "CMRF-control program"

BP, blood pressure; CMRF, cardio-metabolic risk factors; HPAA, hypothalamic-pituitary-adrenal axis; SNS, sympathetic nervous system

10.1161/CIRCOUTCOMES.120.006815

MANAGEMENT OF STRUCTURAL HEART DISEASE AND ACUTE CORONARY SYNDROMES IN THE COVID-19 PANDEMIC

Giordano A, Biondi-Zoccai G, Frati G, Bartorelli AL.. Curr Atheroscler Rep. 2020 Jun 10;22(7):29. doi: 10.1007/s11883-020-00849-5.

Level of Evidence: Other - Expert Opinion

BLUF

The authors make a case for the focused resumption of invasive interventions for structural heart disease (SHD) and acute coronary syndrome (ACS) in select centers in order to prevent the potentially life-threatening consequences of further delaying surgical intervention for these conditions, as was done at the start of the pandemic (Figure 1). They also highlight the importance of primary care physicians recognizing symptoms or signs of cardiovascular disease in their patients, and proceeding with the relevant and safe work-up.

ABSTRACT

Transcatheter interventions for structural heart disease (SHD) now represent an effective alternative to surgery in selected patients. A clear premise is that delay in or neglect of treating patients in need of SHD intervention is associated with unavoidable morbidity and mortality because many of them have life-threatening conditions. However, the recent outbreak of coronavirus-associated disease-2019 (COVID-19) is placing an unprecedented strain on patients, physicians and world healthcare systems that resulted in deferral of elective and semi-elective procedures, such as SHD, and delay in the treatment of patients with acute coronary syndrome (ACS). We hereby present the case for a focused resumption of transcatheter SHD interventions in selected centers, in order to preserve patient safety and avoid that death rate will extend far beyond that directly associated with COVID-19. A similar approach should be applied to the invasive management of ACS. Indeed, a proactive and vigilant stance on managing SHD and ACS is crucial, especially in the context of the COVID-19 pandemic, when the risk of overlooking severely sick patients or postponing life-saving treatments is high. If such corrective measures are not put into effect, we may expect in the near future an excess of avoidable fatalities indirectly due to COVID-19 but truly caused by cardiovascular diseases, as well as an exceedingly large number of patients with severe heart failure leading to shorter life expectancy, reduced quality of life and increased healthcare cost.

FIGURES

Table 1 Highlights of life-saving interventions for structural heart disease and coronary artery disease

Setting	Incidence per year	Treatment	Comparator	Outcome	Results	Number needed to treat to prevent one death	Reference
Aortic stenosis	$150/10^6$	Transcatheter aortic valve implantation	Balloon aortic valvuloplasty	Risk of death at 12 months	31% vs 50%	5	[7]
Secondary mitral regurgitation	$300/10^6$	Transcatheter mitral valve repair	Conservative management	Risk of death at 12 months	19% vs 23%	25	[8]
ST-elevation myocardial infarction	$800/10^6$	Streptokinase and aspirin	Conservative management	Risk of vascular death at 5 weeks	8% vs 13%	20	[9]
ST-elevation myocardial infarction	$800/10^6$	Primary percutaneous coronary intervention	Thrombolysis	Risk of death at 4–6 weeks	7% vs 8%	50	[10].

LOPINAVIR/RITONAVIR AS A THIRD AGENT IN THE ANTIVIRAL REGIMEN FOR SARS-COV-2 INFECTION

Panagopoulos P, Petrakis V, Panopoulou M, Trypsianis G, Penlioglou T, Pnevmatikos I, Papazoglou D.. J Chemother. 2020 Jun 12:1-5. doi: 10.1080/1120009X.2020.1775424. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

This study retrospectively reviewed 16 patients in Greece diagnosed with COVID-19 between March 1st and March 31st. All patients received hydroxychloroquine and azithromycin and were then classified into two groups (Group A received lopinavir/ritonavir as a third agent while Group B did not). The lopinavir/ritonavir combination was added for those with persistent fever and "severe radiological findings (bilateral, diffuse ground glass opacities and pleural effusions)" (n=8). The authors emphasized the following results:

1. Patients in Group A needed fewer days to test negative for SARS-CoV-2 via RT-PCR test (p=0.003) and fewer days in the hospital (p=0.003).
2. Patients in Group A had reduced ferritin serum levels on day 14 compared to baseline (p-value not significant at 0.345) and compared to Group B (p-value not given) (Table 1).
3. Patients in Group A also had increased lymphocyte counts on day 14 compared to baseline (p-value statistically significant at 0.011) and compared to Group B (p-value not given) (Figure 1).
4. C-reactive protein was significantly decreased in both groups on day 14 (p=0.001 for Group A, p=0.014 for Group B).
5. Of note, although Figure 1 presents Ferritin and Lymphocyte counts from both Group A and Group B on the same graph, Group A was not directly compared to Group B in statistical analysis of ferritin level or lymphocyte count. Additionally, Group A and Group B were not directly compared in the statistical analysis of the C-reactive protein level.
6. Further details on findings can be found in Table 1.

Based on their findings, the authors suggested that lopinavir/ritonavir may be effective at reducing the viral load in patients with severe SARS-CoV-2 infections.

ABSTRACT

Corona Virus Disease (CoVID-19) is an emerging public health problem rapidly spread globally. New treatment options for patients with severe symptoms and ways of reducing transmission in the community are taken into consideration. A retrospective study was conducted in the Department of Infectious Diseases of Alexandroupolis (Greece) including 16 patients with CoVID-19. They were classified into two groups, A and B. Group A received lopinavir/ritonavir as a third agent in the antiviral regimen, while group B did not. Lymphocytes were more significantly increased in patients of group A. Ferritin serum levels were also decreased significantly in these patients. Number of days needed for a first negative result of Real Time-Polymerase Chain Reaction (RT-PCR) was lower for Group A. The present study suggests that lopinavir/ritonavir may reduce the viral carriage in a shorter period of time compared with other antiviral regimens. Further studies are needed in order to evaluate the effectiveness of lopinavir/ritonavir in the treatment of patients with SARS-CoV-2 infection.

FIGURES

	Group A-Treatment with Lopinavir/Ritonavir (n = 8)				Group B-Treatment without Lopinavir/Ritonavir (n = 8)			
Gender • Male, n (%)	6(75%)				4(50%)			
Age (years)	55.75 ± 19.71				59.75 ± 10.51			
Comorbidity, n (%)	7(87.5%)				5(71.4%)			
Severe radiological findings, n (%)	8(100%)				3(37.5%)			
	Day 0	Day 7	Day 14	P value	Day 0	Day 7	Day 14	P value
Lymphocyte (/ml)	968.57 ± 301.3	751.43 ± 187.12	1075.71 ± 223.3	0.011	1125 ± 376.12	866.67 ± 391.9	996.67 ± 312.84	0.451
Fibrinogen (mg/dl)	398.14 ± 35.82	490.86 ± 99.26	436.86 ± 93.96	0.048	409.83 ± 75.55	426.5 ± 169.83	373.67 ± 151.84	0.604
D-dimers (mg/dl)	606 (270–985)	866 (401–1261)	604 (149–1368)	0.086	726.5 (173–1291)	897 (235–6415)	1014 (222–2500)	0.107
Ferritin (mg/dl)	850 (102–1682)	532 (103–2137)	311 (90–2321)	0.345	252 (53–1293)	322 (72–1441)	339 (77–2163)	0.291
Procalcitonin (mg/dl)	0.1 (0–0.6)	0.1 (0–16.7)	0.0 (0–1.3)	0.431	0.0 (0–1.5)	0.0 (0–2.2)	0.1 (0–1.1)	0.913
C-reactive protein (mg/dl)	6.14 ± 2.8	10.86 ± 5.18	4.18 ± 3.62	0.001	4.6 ± 6.47	8.46 ± 5.67	1.58 ± 1.69	0.014
Partial pressure of oxygen (mm Hg)	70.57 ± 6.42	66.71 ± 14.64	73.43 ± 3.95	0.401	65.83 ± 10.76	72.67 ± 3.50	72 ± 2.97	0.236
Oxygen saturation (%)	94.71 ± 1.89	94.43 ± 2.07	96.14 ± 0.69	0.171	92.83 ± 3.43	95.83 ± 1.17	96.33 ± 1.8	0.082
								P value
Days of hospitalization	14.71 ± 0.76				11.40 ± 2.07			**0.003**
Days for clinical improvement (no fever)	6.00 ± 1.16				4.4 ± 1.52			0.064
Days for negative result of RT-PCR for SARS-COV-2	8.86 ± 1.68				13.8 ± 2.68			**0.003**
Intubation	1 (12.5%)				3 (37.5%)			

Bold values signifies parameters statically significant.

Table 1. Results.

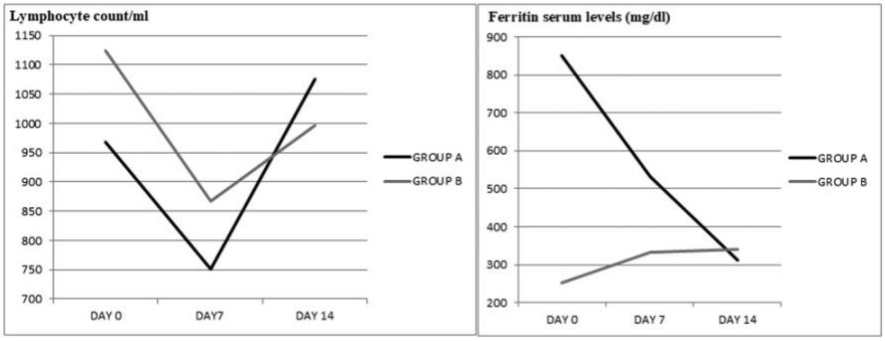


Figure 1. Lymphocyte count/ml and ferritin serum levels at days 0, 7 and 14 for Groups A and B.

CURRENT DIAGNOSTICS

FALSE-POSITIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION SCREENING FOR SARS-COV-2 IN THE SETTING OF URGENT HEAD AND NECK SURGERY AND OTOLARYNGOLOGIC EMERGENCIES DURING THE PANDEMIC: CLINICAL IMPLICATIONS

Katz AP, Civantos FJ, Sargi Z, Leibowitz JM, Nicolli EA, Weed D, Moskovitz AE, Civantos AM, Andrews DM, Martinez O, Thomas GR.. Head Neck. 2020 Jun 12. doi: 10.1002/hed.26317. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

A retrospective study performed by otolaryngologists at the University of Miami Miller School of Medicine from March through April 2020 discovered 3 out of 42 (7.1%) patients with SARS-CoV-2 positive reverse transcriptase polymerase chain reaction (RT-PCR) had a subsequent negative result on repeat testing (Tables 2 and 3). Although the results were considered false positive, one patient was sent to the COVID-19 unit postoperatively and two had urgent surgery delayed, underlining patient risks involved in false positive reads. The authors include hypotheses regarding false-positive SARS-CoV-2 testing (below) and suggest that suspected false-positive RT-PCR tests should be confirmed with chest computed tomography (CT) and repeat RT-PCR.

SUMMARY

Authors include the following hypotheses regarding false-positive SARS-CoV-2 testing:
"1. Pure technical artifacts where fluorescence signal is generated due to nonspecific nuclease degradation of the probe probably associated with off-target probe binding. In short, a technical artifact. This is most likely associated with a weak positive signal.
2 Detection of another non-SARS-CoV-2 virus/microorganism that has not yet been accounted for in the global databases used to design the primers/probes in these assays. Recall that all of these assays are new.
3 Technical cross-contamination at any point along the sample chain of testing. If a manual pipetting step is involved, it could a technologist who accidentally made an error. In some instrument configurations, it could be a sample carryover contamination event. We tend totrust robots and instruments, but they are not infallible."

ABSTRACT

BACKGROUND: No reports describe falsepositive reverse transcriptase polymerase chain reaction (RT-PCR) for novel coronavirus in preoperative screening.
METHODS: Preoperative patients had one or two nasopharyngeal swabs, depending on low or high risk of viral transmission. Positive tests were repeated.
RESULTS: Forty-three of 52 patients required two or more preoperative tests. Four (9.3%) had discrepant results (positive/negative). One of these left the coronavirus disease (COVID) unit against medical advice despite an orbital abscess, with unknown true disease status. The remaining 3 of 42 (7.1%) had negative repeat RT-PCR. Although ultimately considered falsepositives, one was sent to a COVID unit postoperatively and two had urgent surgery delayed. Assuming negative repeat RT-PCR, clear chest imaging, and lack of subsequent symptoms represent the "gold standard," RT-PCR specificity was 0.97.
CONCLUSIONS: If false positives are suspected, we recommend computed tomography (CT) of the chest and repeat RT-PCR. Validated serum immunoglobulin testing may ultimately prove useful.

FIGURES

TABLE 2 Demographics

	Patients with discrepant tests	Patients without discrepant tests	*P*-value
Age Mean (SD)	56.0 (25.7)	61.8 (14.7)	.47
Sex Number (%)	2 (50%) Male 2 (50%) Female	26 (54.2%) Male 22 (45.8%) Female	.77
Mucosal pathology Number (%)	3 (75%)	37 (83.3%)	.92
Current cancer diagnosis Number (%)	2 (50%)	35 (72.9%)	.33
History of radiation Number (%)	1 (25%)	9 (18.7%)	.77

TABLE 3 Characteristics of patients with discrepant results

	Age, sex	Mucosal pathology?	Cancer diagnosis?	History of radiation to head and neck	# Tests after initial 2	Disease status	Implications on patient care
Patient 1	60 M	Yes	Presently	No	1	True negative	Two nights in COVID-19 ward
Patient 2	81 F	Yes	History	Yes	3	True negative	Surgery delayed 4 days
Patient 3	63 F	No	Presently	No	1	True negative	Surgery delayed 3 days; Plastic surgeon schedule change affected other patients
Patient 4	20 M	Yes	No	No	0	Unknown	One night on COVID-19 ward, left AMA

Abbreviations: AMA, against medical advice; F, female; M, male.

DEVELOPMENTS IN DIAGNOSTICS

RAPID DETECTION OF NOVEL CORONAVIRUS/SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) BY REVERSE TRANSCRIPTION-LOOP-MEDIATED ISOTHERMAL AMPLIFICATION

Lamb LE, Bartolone SN, Ward E, Chancellor MB.. PLoS One. 2020 Jun 12;15(6):e0234682. doi: 10.1371/journal.pone.0234682. eCollection 2020.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

This bench-lab investigation developed and validated a rapid (30-45 minute) screening diagnostic test for SARS-CoV-2 using a reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay. This assay was both sensitive (95%) and specific (90%) in detecting SARS-CoV-2 infection in patients by quantitative RT-PCR in vitro. Thus, this assay holds potential as a new diagnostic strategy for rapid detection of SARS-CoV-2 and warrants investigation outside of the laboratory for its practical use in a clinical population.

ABSTRACT

Novel Corona virus/Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 or 2019-nCoV), and the subsequent disease caused by the virus (coronavirus disease 2019 or COVID-19), is an emerging global health concern that requires a rapid diagnostic test. Quantitative reverse transcription PCR (qRT-PCR) is currently the standard for SARS-CoV-2 detection; however, Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP) may allow for faster and cheaper field based testing at point-of-risk. The objective of this study was to develop a rapid screening diagnostic test that could be completed in 30-45 minutes. Simulated patient samples were generated by spiking serum, urine, saliva, oropharyngeal swabs, and nasopharyngeal swabs with a portion of the SARS-CoV-2 nucleic sequence. RNA isolated from nasopharyngeal swabs collected from actual COVID-19 patients was also tested. The samples were tested using RT-LAMP as well as by conventional qRT-PCR. Specificity of the RT-LAMP was evaluated by also testing against other related coronaviruses. RT-LAMP specifically detected SARS-CoV-2 in both simulated patient samples and clinical specimens. This test was performed in 30-45 minutes. This approach could be used for monitoring of exposed individuals or potentially aid with screening efforts in the field and potential ports of entry.

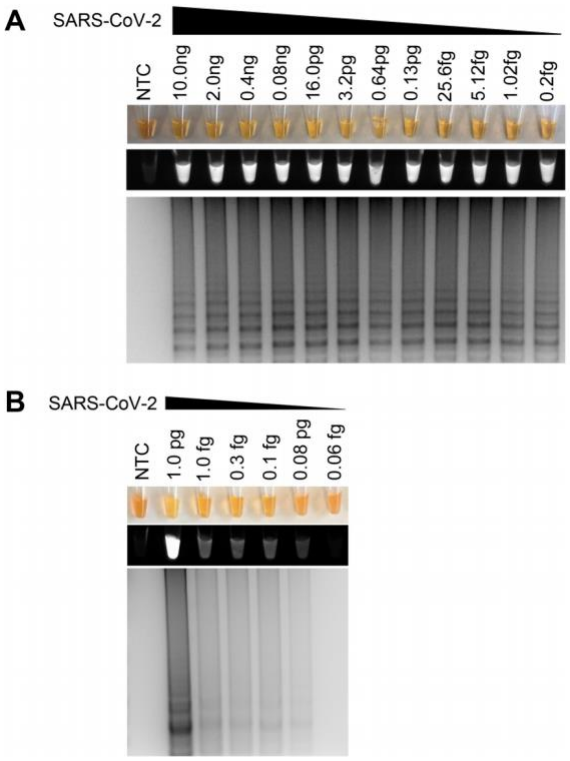


Fig 2. SARS-CoV-2 RT-LAMP sensitivity for SARS-CoV-2. Sensitivity assessment of SARS-CoV-2 RT-LAMP using serial dilutions of SARS-CoV-2 PCR Standard from 10.0 ng/reaction to 0.06 fg/reaction as visualized by addition of SYBR Green I by eye (upper panel), fluorescence (middle panel), or gel electrophoresis (bottom panel). NTC: No template control (negative control).

https://doi.org/10.1371/journal.pone.0234682.g002

Figure 2. SARS-CoV-2 RT-LAMP sensitivity for SARS-CoV-2.

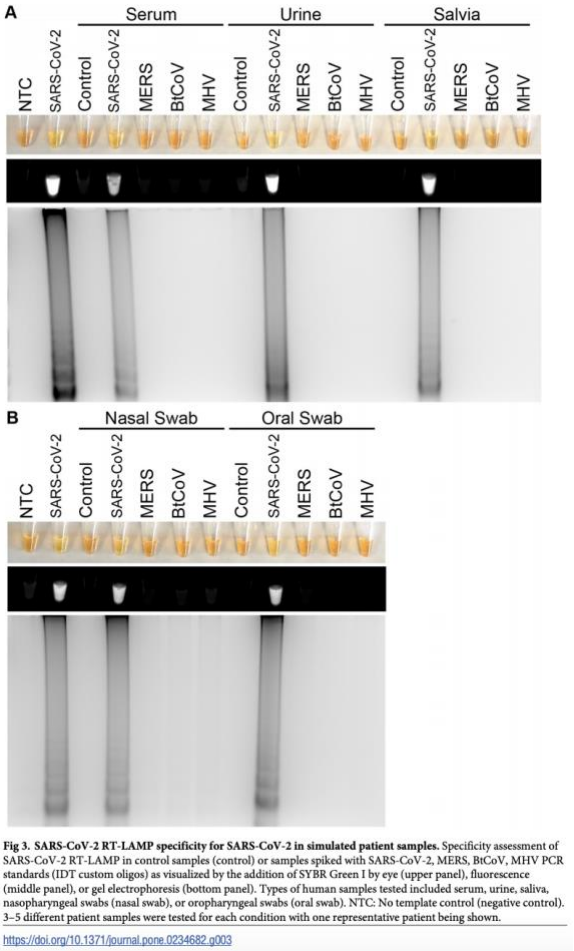


Fig 3. SARS-CoV-2 RT-LAMP specificity for SARS-CoV-2 in simulated patient samples. Specificity assessment of SARS-CoV-2 RT-LAMP in control samples (control) or samples spiked with SARS-CoV-2, MERS, BtCoV, MHV PCR standards (IDT custom oligos) as visualized by the addition of SYBR Green I by eye (upper panel), fluorescence (middle panel), or gel electrophoresis (bottom panel). Types of human samples tested included serum, urine, saliva, nasopharyngeal swabs (nasal swab), or oropharyngeal swabs (oral swab). NTC: No template control (negative control). 3–5 different patient samples were tested for each condition with one representative patient being shown.

https://doi.org/10.1371/journal.pone.0234682.g003

Figure 3. SARS-CoV-2 RT-LAMP specificity for SARS-CoV-2 in simulated patient samples.

SALIVARY DETECTION OF SARS-COV-2 (COVID-19) AND IMPLICATIONS FOR ORAL HEALTH-CARE PROVIDERS

Bajaj N, Granwehr BP, Hanna EY, Chambers MS.. Head Neck. 2020 Jun 13. doi: 10.1002/hed.26322. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

This report from MD Anderson Cancer Center endorses saliva-based COVID-19 testing as an alternative to the current use of nasopharyngeal swabs based on multiple studies suggesting that saliva-based tests may have higher sensitivity depending on timing of sample procurement, and as the non-invasive nature of saliva procurement can be advantageous for patients. Given the unique danger the presence of SARS-CoV-2 in saliva poses to oral health care specialists, they also offer recommendations for dentists and oral specialists that include using the highest level of PPE available, postponing elective procedures, minimizing use of aerosol-generating instruments, and other clinical practice considerations that can protect healthcare workers and their patients.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has become a major public health crisis. The diagnostic and containment efforts for the disease have presented significant challenges for the global health-care community. In this brief report, we provide perspective on the potential use of salivary specimens for detection and serial monitoring of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), based on current literature. Oral health-care providers are at an elevated risk of exposure to COVID-19 due to their proximity to nasopharynx of patients, and the practice involving the use of aerosol-generating equipment. Here, we summarize the general guidelines for oral health-care specialists for prevention of nosocomial transmission of COVID-19, and provide specific recommendations for clinical care management.

DEVELOPMENTS IN TREATMENTS

INTRACELLULAR ABCB1 AS A POSSIBLE MECHANISM TO EXPLAIN THE SYNERGISTIC EFFECT OF HYDROXYCHLOROQUINE-AZITHROMYCIN COMBINATION IN COVID-19 THERAPY

Scherrmann JM.. AAPS J. 2020 Jun 12;22(4):86. doi: 10.1208/s12248-020-00465-w.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A researcher from the Faculty of Pharmacy, University of Paris proposes a supplementary mechanistic explanation for the synergic interaction between hydroxychloroquine and azithromycin. Theoretically, the P-glycoprotein ABCB1 in endosomes and lysosomes increases azithromycin intracellular confinement, leading to more rapid virus clearance (Figure 1). The author hypothesizes that the intracellular ABCB1 may be a potent target for COVID-19 therapies and suggests future in vitro experiments for further confirmation.

ABSTRACT

The co-administration of hydroxychloroquine with azithromycin is proposed in COVID-19 therapy. We hypothesize a new mechanism supporting the synergistic interaction between these drugs. Azithromycin is a substrate of ABCB1 (P-glycoprotein) which is localized in endosomes and lysosomes with a polarized substrate transport from the cell cytosol into the vesicle interior. SARS-CoV-2 and drugs meet in these acidic organelles and both basic drugs, which are potent lysosomotropic compounds, will become protonated and trapped within these vesicles. Consequently, their intra-vesicular concentrations can attain low micromolar effective cytotoxic concentrations on SARS-CoV-2 while concomitantly increase the intra-vesicular pH up to around neutrality. This last effect inhibits lysosomal enzyme activities responsible in virus entry and replication cycle. Based on these considerations, we hypothesize that ABCB1 could be a possible enhancer by confining azithromycin more extensively than expected when the trapping is solely dependent on the passive diffusion. This additional mechanism may therefore explain the synergistic effect when azithromycin is added to hydroxychloroquine, leading to apparently more rapid virus clearance and better clinical benefit, when compared to monotherapy with hydroxychloroquine alone.

FIGURES

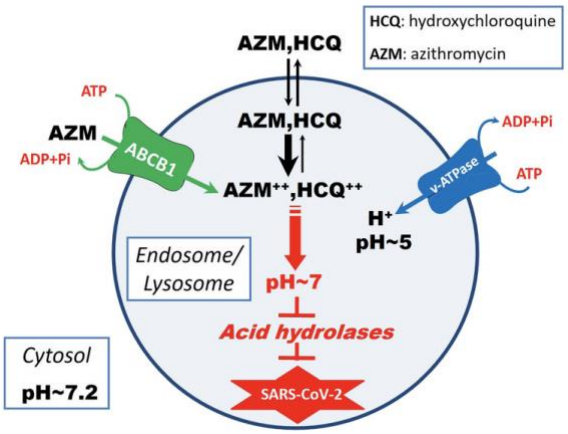


Figure 1. A proposed model of the possible role of ABCB1 to synergize the lysosomotropic effect of azithromycin and hydroxychloroquine and to alter SARS-CoV-2 replication cycle via the endolysosomal pathway. The diagram shows how the unionized drugs can readily diffuse across lysosomal membranes. Due to the acidic environment of the lysosome, the equilibrium between charged and uncharged drug species shifts in favor of the ionized species, thus limiting their backward diffusion into the cytosol. As a substrate of ABCB1, the active uptake of azithromycin contributes to the enhancement of this trapping effect and to the neutralization of the acidic pH. This last effect contributes to a cascade of antiinflammatory and antiviral activities

PASSIVE ANTIBODY THERAPY IN COVID-19

Abraham J.. Nat Rev Immunol. 2020 Jun 12. doi: 10.1038/s41577-020-0365-7. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

This article reviews several studies involving the use of convalescent plasma (CP) taken from COVID-19 survivors and describes how CP may be able to improve COVID-19 outcomes and hospital time if administered within an appropriate time

frame. Therefore, the authors recommend more studies to investigate the interactions between CP and the virus (Figure 1) in order to further define an effective therapeutic window and develop a means for prophylaxis or "a bridge to a vaccine."

FIGURES

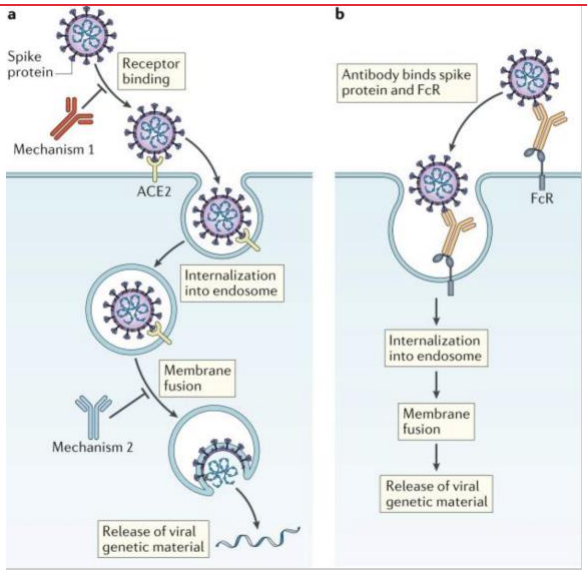


Figure 1: Potential mechanisms of coronavirus antibody neutralization and antibody enhancement of infection.
a) Mechanism 1: neutralizing antibodies could block viral infection by binding to the viral spike protein and preventing it from interacting with the cellular receptor angiotensin-converting enzyme 2 (ACE2). Mechanism 2: neutralizing antibodies could bind to the viral spike protein and block the conformational changes that the spike protein must undergo to facilitate fusion of the viral and host cell membranes.
b) Antibodies could enhance viral entry into immune cells by binding to the viral spike protein with their Fab portion and to Fc receptors (FcRs) with their Fc domain.

WHY YOUR PATIENTS' BELIEVING HYDROXYCHLOROQUINE AND CHLOROQUINE ARE 90% EFFECTIVE FOR COVID-19 IS 100% DANGEROUS

White CM, Hernandez AV.. J Clin Pharmacol. 2020 Jun 12. doi: 10.1002/jcph.1687. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

Authors from the University of Connecticut School of Pharmacy and Hartford Hospital Department of Research Administration reviewed claims made by the Association of American Physicians and Surgeons (AAPS) about the efficacy of hydroxychloroquine and chloroquine in treating COVID-19 and found insufficient evidence to support the claims made by AAPS. The authors believe these publications are perpetrating a false narrative that could lead to patient harm, and recommend health professionals educate patients about the evidence behind such claims and known risk factors of these medications.

SUMMARY

The authors analyzed claims made by the Association of American Physicians and Surgeons (AAPS) that “hydroxychloroquine and chloroquine have 90% success for COVID-19." In this case, success was defined as “% of no mortality or probability of preventing death” in a study performed without a control group. They also reviewed data from biomedical journals which showed variable mortality findings, no beneficial effects, and no significant differences in outcome with the use of hydroxychloroquine and chloroquine. The authors report there is insufficient evidence to support the AAPS claims and believes there is a greater concern for adverse effects from these medications (QT prolongation and ventricular arrhythmia). In addition, chronic overexposure to hydroxychloroquine and chloroquine could lead to drug shortages and a potential risk of increased malarial resistance. Finally, they recommended health professionals educate and properly inform patients about the evidence for both risks and benefits from these medications.

MENTAL HEALTH & RESILIENCE NEEDS

COVID-19'S IMPACT ON HEALTHCARE WORKFORCE

RESILIENCE STRATEGIES TO MANAGE PSYCHOLOGICAL DISTRESS AMONGST HEALTHCARE WORKERS DURING THE COVID-19 PANDEMIC: A NARRATIVE REVIEW

Heath C, Sommerfield A, von Ungern-Sternberg BS.. Anaesthesia. 2020 Jun 13. doi: 10.1111/anae.15180. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A narrative review conducted in Australia investigated the psychological impact on healthcare providers during the COVID-19 pandemic and offer possible resilience strategies for this population. Based on their findings, the authors suggest that implementing short-term and long-term positive work environments may promote resilience, minimize psychological distress, and reduce burnout among healthcare workers during the COVID-19 pandemic and future healthcare crises.

SUMMARY

Specific observations of this review include, but are not limited to, the following:
- Immediate issues and long-term ramifications of the COVID-19 pandemic "perpetuate the stress on healthcare workers and strain the future health care system."
- "Burnout has been associated with predisposition to depression and anxiety, substance abuse, and increased risk of medical errors and poor clinical decision making."
- Implementing appropriate workplace culture (i.e. organizational justice) that promotes self-care, resilience, reflective practice, group discussions, mindfulness practice, and stress management is important for preventing psychological burnout in healthcare professionals.
- Physical activity and proper sleep hygiene have a positive impact on promoting resilience.
- In previous pandemics, computer-based resilience training was offered freely to individuals and showed higher resilience scores in the post-testing compared to pre-testing.
- Staff feedback sessions allow for healthcare workers to feel supported and heard by their organization.

ABSTRACT

The COVID-19 pandemic marks an extraordinary global public health crisis unseen in the last century, with its rapid spread worldwide and associated mortality burden. The longevity of the crisis, and disruption to normality is unknown. With COVID-19 set to be a chronic health crisis, clinicians will be required to maintain a state of high alert for an extended period. The support received before and during an incident is likely to influence whether clinicians experience psychological growth or injury. An abundance of information is emerging on disease epidemiology, pathogenesis and infection control prevention. However, literature on interventions for supporting the psychological wellbeing of healthcare workers during disease outbreaks is limited. This article summarises the available management strategies to increase resilience in healthcare workers during the COVID-19 pandemic and beyond. It focuses on self care and organisational justice. It highlights various individual as well as organisational strategies. With the success of slowing disease spread in many countries to date, and reduced workload due to limitations on elective surgery in many institutions, there is more time and opportunity to be proactive in implementing measures to mitigate or minimise potential adverse psychological effects and improve, restore and preserve the wellbeing of the workforce now and for years to come. The purpose of this review is to review available literature on strategies for minimising the psychological impact of the COVID-19 pandemic on clinicians and to identify proactive holistic approaches which may be beneficial for healthcare workers both for the current crisis and into the future.

IMPACT ON PUBLIC MENTAL HEALTH

INFLUENCE OF PERCEIVED THREAT OF COVID-19 AND HEXACO PERSONALITY TRAITS ON TOILET PAPER STOCKPILING

Garbe L, Rau R, Toppe T.. PLoS One. 2020 Jun 12;15(6):e0234232. doi: 10.1371/journal.pone.0234232. eCollection 2020.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

Authors affiliated with various universities in Switzerland and Germany conducted an online survey from March 23-29, 2020 enrolling 996 participants from 22 countries to analyze the relationship between personality traits, perceived COVID-19 threat, and toilet paper stockpiling. A brief HEXACO (Honesty-Humility, Emotionality, Extraversion, Agreeableness, Conscientiousness, and Openness to Experience) inventory was used to determine personality dimensions and additional questions assessed toilet paper shopping and stocking habits. Results (summarized below) suggested that public health communications aimed at decreasing anxiety levels might decrease stockpiling behaviors during the current and future pandemics.

SUMMARY

The authors found that perceived threat of COVID-19 was higher in females (p=0.001), with increased age (p=0.019), and with increased quarantine duration (p=0.002) and these features predicted toilet paper stockpiling (p<0.025) (Table 2). Furthermore, 'Emotionality' predicted perceived threat of COVID-19 (p<0.01), which may have indirectly affected stockpiling behavior and individuals high in 'Conscientiousness' engaged in more toilet paper stockpiling (p=0.048). Thus, it was suggested that effective communication by public authorities may lead to decreased anxiety levels and reduce commodity stockpiling during a pandemic.

ABSTRACT

Following the fast spread of Covid-19 across Europe and North America in March 2020, many people started stockpiling commodities like toilet paper. Despite the high relevance for public authorities to adequately address stockpiling behavior, empirical studies on the psychological underpinnings of toilet paper stockpiling are still scarce. In this study, we investigated the relation between personality traits, perceived threat of Covid-19, and stockpiling of toilet paper in an online survey (N = 996) across 22 countries. Results suggest that people who felt more threatened by Covid-19 stockpiled more toilet paper. Further, a predisposition towards Emotionality predicted the perceived threat of Covid-19 and affected stockpiling behavior indirectly. Finally, Conscientiousness was related to toilet paper stockpiling, such that individuals higher in Conscientiousness tended to stockpile more toilet paper. These results emphasize the importance of clear communication by public authorities acknowledging anxiety and, at the same time, transmitting a sense of control.

FIGURES

Predictors	Dependent Variable							
	Perceived Threat of Covid-19		*ToP Shopping Frequency*		*ToP Shopping Intensity*		*Stocked ToP*	
Baseline Model	*b*	*SE*	*b*	*SE*	*b*	*SE*	*b*	*SE*
Age	**0.072**	**0.030**	**0.085**	**0.032**	**0.099**	**0.032**	**0.069**	**0.031**
Female gender (ref: male)	**-0.226**	**0.069**	-0.028	0.073	0.016	0.073	-0.063	0.070
Other gender (ref: male)	-0.355	0.248	-0.224	0.262	-0.102	0.261	0.256	0.249
Household size	0.012	0.030	0.053	0.032	**0.069**	**0.032**	0.044	0.030
Personal mobility restriction	-0.125	0.075	0.055	0.080	0.080	0.080	-0.087	0.076
Public transport restriction	-0.021	**0.063**	-0.065	0.066	-0.080	0.080	-0.065	0.063
Days in quarantine	**0.097**	**0.031**	0.061	0.032	0.049	0.032	0.031	0.031
Political orientation (left to right)	-0.007	0.031	-0.008	0.032	0.013	0.032	**0.127**	**0.031**
Place of residence	**-0.614**	**0.079**	**0.172**	**0.083**	-0.055	0.083	**-0.642**	**0.080**
Days since first Covid-19 case	-0.006	0.004	0.000	0.004	-0.001	0.004	-0.055	0.033
Incremental main effects of psychological variables	*b*	*SE*	*b*	*SE*	*b*	*SE*	*b*	*SE*
Perceived threat of Covid-19	—	—	**0.076**	**0.033**	**0.077**	**0.033**	**0.100**	**0.032**
Honesty-Humility	0.026	0.032	-0.002	0.033	-0.008	0.033	0.045	0.032
Emotionality	**0.188**	**0.031**	0.041	0.033	0.018	0.033	0.039	0.032
Extraversion	-0.039	0.030	0.012	0.032	0.018	0.032	-0.009	0.031
Agreeableness	-0.026	0.030	-0.020	0.032	-0.004	0.032	0.001	0.031
Conscientiousness	-0.047	0.030	0.059	0.032	**0.064**	**0.032**	**0.061**	**0.031**
Openness to experience	-0.039	0.030	0.000	0.032	0.040	0.032	**-0.075**	**0.030**
Interaction effects of psychological variables and place of residence	*b*	*SE*	*b*	*SE*	*b*	*SE*	*b*	*SE*
Perceived threat of Covid-19			0.136	0.078	0.091	0.078	0.071	0.074
Honesty-Humility								
Emotionality	0.101	0.066						
Extraversion								
Agreeableness								
Conscientiousness			0.087	0.070	0.112	0.070	0.004	0.066
Openness to experience							0.010	0.065
Upper limit model determination[a]	$R^2 = .147$		$R^2 = .024$		$R^2 = .024$		$R^2 = .116$	

Significant regression weights ($p < .05$) are printed in bold. Interaction effects were only tested for models that involved a significant main effect for the psychological variable at hand. ToP = Toilet Paper. Coding of place of residence: 0 = US/Canada; 1 = EU.

[a] Model determination is presented for the model with the most influential psychological variable for the respective dependent variable.

https://doi.org/10.1371/journal.pone.0234232.t002

Table 2.

GUIDANCE FOR THE PROCUREMENT OF COVID-19 CONVALESCENT PLASMA: DIFFERENCES BETWEEN HIGH AND LOW-MIDDLE INCOME COUNTRIES

Bloch EM, Goel R, Wendel S, Burnouf T, Al-Riyami AZ, Ang AL, DeAngelis V, Dumont LJ, Land K, Lee CK, Oreh A, Patidar G, Spitalnik SL, Vermeulen M, Hindawi S, Van den Berg K, Tiberghien P, Vrielink H, Young P, Devine D, So-Osman C; ISBT Convalescent Plasma Working Group.. Vox Sang. 2020 Jun 13. doi: 10.1111/vox.12970. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

An international group of experts in transfusion medicine, infectious diseases, and hematology developed guidelines for the procurement of COVID-19 convalescent plasma (CCP) as a potential treatment for COVID-19. In particular, the authors discuss the identification, recruitment, collection, processing, and distribution of CCP to meet the needs of high- and low-income countries. Challenges specific to the low income countries included suboptimal donor recruitment models, limited laboratory capacity, and transfusion deficits. These findings suggest that CCP needs to be modeled and adapted to address these specific barriers in a low income setting.

ABSTRACT

BACKGROUND AND OBJECTIVES: COVID-19 convalescent plasma (CCP) has been used, predominantly in high-income countries (HICs) to treat COVID-19; available data suggest the safety and efficacy of use. We sought to develop guidance for procurement and use of CCP, particularly in low and middle-income countries (LMICs) for which data are lacking.
MATERIALS AND METHODS: A multidisciplinary, geographically representative group of individuals with expertise spanning transfusion medicine, infectious diseases and hematology was tasked with the development of a guidance document for CCP, drawing on expert opinion, survey of group members and review of available evidence. Three subgroups (i.e. donor, product and patient) were established based on self-identified expertise and interest. Here, the donor and product-related challenges are summarized and contrasted between HICs and LMICs with a view to guide related practices.
RESULTS: The challenges to advance CCP therapy are different between HICs and LMICs. Early challenges in HICs related to recruitment and qualification of sufficient donors to meet the growing demand. Antibody testing also posed a specific obstacle given lack of standardization, variable performance of the assays in use and uncertain interpretation of results. In LMICs, an extant transfusion deficit, suboptimal models of donor recruitment (e.g. reliance on replacement and paid donors), limited laboratory capacity for pre-donation qualification and operational considerations could impede wide adoption.
CONCLUSION: There has been wide scale adoption of CCP in many HICs, which could increase if clinical trials show efficacy of use. By contrast, LMICs, having received little attention, require locally applicable strategies for adoption of CCP.

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CONTRIBUTORS

Alvin Rafou
Amanda Nguyen
Carter Butuk
Casey-John Keyes
Colin Bartz-Overman
Dax Cvancara
Diep Nguyen
Ellen Reidy
Jesse Abelson
Jonathan Baker
Julia Ghering
Julie Tran
Kate Buhrke
Kinza Sultan
Krithika Kumarasan
Maya Patel
Michael Olson
Raj Shekhar
Rechel Geiger
Renate Meckl
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