

The Daily COVID-19 Literature Surveillance Summary

May 29, 2020



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COVID-19 Daily Literature Surveillance

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

- Irish psychiatrists urge the international community to [take action to reduce transmission among prisoner populations](#). They make recommendations for public health and screening, psychiatric and medical care. Finally, they call for reforms in the accommodations provided for prisoners in addition to those the criminal justice system itself.

Understanding Pathology

- Physicians from Duke University School of Medicine hypothesize that the mortality in COVID-19 patients may arise from [autonomic dysfunction](#). They suggest that targeting the cholinergic pathway would have an anti-inflammatory effect due to the suppression of the cytokine storm, and promote further study surrounding the role of the parasympathetic nervous system in SARS-CoV2's hyperinflammatory effects.

Transmission & Prevention

- A study conducted at the Virginia Tech Carilion School of Medicine by the authors found no statistically significant difference in filtration efficiency between [expired P100 filter cartridges](#) and N95 respirators, suggesting that expired P100 respirators could potentially be effective during PPE shortages.

Management

- Guidelines and recommendations for managing COVID-19 patients include:
 - The International Society on Thrombosis and Hemostasis' report on [venous thromboembolisms](#)
 - [Extracorporeal blood purification](#)
- [Elevated soluble E-selectin and angiopoietin-2 levels](#) (markers of endothelial activation/microvascular dysfunction) were strongly correlated with admission to the ICU, suggesting potential prognostic value of these biomarkers – based on a prospective study of 40 consecutive patients with COVID-19 admitted to Georges Pompidou European hospital in Paris, France.
- The [Neutrophil to Lymphocyte Ratio \(NLR\)](#) on admission for non-survivors was significantly higher than for survivors in a retrospective cohort study of 1,004 COVID-19 patients.
 - Multivariate logistic regression modelling showed an NLR greater than 11.75 was significantly associated with all-cause mortality in the hospital.

Adjusting Practice During COVID-19

- Guidelines and recommendations for practice from today include:
 - [Drug conservation](#) strategies and alternatives
 - Triage guidelines for [dermatological surgery](#)
 - Use of systemic medications for [psoriasis and atopic dermatitis](#)
 - Management of patients of [warfarin](#)
 - [Gynecologic oncology](#)
- Case reports illustrating devastating complications due to [intracranial hemorrhage in severe COVID-19 patients](#) lead clinicians to urge the close monitoring of neurological status in critical patients.
- Through a review of the literature, surgeons in Europe and Asia found no literature demonstrating SARS-CoV-2 transmission through [surgical smoke](#)--though they suggest that laparoscopy may have lower risk than laparotomy for possible transmission through surgical smoke

R&D: Diagnosis and Treatments

- Researchers in Hong Kong compared point-of-care reverse transcriptase PCR (Xpert Xpress) on posterior oropharyngeal saliva samples to nasopharyngeal (NPS) swabs and found no significant difference in SARS-CoV-2 detection rate, [supporting the potential use of saliva specimens](#) in COVID-19 testing.

- An analysis of remdesivir therapy indicates that a [combination of nebulizer inhalation and IV administration should be performed for increased efficacy](#). This is based on observations in monkey model studies that plasma concentrations of remdesivir may not be associated with effectiveness and currently utilized IV doses may provide drug concentrations insufficient to eliminate SARS-CoV-2 in the lungs.

Mental Health & Resilience Needs

- A cross-section study of 2,025 people in the United Kingdom found a [positive correlation with anxiety and somatic symptoms](#), particularly gastrointestinal and fatigue symptoms, suggesting the possibility of additional public health strain resulting from the COVID-19 pandemic.
- Researchers at Dartmouth College analyzed public Google search data between March 16 and 23, 2020 and found that [stay-at-home orders were associated with a “flattening of the curve” for mental-health related searches](#), suggesting that increased mental health concerns due to the COVID-19 pandemic leveled off following implementation of state-wide stay-at-home orders.

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CLIMATE

STRUGGLING TO GET STARTED

Tay A.. Elife. 2020 May 27;9:e59147. doi: 10.7554/eLife.59147.

Level of Evidence: Other

BLUF

Andy Tay, an assistant professor at the National University of Singapore and a member of the eLife Early-Career Advisory Group, shares the perspectives of upcoming and current PhDs and others affiliated with postdoctoral programs to exhibit the concerns of this population during the pandemic. These concerns include limited experimental work to graduate with a PhD, possible delaying of PhD program start dates due to travel restrictions, competitiveness for funding if research is delayed, and uncertain answers as to travel visa processing for international students and changes to the upcoming academic quarter.

ABSTRACT

As the world attempts to cope with the devastating impact of the COVID-19 pandemic, researchers about to start PhDs and postdocs face particular challenges.

GLOBAL

PROMOTING HEALTHY MOVEMENT BEHAVIOURS AMONG CHILDREN DURING THE COVID-19 PANDEMIC

Guan H, Okely AD, Aguilar-Farias N, Del Pozo Cruz B, Draper CE, El Hamdouchi A, Florindo AA, Jáuregui A, Katzmarzyk PT, Kontsevaya A, Löf M, Park W, Reilly JJ, Sharma D, Tremblay MS, Veldman SLC.. Lancet Child Adolesc Health. 2020 Jun;4(6):416-418. doi: 10.1016/S2352-4642(20)30131-0. Epub 2020 Apr 29.

Level of Evidence: Other

BLUF

A multi-national group of authors recommend that physical activity should be incorporated into children's daily routine during the COVID-19 pandemic, and that parents, teachers, medical professionals, governments, and the media all have a responsibility to encourage these behaviors while observing pandemic restrictions.

SUMMARY

The following recommendations are promoted by the authors:

- " Parents and carers should incorporate physical activity into children's daily routine (including using electronic media to facilitate participation) and encourage the whole family to join while adhering to regulations on physical distancing and access to outdoor spaces. Extended periods of sitting should be broken up every 30–60 min (eg, by standing and stretching for 1 min). They should follow sedentary recreational screentime recommendations and encourage co-viewing and positive social interactions and experiences. To help children to get enough sleep, keep bed and wake times consistent, keep screens out of the room where children sleep, and avoid screen use before bedtime.
- Educators and teachers should know and promote the movement behavior guidelines, and embrace opportunities to incorporate healthy movement messages, practices, and policies into daily home-school

- routines and lessons—eg, when scheduling online lessons, limit prolonged sitting and encourage changes in posture such as regularly standing, stretching, or moving on the spot.
- Health professionals should understand and recommend the current guidelines to parents, family members, and caregivers and reinforce their positive association with children's health during all visits, including remote contacts and telemedicine.
 - Governments should promote healthy movement behaviours in children as part of response strategies and public messaging, and should engage influential people in promotion of such messages.
 - The media should provide regular messages to promote physical activity and break up extended periods of sitting.
 - Children should speak up and advocate for their right to a healthy, active life, while carefully observing pandemic restrictions. Forming peer groups can help with maintaining healthy movement behaviour patterns."

AFFECTING THE HEALTHCARE WORKFORCE

SOCIAL WORK VALUES IN ACTION DURING COVID-19

Miller VJ, Lee H.. J Gerontol Soc Work. 2020 May 27:1-5. doi: 10.1080/01634372.2020.1769792. Online ahead of print.

Level of Evidence: Other

BLUF

Two professors of social work at Bowling Green State University discuss the manifestation of the values of their profession amidst the COVID-19 pandemic, focusing specifically on older populations and access to care and social connection. Acknowledging the social responsibility of providing connections to resources and justice, they highlight the importance of social work through a number of ongoing initiatives:

- Maintaining relationships through Meals on Wheels and telephone friendships
- Arranging telehealth to provide mental and physical healthcare
- Planning for the transition from hospital admission to discharge
- Educating assisted care facility staff and residents on disease prevention
- Facilitating food pantry delivery networks

ABSTRACT

COVID-19 has ravaged through the lives of individuals, families, communities, and societies and, in the process, exacerbated existing vulnerabilities, oppression, and poverty among our most at-risk community members. Social workers, guided by values and ethics, are counteracting these ailments in society, concentrating on protecting the most vulnerable, older adults. In this letter we describe the impact of COVID-19 on older adults, note social work values from the National Association of Social Workers, and expand on the current role of the practicing social worker values in action during COVID.

DISPARITIES

PRISONS AND THE COVID-19 PANDEMIC

Gulati G, Dunne CP, Kelly BD.. Ir J Psychol Med. 2020 May 27:1-5. doi: 10.1017/ijpm.2020.65. Online ahead of print.

Level of Evidence: Other

BLUF

Irish psychiatrists pen a letter to the editor highlighting that prisoners are a vulnerable population during the COVID-19 pandemic. They make recommendations to the international community to reduce transmission of COVID-19 among prisoner populations (summarized below).

SUMMARY

Recommendations:

- 1) Reduce the prison population through alternative criminal justice avenues and early release programs
- 2) Provide sanitary, single-cell accommodation
- 3) Screen new prisoners
- 4) Make arrangements to have a designated local hospital for prisoner transfers
- 5) Continue physical and mental healthcare services in prisons
- 6) Address COVID-19 related anxiety of prisoners and their families
- 7) Include the prisoner population as new treatments and vaccines become available

PEOPLE WITH INTELLECTUAL DISABILITIES AND THE COVID-19 PANDEMIC

Gulati G, Fistein E, Dunne CP, Kelly BD, Murphy VE.. Ir J Psychol Med. 2020 May 27:1-5. doi: 10.1017/ipm.2020.66. Online ahead of print.

Level of Evidence: Other

BLUF

The authors discuss their concerns about the redistribution of mental health and disability services workers to other areas of medicine due to the COVID-19 pandemic in Ireland. They argue that "people with intellectual disabilities already experience substantial barriers to accessing medical care and are, therefore, likely to be at increased risk of both the infection itself and challenges in accessing information, testing and treatment." Services for people with intellectual disabilities should be maintained as they significantly help reduce infections as well as improve the physical and mental well-being of these patients.

SOCIAL WORK RESPONSE NEEDED TO THE CHALLENGE OF COVID-19 FOR AGING PEOPLE WITH INTELLECTUAL AND DEVELOPMENTAL DISABILITIES

McCallion P.. J Gerontol Soc Work. 2020 May 27:1-3. doi: 10.1080/01634372.2020.1769791. Online ahead of print.

Level of Evidence: Other

BLUF

An author affiliated with the School of Social Work at Temple University comments on the upcoming challenges for patients with Intellectual and Developmental Disabilities (I/DD) and the healthcare workers attending to them, suggesting that more social work research is needed on how the COVID-19 pandemic affects patients with I/DD and may inform effective interventions.

SUMMARY

The author hypothesizes that there are multiple reasons to assume the potential susceptibility of patients with I/DD to the COVID-19 pandemic: lack of access to healthcare, stigmatization as less valuable members of society, and greater levels of health comorbidities. Patients with I/DD may not be able to communicate their concerns, and there have been few studies on the protective personal equipment shortage for social workers. The author advocates for more research for patients with I/DD to avoid marginalizing them during the COVID-19 pandemic.

EPIDEMIOLOGY

MODELING

CONSTRUCTING CO-OCCURRENCE NETWORK EMBEDDINGS TO ASSIST ASSOCIATION EXTRACTION FOR COVID-19 AND OTHER CORONAVIRUS INFECTIOUS DISEASES

Oniani D, Jiang G, Liu H, Shen F.. J Am Med Inform Assoc. 2020 May 27:ocaa117. doi: 10.1093/jamia/ocaa117. Online ahead of print.

Level of Evidence: 5

BLUF

Utilizing the new COVID-19 machine readable dataset (CORD-19), authors created a co-occurrence network that uses unsupervised clustering algorithms to explore specific COVID-19 related associations by focusing on medical entities falling into the categories of chemical, disease, gene, and mutation and linking biomedical entities that have co-occurred at least once. The co-occurrence network was able to perform link prediction task well and detect explicit and implicit associations (Table 2), suggesting it could be a useful tool for discovering disease management and treatment plans for COVID-19.

ABSTRACT

OBJECTIVE: As COVID-19 started its rapid emergence and gradually transformed into an unprecedented pandemic, the need for having a knowledge repository for the disease became crucial. To address this issue, a new COVID-19 machine readable dataset known as COVID-19 Open Research Dataset (CORD-19) has been released. Based on this, our objective was to build a computable co-occurrence network embeddings to assist association detection amongst COVID-19 related biomedical entities.

MATERIALS AND METHODS: Leveraging a Linked Data version of CORD-19 (i.e., CORD-19-on-FHIR), we first utilized SPARQL to extract co-occurrences among chemicals, diseases, genes, and mutations and build a co-occurrence network. We then trained the representation of the derived co-occurrence network using node2vec with four edge embeddings operations (L1, L2, Average, and Hadamard). Six algorithms (Decision Tree, Linear Regression, Support Vector Machine, Random Forest, Naive Bayes, and Multi-layer Perceptron) were applied to evaluate performance on link prediction. An unsupervised learning strategy was also developed incorporating the t-SNE and DBSCAN algorithms for case studies.

RESULTS: Random Forest classifier showed the best performance on link prediction across different network embeddings. For edge embeddings generated using the Average operation, Random Forest achieved the optimal average precision of 0.97 and F1 score of 0.90. For unsupervised learning, 63 clusters were formed with silhouette score of 0.128. Significant associations were detected for five coronavirus infectious diseases in their corresponding subgroups.

CONCLUSION: In this study, we constructed COVID-19-centered co-occurrence network embeddings. Results indicated that the generated embeddings were able to extract significant associations for COVID-19 and coronavirus infectious diseases.

FIGURES

Table 2. Top 10 intra-cluster closest biomedical entities for five selected coronavirus infectious diseases. Cluster ID and the type of entities are marked in parentheses.

Coronavirus infectious diseases	Top 10 closest entities	Cosine similarity score
COVID-19 (Cluster #6)	VP35 (Gene) HD11 (Gene) Coronavirus infection process (Disease) Fibroblast growth factor (FGF)-2 (Gene) Acute respiratory infection illness PIGS (Gene) TGF alpha (Gene) SFPQ (Gene) Tumour necrosis factor (TNF) (Gene) Praziquantel (Chemical)	0.9777 0.9774 0.9700 0.9655 0.9596 0.9576 0.9571 0.9561 0.9549 0.9537
Pulmonary coronavirus infection (Cluster #1)	PTP (Gene) SARS-CoV-infected human airway	0.9754 0.9699

<https://mc.manuscriptcentral.com/jamia>

"5'-gg gat tca aca" (Chemical)	0.9672
Trachea nasal respiratory epithelial cells	0.9658
Suppressor of cytokine signaling 3	0.9620
KAT (Gene)	0.9604
CD32 (Gene)	0.9573
Maternal SARS infection (Disease)	0.9553
Respiratory syndrome coronavirus	0.9547
S27 (Gene)	0.9546

Sars-cov infection damages lung (Cluster #2)	IL-1-alpha (Gene) Sucratate prn (Chemical) Acute respiratory syndrome-cov IL-5- and IL-13-producing ilc-iis (Gene) HAPI (Gene) FSK (Chemical) Low fever (Disease) HIV and Ebola virus infection (Disease) YKL-40 (Gene) ETF (Gene)	0.9560 0.9589 0.9555 0.9487 0.9342 0.9337 0.9328 0.9327 0.9288 0.9280
Coronavirus upper respiratory infection (Cluster #23)	Viruses actinobacillus Plasmin (Gene) JAM-1 (Gene) TNF receptor-associated factor 6 (Gene) GIPC3 (Gene) Rennin (Gene) ZO-1 (Gene) Cathepsin G (Gene) rs5743313 (Mutation) Alpha1 antitrypsin (Gene)	0.9890 0.9719 0.9654 0.9648 0.9613 0.9582 0.9563 0.9556 0.9547 0.9544
Coronavirus-infected pneumonia (Cluster #10)	Respiratory syncytial viral infection Pegylated interferon-alpha (Chemical) IFITM6 (Gene) Feline b (Chemical) E119V (Mutation) Epac2 (Gene) GFTP2 (Gene) Hepatitis coronavirus infection (Disease) Ouabain (Chemical)	0.9923 0.9891 0.9872 0.9858 0.9854 0.9850 0.9849 0.9843 0.9797 1 Vsf1 (Gene) 0.9786

EVALUATION OF THE POTENTIAL INCIDENCE OF COVID-19 AND EFFECTIVENESS OF CONTAINMENT MEASURES IN SPAIN: A DATA-DRIVEN APPROACH

Aleta A, Moreno Y.. BMC Med. 2020 May 27;18(1):157. doi: 10.1186/s12916-020-01619-5.

Level of Evidence: Other

BLUF

Using data through February 28, 2020, the authors created a Susceptible-exposed-infectious-removed (SEIR) compartmental metapopulation model to assess the temporal and spatial transmission of COVID-19 cases in Spain. The model classified individuals according to health status and inter-province mobility using all transportation methods reported by Spain's Ministry of Development. The authors simulated various transmission dynamics and countermeasures (Figure 6) and concluded that the most cost-effective strategy in reducing transmission is to isolate or quarantine the detected infectious cases. Interventions with second order

benefit included containment, traffic restrictions, self-protection methods, and social distancing. Of note, the model was based on data through February 28, 2020 when a smaller number of cases had been detected. However, the authors stated their model was updated with data obtained through April 13, 2020.

ABSTRACT

BACKGROUND: We are currently experiencing an unprecedented challenge, managing and containing an outbreak of a new coronavirus disease known as COVID-19. While China—where the outbreak started—seems to have been able to contain the growth of the epidemic, different outbreaks are nowadays present in multiple countries. Nonetheless, authorities have taken action and implemented containment measures, even if not everything is known.

METHODS: To facilitate this task, we have studied the effect of different containment strategies that can be put into effect. Our work referred initially to the situation in Spain as of February 28, 2020, where a few dozens of cases had been detected, but has been updated to match the current situation as of 13 April. We implemented an SEIR metapopulation model that allows tracing explicitly the spatial spread of the disease through data-driven stochastic simulations.

RESULTS: Our results are in line with the most recent recommendations from the World Health Organization, namely, that the best strategy is the early detection and isolation of individuals with symptoms, followed by interventions and public recommendations aimed at reducing the transmissibility of the disease, which, although might not be sufficient for disease eradication, would produce as a second order effect a delay of several days in the raise of the number of infected cases. **CONCLUSIONS:** Many quantitative aspects of the natural history of the disease are still unknown, such as the amount of possible asymptomatic spreading or the role of age in both the susceptibility and mortality of the disease. However, preparedness plans and mitigation interventions should be ready for quick and efficacious deployment globally. The scenarios evaluated here through data-driven simulations indicate that measures aimed at reducing individuals' flow are much less effective than others intended for early case identification and isolation. Therefore, resources should be directed towards detecting as many and as fast as possible the new cases and isolate them.

FIGURES

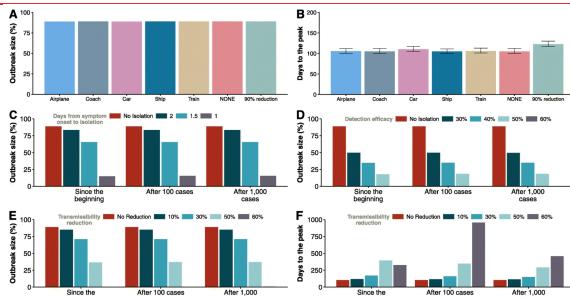


Figure 6: Strategies to mitigate the impact of the disease. a, b The impact of mobility reduction. c–f The effect of different measures aimed at reducing the spreading of the epidemic when they are applied since the beginning of the outbreak and after 100 or 1000 cases are detected in the whole country. A The fraction of individuals who were affected by the disease by the end of the epidemic. b The time from the arrival of the first infected individual to the country until the peak of the epidemic, i.e., the day with the maximum number of infected individuals. In c, we evaluate the size of the epidemic if individuals are hospitalized or isolated after a given number of days from the onset of disease symptoms. In d, we show the effect of only hospitalizing or isolating a certain fraction of individuals after they experience the first symptoms. In e, f, we show the size of the epidemic and the time for the disease to peak when transmission is reduced. Note that reducing the transmissibility always delays the spreading, except in situations where the disease dies out, for which the peak occurs earlier. In all cases, the spreading starts with 10 infected individuals in Barcelona.

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

MECHANISTIC INFERENCES FROM CLINICAL REPORTS OF SARS-COV-2

Jenkins MM, McCaw TR, Goepfert PA.. Infect Dis (Lond). 2020 May 27:1-11. doi:

10.1080/23744235.2020.1769853. Online ahead of print.

Level of Evidence: 2=3

BLUF

This review by researchers from the University of Alabama assesses data from currently available case series' in order to identify differences in the clinical presentations of severe and non-severe cases. They also suggest potential pathological mechanisms that may underlie the difference in disease severity.

SUMMARY

After reviewing multiple case series', Researchers from the University of Alabama found:

1) Clinical Presentation: The clinical presentations for both severe and non-severe COVID-19 infections both consisted of fever, cough, sputum, fatigue, dyspnea, myalgia, and diarrhea. However, the frequency of symptoms varied between severe and non-severe cases (Table 1).

2) Pathology: Lymphocytes, including B cells, helper T cells, and cytotoxic T cells, appear to be necessary for effective viral clearance and a milder disease course. In contrast, increased neutrophil recruitment to the lungs and subsequent interleukin-6 and interleukin-8 activation seems to increase the severity of the illness. Similarly, tumor necrosis factor-alpha (TNF-alpha) and interferon (IFN) signaling may cause increased macrophage recruitment to the lungs, also potentially worsening the disease course.

ABSTRACT

SARS-CoV-2 was identified as the causative pathogen in an outbreak of viral pneumonia cases originating in Wuhan, China, with an ensuing rapid global spread that led it to be declared a pandemic by the WHO on March 11, 2020. Given the threat to public health posed by sequelae of SARS-CoV-2 infection, the literature surrounding patient presentation in severe and non-severe cases, transmission rates and routes, management strategies, and initial clinical trial results have become available at an unprecedented pace. In this review we collate current clinical and immunologic reports, comparing these to reports of previous coronaviruses to identify mechanisms driving progression to severe disease in some patients. In brief, we propose a model wherein dysregulated type I interferon signalling leads to aberrant recruitment and accumulation of innate immune lineages in the lung, impairing establishment of productive adaptive responses, and permitting a pathologic pro-inflammatory state. Finally, we extend these findings to suggest possible treatment options that may merit investigation in randomized clinical trials.

FIGURES

Symptoms (%)	Non-severe	Severe
Fever	91.04 (83-97.7)	94.29 (87-100)
Cough	66.27 (33.7-82)	71.36 (33.6-85)
Sputum	31.01 (33.6-85)	42.59 (26-64.7)
Fatigue	35.54 (21-52.3)	42.57 (22-70.6)
SOB	30.18 (9.1-62)	52.02 (17.6-87)
Myalgia/arthralgia	16.23 (14.4-19.3)	18.87 (15-23.1)

Table 1. Compiled clinical data from multiple studies of severe and non-severe COVID-19 patients.

KAWASAKI DISEASE LINKED TO COVID-19 IN CHILDREN

Moreira A.. Nat Rev Immunol. 2020 May 27. doi: 10.1038/s41577-020-0350-1. Online ahead of print.

Level of Evidence: 4

BLUF

A prospective observational study conducted by a group of interdisciplinary experts at the Necker Hospital for Sick Children in Paris, France, between April 27 and May 7, 2020 found that 17 children were admitted and diagnosed with Kawasaki Disease, which was significantly higher than the average number of children admitted with this condition over the same period in 2018-2019 (95% confidence interval: 7.3 to 24.1, $p<0.001$). Seven (41%) of the children tested positive for SARS-CoV-2 via RT-PCR. The most common symptoms included polymorphous skin rash, bilateral conjunctival injection, and gastrointestinal symptoms (Table 1). Twelve (71%) of the patients were diagnosed with myocarditis, and coronary artery abnormalities were found in eight (47%) of the patients (Table 2). Overall, their findings suggest that providers must maintain a high degree of suspicion of Kawasaki Disease in pediatric patients in the context of the current COVID-19 pandemic.

SUMMARY

"An unusually high incidence of Kawasaki disease in children was reported in a French centre for emerging infectious diseases: 17 cases in 11 days, in contrast to an average of 2 cases per month in 2018–2019. In 82% of the cases, IgG antibodies for SARS-CoV-2 were detected, suggesting an association between the virus and this syndrome in children. Although only six patients had recent history of an acute respiratory infection, all patients had gastrointestinal symptoms before the onset of Kawasaki disease symptoms. Remarkably, almost 60% of the patients originated from sub-Saharan Africa or Caribbean islands, and 12% from Asia, raising a possible genetic predisposition. Although Kawasaki disease-like syndromes have previously been linked to other viral infections, these patients showed higher levels of pro-inflammatory markers than other cohorts, which may reflect a particularly strong immunological reaction to SARS-CoV-2."

FIGURES

Characteristics, (%) otherwise stated	Value
Demographic features	
Age, years; Median (range)	7.5 (3.7-16.6)
Female	10 (59)
Parents origin	
sub-Saharan Africa/Caribbean islands	20 (59)
Asia	10 (29)
Europe	4 (12)
KD principal clinical criteria	
Complete presentation (Fever > 4 days and ≥ 4 principal criteria)	8 (47)
Lips and oral cavity changes	12 (71)
Bilateral bulbar conjunctival injection	13 (76)
Rash	13 (76)
Extremities changes	6 (35)
Cervical lymphadenopathy	11 (65)
Days of fever before IVIG; Median (range)	6 (1-13)
KD associated clinical features	
Gastrointestinal symptoms	17 (100)
Perineal or face desquamation	4 (24)
Arthralgia	2 (12)
Irritability	11 (65)
Other neurological features	5 (29)
Myocarditis	12 (71)
Left ventricular ejection fraction rate; median (range)*	38 (10-57)
Serous effusion	8 (47)

*patients with myocarditis; IVIG: intravenous immunoglobulin. KD: Kawasaki disease.

Table 1. Clinical characteristics of included patients (N=17)

Characteristics, (%) otherwise stated	Value
Ultrasound findings on coronary arteries during hospitalisation	
Increased visibility	3 (16)
Dilation (Z-score 2 to <2.5)	5 (29)
Aneurysm (Z-score ≥ 2.5)	0
Chest X-ray or CT abnormalities	
Ground glass opacity, local patchy shadowing or interstitial abnormalities	6/14 (43)
Biological features	
WBC, $\times 10^9/\text{mL}$; Median (range)	16.8 (5.4-42.8)
Neutrophils $\times 10^9/\text{mL}$; Median (range)	11 (3.3-36.4)
Haemoglobin g/dL; Median (range)	8.1 (5.3-12.2)
Platelets $\times 10^9/\text{mL}$; Median (range)	432 (78-838)
CRP, mg/L; Median (range)	219 (89-363)
PCT, ng/mL; Median (range)	23.3 (0.1-448)
IL-6, pg/ml; Median (range) ¹	218 (80-1366)
Sterile pyuria ²	8 (67)
Albumin g/L; Median (range)	20 (16-37)
Natrium, mmol/L; Median (range)	130 (116-134)
Creatinine, $\mu\text{mol}/\text{L}$; Median (range)	63 (27-417)
ALT, IU/L; Median (range)	44 (6-148)
GGT IU/L; Median (range)	55 (10-205)
Lipase IU/L; Median (range) ²	103 (13-527)
Lactates, mmol/L; Median (range) ¹	2.8 (1.6-9)
D-dimers, ng/ml; Median (range) ³	4762 (350-19330)
Troponin, ng/L; Median (range)	136 (10-6900)
BNP, pg/mL; Median (range) ⁴	2879 (16-16017)
Microbiological findings	
Positive nasopharyngeal SARS-CoV-2 RT-PCR	7 (41)
Positive SARS-CoV-2 serum serology (IgG) ³	14 (88)
Positive nasopharyngeal PCR for other viruses ⁴	0

¹Missing data for 4 cases; ²Missing data for 5 cases; ³Missing data for 1 case; ⁴Missing data for 2 cases;
ALT: alanine aminotransferase; BNP: B-type natriuretic peptide; CRP: C-reactive protein; GGT: gamma-glutamyl transferase; IgG: immunoglobulin G; IL-6: interleukine 6; PCR: polymerase chain reaction; PCT: procalcitonin; PLT: platelets; RT-PCR: reverse transcription polymerase chain reaction; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; WBC: white blood cells.

Table 2. Imaging and laboratory findings of included patients (N=17)

UNDERSTANDING THE PATHOLOGY

IMPLICATIONS FOR NEUROMODULATION THERAPY TO CONTROL INFLAMMATION AND RELATED ORGAN DYSFUNCTION IN COVID-19

Fudim M, Qadri YJ, Ghadimi K, MacLeod DB, Molinger J, Piccini JP, Whittle J, Wischmeyer PE, Patel MR, Ulloa L.. J Cardiovasc Transl Res. 2020 May 26. doi: 10.1007/s12265-020-10031-6. Online ahead of print.

Level of Evidence: 5

BLUF

In this review, the authors hypothesize that the mortality in COVID-19 patients may arise from a dysfunctional autonomic tone. They present the argument that therapeutically targeting the cholinergic pathway would have an anti-inflammatory effect due to the suppression of the cytokine release syndrome (Fig. 1). The authors state the need for ongoing study of the role of the parasympathetic nervous system in SARS-CoV2's hyperinflammatory effects and how modulation of autonomic nerves may play a role in the prevention and treatment of COVID-19.

ABSTRACT

COVID-19 is a syndrome that includes more than just isolated respiratory disease, as severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) also interacts with the cardiovascular, nervous, renal, and immune system at multiple levels, increasing morbidity in patients with underlying cardiometabolic conditions and inducing myocardial injury or dysfunction. Emerging evidence suggests that patients with the highest rate of morbidity and mortality following SARS-CoV2 infection have also developed a hyperinflammatory syndrome (also termed cytokine release syndrome). We lay out the potential contribution of a dysfunction in autonomic tone to the cytokine release syndrome and related multiorgan damage in COVID-19. We hypothesize that a cholinergic anti-inflammatory pathway could be targeted as a therapeutic avenue. Graphical Abstract .

FIGURES

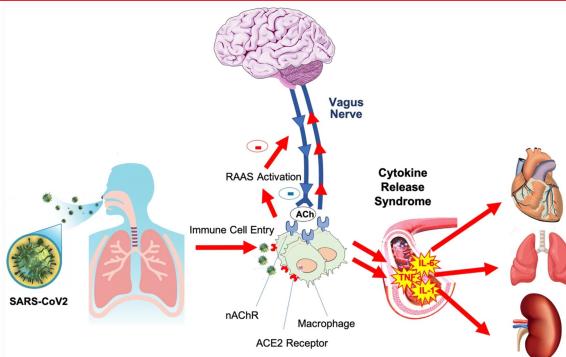


Figure 1. Connection between the vagus nerve and immune system. ACh, acetylcholine; nAChR, nicotinic acetylcholine receptor; RAAS, renin angiotensin aldosterone system; ACE2, angiotensin-converting enzyme 2; SARS-CoV2, severe acute respiratory syndrome–coronavirus

CLINICAL SEQUELAE OF THE NOVEL CORONAVIRUS: DOES COVID-19 INFECTION PREDISPOSE PATIENTS TO CANCER?

Hays P.. Future Oncol. 2020 May 27. doi: 10.2217/fon-2020-0300. Online ahead of print.

Level of Evidence: Other

BLUF

In this literature review, authors detail the mechanisms of SARS-CoV-2 infection (Figure 3), signaling and potential oncogenic pathways (such as JAK-STAT), the body's initial robust immune response with subsequent inflammation cascade (Figure 4), and the possibility of long-term immune system suppression, all of which have potential implications for the development of cancer. They conclude that patients infected with SARS-CoV-2 should be monitored closely for oncologic sequelae following this pandemic.

ABSTRACT

As cancer patients are clinically known to be predisposed to COVID-19 infection, a corollary question of whether COVID-19 infection predisposes to cancer is explored. This article seeks to establish an association between novel coronavirus sequelae and cancer. A literature review on COVID-19 mechanisms of action, molecular responses it elicits upon infection and tumorigenesis pathways is conducted to establish this association. Major signaling pathways implicated in aberrant cellular growth are activated, the ensuing cytokine storm weakens the immune system response to tumors, and patients may develop cancer as a result of superimposed mutagenic and/or carcinogenic events. Future work needs to be performed to support this hypothesis, both in in vitro models and preclinical studies. COVID-19 patients may need to be monitored post-infection for developing cancer.

FIGURES

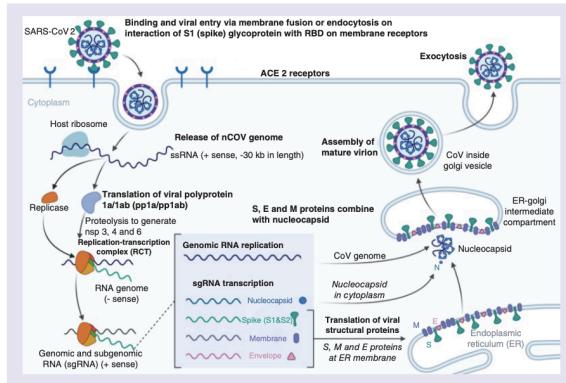


Figure 3. Coronavirus Infection Course. How the novel coronavirus infects host cells.
E: Envelope; ER: Endoplasmic reticulum; M: Membrane; S: Spike.
Reproduced with permission from [3].

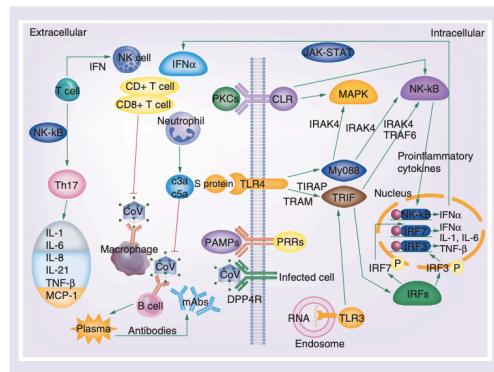


Figure 4. COVID-19 infection and the immune response. Activated signaling pathways such as JAK-STAT and MAPK, cytokine storm, T-cell depletion, humoral responses and high levels of inflammation may predispose patients infected with novel coronavirus to cancer.
Reproduced with permission from [12].

POTENTIAL NEW TREATMENT STRATEGIES FOR COVID-19: IS THERE A ROLE FOR BROMHEXINE AS ADD-ON THERAPY?

Level of Evidence: Other

BLUF

An international group of physicians reviews the literature on potential drug targets and candidates for COVID-19 prophylaxis and treatment. Although they discuss several drugs, in their opinion based on theoretical mechanism, the most promising drug is bromhexine, a drug that could prevent viral entry into host cell (Figure 3); they suggest that the scientific and medical community explore this option in conjunction with other standard of care techniques.

ABSTRACT

Of huge importance now is to provide a fast, cost-effective, safe, and immediately available pharmaceutical solution to curb the rapid global spread of SARS-CoV-2. Recent publications on SARS-CoV-2 have brought attention to the possible benefit of chloroquine in the treatment of patients infected by SARS-CoV-2. Whether chloroquine can treat SARS-CoV-2 alone and also work as a prophylactic is doubtful. An effective prophylactic medication to prevent viral entry has to contain, at least, either a protease inhibitor or a competitive virus ACE2-binding inhibitor. Using bromhexine at a dosage that selectively inhibits TMPRSS2 and, in so doing, inhibits TMPRSS2-specific viral entry is likely to be effective against SARS-CoV-2. We propose the use of bromhexine as a prophylactic and treatment. We encourage the scientific community to assess bromhexine clinically as a prophylactic and curative treatment. If proven to be effective, this would allow a rapid, accessible, and cost-effective application worldwide.

FIGURES

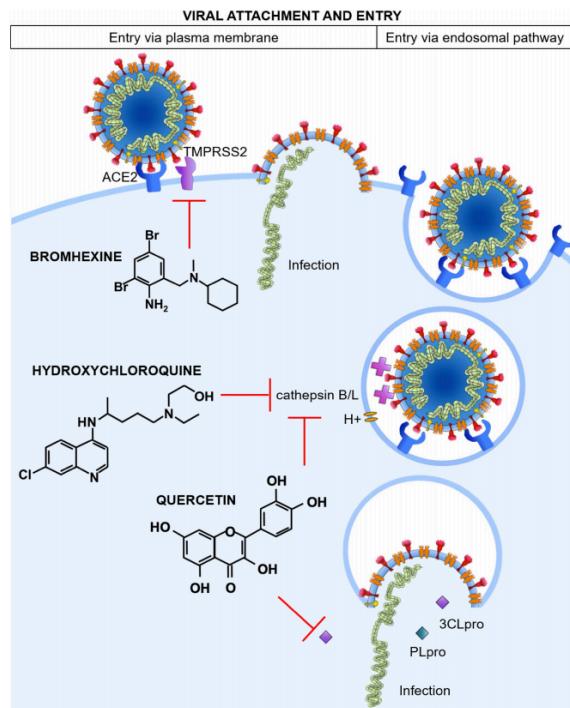


Figure. 3 Host–virus interaction: how we can exploit these mechanisms to treat SARS-CoV-2 using bromhexine and/or hydroxychloroquine (HCQ) and/or quercetin. SARS-CoV-2 employs two routes for host cell entry, which are dependent on the localization of the proteases required for activation of the S protein. Binding of SARS-CoV-2 to the cellular receptor, ACE2, can result in uptake of virions into endosomes, where the S protein is activated by the pH-dependent cysteine protease cathepsin B/L. Activation of the S protein by

cathepsin B/L can be blocked by HCQ and quercetin. Alternatively, the S protein can be activated by TMPRSS2, resulting in fusion of the viral membrane with the plasma membrane. Activation of the S protein by TMPRSS2 can be blocked by bromhexine. Quercetin also blocks viral replication via inhibition of the viral cysteine protease 3CLpro. (Adapted from Simmons et al. [24])

TRANSMISSION & PREVENTION

DEVELOPMENTS IN TRANSMISSION & PREVENTION

FILTRATION EVALUATION AND CLINICAL USE OF EXPIRED ELASTOMERIC P-100 FILTER CARTRIDGES DURING THE COVID-19 PANDEMIC

Patolia H, Pan J, Harb C, Marr LC, Baffoe-Bonnie A.. Infect Control Hosp Epidemiol. 2020 May 27:1-6. doi: 10.1017/ice.2020.257. Online ahead of print.

Level of Evidence: Other

BLUF

A mechanistic study conducted at the Virginia Tech Carilion School of Medicine by the authors found no statistically significant difference in filtration efficiency (p greater than 0.05) between expired P100 filter cartridges and N95 respirators, though the P100 showed slightly less efficiency overall. Their results suggest that expired filtration may be effective alternatives during the COVID-19 pandemic's personal protective equipment (PPE) shortage.

PREVENTION IN THE HOSPITAL

COVID-19 INFECTIONS AMONG HEALTHCARE WORKERS EXPOSED TO A PATIENT WITH A DELAYED DIAGNOSIS OF COVID-19

Baker MA, Rhee C, Fiumara K, Bennett-Rizzo C, Tucker R, Williams SA, Wickner P, Beloff J, McGrath C, Poulton A, Klompas M.. Infect Control Hosp Epidemiol. 2020 May 27:1-9. doi: 10.1017/ice.2020.256. Online ahead of print.

Level of Evidence: 5

BLUF

A case report conducted in Boston, MA reviews the infection risk of healthcare workers exposed to one patient who tested positive for SARS-CoV-2 by RT-PCR on day 14 of his hospitalization for cholecystitis. Assuming he may have had COVID-19 the entirety of his admission, they determined that 44 workers may have been exposed, and found that two of these workers (5%) subsequently tested positive for COVID-19. This study demonstrates the potential value in testing all admitted patients for SARS-CoV-2.

ABSTRACT

We report on Covid-19 infection risk amongst healthcare workers exposed to a patient diagnosed with Covid-19 on day 13 of hospitalization. There were 44 healthcare workers exposed to the patient before contact and droplet precautions were implemented: of these, 2/44 (5%) developed Covid-19 potentially attributable to the exposure.

HOSPITAL INFECTION AND COVID-19: DO NOT PUT ALL YOUR EGGS ON THE "SWAB" TESTS

Chirico F, Nucera G, Magnavita N.. Infect Control Hosp Epidemiol. 2020 May 27:1-3. doi: 10.1017/ice.2020.254. Online ahead of print.

Level of Evidence: Other

BLUF

This letter by three Italian physicians raises the concern of screening all hospitalized patients and health-care workers with nasopharyngeal and oropharyngeal (NP/OP) swab, citing sensitivity ranging from 42% to 71%. The authors urge hospitals to use additional methods, such as repeated quantitative reverse transcription PCR

(RT-qPCR), chest CT scans, and chest x-rays to help isolate SARS-CoV-2 positive patients earlier instead of relying on one method with low and variable sensitivity.

SUMMARY

The authors recommend the following to reduce nosocomial infections of SARS-CoV-2:

1. Swab tests should be done with deep tracheal aspirate to generate less aerosolization.
2. All hospitalized patients without respiratory symptoms should be checked with repeated RT-qPCR and chest x-ray.
3. Healthcare providers should be tested with serological tests and swabs with constant monitoring of their symptoms
4. All healthcare providers working directly with patients should have universal masking and eye shielding policy.

MANAGEMENT

ACUTE CARE

ANGIOPOETIN-2 AS A MARKER OF ENDOTHELIAL ACTIVATION IS A GOOD PREDICTOR FACTOR FOR INTENSIVE CARE UNIT ADMISSION OF COVID-19 PATIENTS

Smadja DM, Guerin CL, Chocron R, Yatim N, Boussier J, Gendron N, Khider L, Hadjadj J, Goudot G, Debuc B, Juvin P, Hauw-Berlemont C, Augy JL, Peron N, Messas E, Planquette B, Sanchez O, Charbit B, Gaussem P, Duffy D, Terrier B, Mirault T, Diehl JL.. Angiogenesis. 2020 May 27. doi: 10.1007/s10456-020-09730-0. Online ahead of print.

Level of Evidence: 4

BLUF

A prospective study of 40 consecutive patients with COVID-19 (diagnosed by chest CT and RT-PCR) admitted to Georges Pompidou European hospital in Paris, France found that elevated soluble E-selectin and angiopoietin-2 levels (markers of endothelial activation/microvascular dysfunction) were strongly correlated with admission to the ICU, suggesting potential prognostic value of these biomarkers.

SUMMARY

The authors found a strong correlation of plasma angiopoietin-2 levels with CRP, creatinine and D-dimer levels (Figure 3). ROC curve analysis showed an angiopoietin-2 cut-off of 5000 pg/mL as the best predictor for admission to the ICU with a sensitivity of 80.1% and a specificity of 70% (Figure 4). Additionally, they found that among COVID-19 patients admitted to the ICU, angiopoietin-2 had a significant negative correlation with pulmonary compliance, indicating that the pulmonary endothelial insult (measured by angiopoietin-2 levels) could be a co-indicator of pulmonary disease severity. The authors conclude that since endothelial damage, vascular insult, and thrombosis appear to be major players in the severity of COVID-19, angiopoietin-2 levels could be a useful predictor of ICU admission and prognosis.

ABSTRACT

BACKGROUND: Coronavirus disease-2019 (COVID-19), a respiratory disease has been associated with ischemic complications, coagulation disorders, and an endotheliitis. **OBJECTIVES:** To explore endothelial damage and activation-related biomarkers in COVID-19 patients with criteria of hospitalization for referral to intensive care unit (ICU) and/or respiratory worsening.

METHODS: Analysis of endothelial and angiogenic soluble markers in plasma from patients at admission.

RESULTS: Study enrolled 40 consecutive COVID-19 patients admitted to emergency department that fulfilled criteria for hospitalization. Half of them were admitted in conventional wards without any ICU transfer during hospitalization; whereas the 20 others were directly transferred to ICU. Patients transferred in ICU were more likely to have lymphopenia, decreased SpO₂ and increased D-dimer, CRP and creatinine levels. In those patients, soluble E-selectin and angiopoietin-2 were significantly increased (p value at 0.009 and 0.003, respectively). Increase in SELE gene expression (gene coding for E-selectin protein) was confirmed in an independent cohort of 32 patients using a whole blood gene expression profile analysis. In plasma, we found a strong association between angiopoietin-2 and CRP, creatinine and D-dimers (with p value at 0.001, 0.001 and 0.003, respectively). ROC curve analysis identified an Angiopoietin-2 cut-off of 5000 pg/mL as the best predictor for ICU outcome (Se = 80.1%, Sp = 70%, PPV = 72.7%, NPV = 77%), further confirmed in multivariate analysis after adjustment for creatinine, CRP or D-dimers.

CONCLUSION: Angiopoietin-2 is a relevant predictive factor for ICU direct admission in COVID-19 patients. This result showing an endothelial activation reinforces the hypothesis of a COVID-19-associated microvascular dysfunction.

NEUTROPHIL TO LYMPHOCYTE RATIO AS PROGNOSTIC AND PREDICTIVE FACTOR IN PATIENTS WITH CORONAVIRUS DISEASE 2019: A RETROSPECTIVE CROSS-SECTIONAL STUDY

Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, Deng Y, Wang H, Chen R, Yu Z, Li Y, Shang J, Zeng L, Zhao J, Guan C, Liu Q, Chen H, Gong W, Huang X, Zhang YJ, Liu J, Dong X, Zheng W, Nie S, Li D.. J Med Virol. 2020 May 26. doi: 10.1002/jmv.26061. Online ahead of print.

Level of Evidence: 5

BLUF

Researchers at Tongren Hospital of Wuhan University conducted a retrospective cohort study of 1,004 patients with COVID-19 between January 11 and March 3, 2020, and found that the Neutrophil to Lymphocyte Ratio (NLR) at admission for non-survivors was significantly higher than for survivors. Multivariate logistic regression modelling showed a NLR greater than 11.75 was significantly associated with all-cause mortality in the hospital. Authors suggest that NLR at admission could be used as a prognostic value, although larger studies are needed to validate the results.

ABSTRACT

OBJECTIVE: This retrospective study was designed to explore whether neutrophil to lymphocyte ratio (NLR) is a prognostic factor in patients with coronavirus disease 2019 (covid-19).

METHODS: A cohort of patients with covid-19 admitted to the Tongren Hospital of Wuhan University from January 11, 2020 to March 3, 2020 was retrospectively analyzed. Patients with hematologic malignancy were excluded. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. NLR values were measured at the time of admission. The primary outcome was all-cause in-hospital mortality. A multivariate logistic analysis was performed.

RESULTS: 1004 patients with covid-19 were included in this study. The mortality rate was 4.0% (40 cases). The median age of nonsurvivors (68 years) was significantly older than survivors (62 years). Male sex was more predominant in nonsurvival group (27; 67.5%) than in the survival group (466; 48.3%). NLR value of nonsurvival group (median 49.06, IQR 25.71-69.70) was higher than that of survival group (median 4.11, IQR 2.44-8.12, $P < 0.001$). In multivariate logistic regression analysis, after adjusting for confounding factors, NLR > 11.75 was significantly correlated with all-cause in-hospital mortality ($OR = 44.351$, 95% CI = 4.627-425.088).

CONCLUSIONS: These results suggest that the NLR at hospital admission is associated in-hospital mortality among patients with covid-19. Therefore, the NLR appears to be a significant prognostic biomarker of outcomes in critically ill patients with covid-19. However, further investigation is needed to validate this relationship with data collected prospectively. This article is protected by copyright. All rights reserved.

SCIENTIFIC AND STANDARDIZATION COMMITTEE COMMUNICATION: CLINICAL GUIDANCE ON THE DIAGNOSIS, PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM IN HOSPITALIZED PATIENTS WITH COVID-19

Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Thachil J, Giannis D, Douketis JD; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis, Haemostasis+.. J Thromb Haemost. 2020 May 27. doi: 10.1111/jth.14929. Online ahead of print.

Level of Evidence: Other

BLUF

Physicians from the International Society on Thrombosis and Hemostasis review the literature (from April 2020) and survey experts to formulate guidance on the diagnosis, prophylaxis, and treatment of venous thromboembolism (VTE) in COVID-19 patients. Guidance includes VTE screening via CT pulmonary

angiography, V/Q scan, MRI venography, or doppler, based on clinical suspicion; implementing VTE prophylaxis for hospital and ICU COVID-19 patients via low molecular weight heparin (LMWH); and continuation of thromboprophylaxis therapy through stay and up to 30 days post discharge.

ABSTRACT

The novel coronavirus disease of 2019 (COVID-19) pandemic, as declared by the World Health Organization, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Cardiovascular disease and, in particular, venous thromboembolism (VTE) has emerged as an important consideration in the management of hospitalized patients with COVID-19. The diagnosis of VTE using standardized objective testing is problematic in these patients, given the risk of infecting non-COVID-19 hospitalized patients and hospital personnel, coupled with the usual challenges of performing diagnostic testing in critically-ill patients. Early reports suggest a high incidence of VTE in hospitalized COVID-19 patients, particularly those with severe illness, that is similar to the high VTE rates observed in patients with other viral pneumonias, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS-CoV).

EMERGENCY MEDICINE

EXTRACORPOREAL BLOOD PURIFICATION AND ORGAN SUPPORT IN THE CRITICALLY ILL PATIENT DURING COVID-19 PANDEMIC: EXPERT REVIEW AND RECOMMENDATION

Ronco C, Bagshaw SM, Bellomo R, Clark WR, Husain-Syed F, Kellum JA, Ricci Z, Rimmelé T, Reis T, Ostermann M.. Blood Purif. 2020 May 26:1-11. doi: 10.1159/000508125. Online ahead of print.

Level of Evidence: Other

BLUF

A multinational group of experts review the available extracorporeal blood purification therapies and provide the following recommendations based on their clinical experience, but note that a large scale clinical trial is needed to determine the most efficacious approach.

1. Use of jugular double-lumen catheters
2. Anticoagulation
 - a. unfractionated heparin, 10 IU/kg/h, can increase to 15 - 20 IU/kg/h
 - b. if long term, use regional citrate anticoagulation in circuit
3. Extracorporeal organ support devices
 - a. use only in cases with proven cytokine storm or severe organ dysfunction, hemodynamic instability, etc.
 - b. use diffusive techniques with minimal filtration fraction and blood flow above 150mL/min
 - c. prolonged intermittent sessions (PIRRT) to allow nursing maneuvers such as pronation

ABSTRACT

Critically ill COVID-19 patients are generally admitted to the ICU for respiratory insufficiency which can evolve into a multiple-organ dysfunction syndrome requiring extracorporeal organ support. Ongoing advances in technology and science and progress in information technology support the development of integrated multi-organ support platforms for personalized treatment according to the changing needs of the patient. Based on pathophysiological derangements observed in COVID-19 patients, a rationale emerges for sequential extracorporeal therapies designed to remove inflammatory mediators and support different organ systems. In the absence of vaccines or direct therapy for COVID-19, extracorporeal therapies could represent an option to prevent organ failure and improve survival. The enormous demand in care for COVID-19 patients requires an immediate response from the scientific community. Thus, a detailed review of the available technology is

provided by experts followed by a series of recommendation based on current experience and opinions, while waiting for generation of robust evidence from trials.

FIGURES

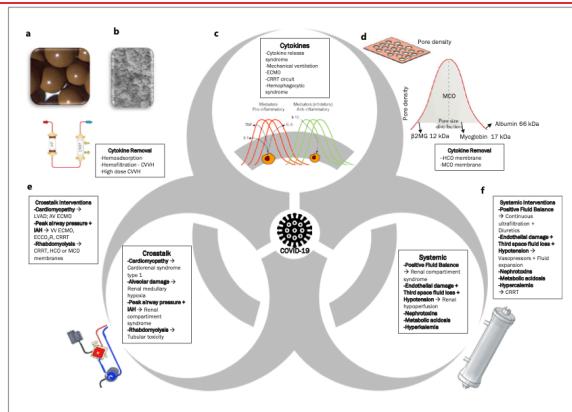


Figure 3. Pathways of kidney damage and proposed treatments in COVID-19 infections. Didactically 3 broad aspects are involved in COVID-19-associated AKI. Bidirectional involvement of each element occurs, represented by Set Theory and the presence of inter- sections. Treatment strategies also influence different elements simultaneously. a - Neutro-macroporous resin adsorbing beads magnified picture. b - Bead on transmission electron microscopy. c Cytokine release syndrome and other triggers for cytokine generation. d MCO has more uniformity in pore size distribution and pore density; these characteristics enable the membrane to effectively remove middle molecules in the range of most cytokines. with tolerable albumin loss. e - ECMO circuit. f - Filter used in CRRT for fluid balance control, removal of nephrotoxins, correction of hyperkalemia, and metabolic acidosis.

MEDICAL SUBSPECIALTIES

DERMATOLOGY

A CASE OF CEFDITOREN-INDUCED ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS DURING COVID-19 PANDEMICS. SEVERE CUTANEOUS ADVERSE REACTIONS (SCARS) ARE AN ISSUE

Torres-Navarro I, Abril-Pérez C, Roca-Ginés J, Sánchez-Arráez J, Botella-Estrada R.. J Eur Acad Dermatol Venereol. 2020 May 26. doi: 10.1111/jdv.16664. Online ahead of print.

Level of Evidence: Other

BLUF

This letter to the editor, written by dermatology experts from Spain, is in response to a recent publication by [Recalcati et al.](#) on the possible cutaneous manifestations of COVID-19. The authors of this correspondence urge readers to consider that skin lesions may manifest from medications related to COVID-19 treatments, rather than COVID-19 itself.

ABSTRACT

We read with interest the article by [Recalcati et al.](#) about the report of cutaneous manifestations in COVID-19 patients. We would like to highlight that some potentially severe manifestations in these patients are not directly related to the coronavirus but to the medications administered.

IMMUNOSUPPRESSIVE AND IMMUNOMODULATOR THERAPY FOR RARE OR UNCOMMON SKIN DISORDERS IN PANDEMIC DAYS

Karadag AS, Aslan Kayiran M, Lotti T, Wollina U.. Dermatol Ther. 2020 May 27:e13686. doi: 10.1111/dth.13686. Online ahead of print.

Level of Evidence: Other

BLUF

A literature review conducted by an international group of experts after the outbreak of COVID-19 in Wuhan, China, compiled current evidence regarding the use of immunomodulators in the treatment of rare dermatologic conditions such as dermatomyositis, lupus erythematosus, scleroderma, and neutrophilic dermatoses in light of the current pandemic. They found that azathioprine, mycophenolate mofetil, and methotrexate may increase one's risk of infection with SARS-CoV-2, while biological agents such as anti-TNF-alpha drugs may mitigate cytokine storm caused by COVID-19 and be beneficial. Overall, while the authors emphasize that overall research has not been definitive, their findings may be useful for providers when considering treatment for patients with certain dermatologic conditions.

GASTROENTEROLOGY

BOWEL PERFORATION IN A COVID-19 PATIENT: CASE REPORT

De Nardi P, Parolini DC, Ripa M, Racca S, Rosati R.. Int J Colorectal Dis. 2020 May 27. doi: 10.1007/s00384-020-03627-6. Online ahead of print.

Level of Evidence: 5

BLUF

Physicians in Italy report the case of a 53 year-old male who presented with confirmed COVID-19 with typical symptoms and imaging (Figure 1) and required admission to the ICU after acute respiratory deterioration. The patient subsequently developed GI symptoms, such as diarrhea, abdominal pain, and abdominal distention that were determined to be secondary to perforation of the ascending colon (Figures 2 and 3), illuminating a potentially serious complication of COVID-19 that has not been widely reported.

SUMMARY

COVID-19 is widely recognized to have primarily respiratory symptoms, but has also been noted to have serious effects in other organ systems. This is a case of a 53 year old male with a history of hypertension and an episode of paroxysmal supraventricular tachycardia (PSVT) presenting in Italy with typical signs and respiratory symptoms of COVID-19. This patient required admission to the ICU where he was intubated and treated with lopinavir/ritonavir, anakinra, hydroxychloroquine, and broad-spectrum antibiotics which resulted in clinical improvement in the span of four days. Several days after being discharged from ICU, the patient developed diarrhea and abdominal pain/distention that were determined to be secondary to perforation of the ascending colon and free air in the abdominal cavity. The patient required emergency laparotomy, which revealed no presence of obstruction. Histology of surgical samples revealed transmural granulocytic inflammation, edema of the mucosal layers, and fibrinous-granulocytic perivisceritis; however, confirmation of viral RNA via real-time reverse-transcriptase-polymerase-chain-reaction (rRT-PCR) was not confirmed.

ABSTRACT

INTRODUCTION: Since the outbreak of novel coronavirus (2019-nCoV), it became evident that a proportion of patients may present with gastrointestinal symptoms. **CASE:** We report the case of a Covid-19-infected patient who, during recovery from the pulmonary pneumonia, had gastrointestinal symptoms followed by a diastatic right colon perforation due to acute over distension of the bowel. **CONCLUSION:** This case highlights

the importance of paying attention to initial gastrointestinal symptoms in order to prevent possible complications.

FIGURES

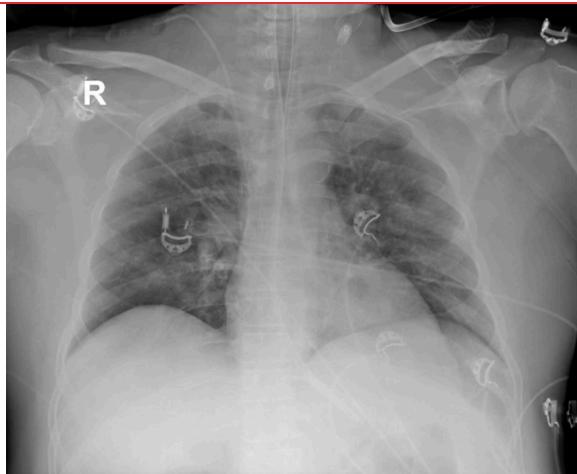


Figure 1: Chest X-ray showing multiple bilateral ground-glass opacities.

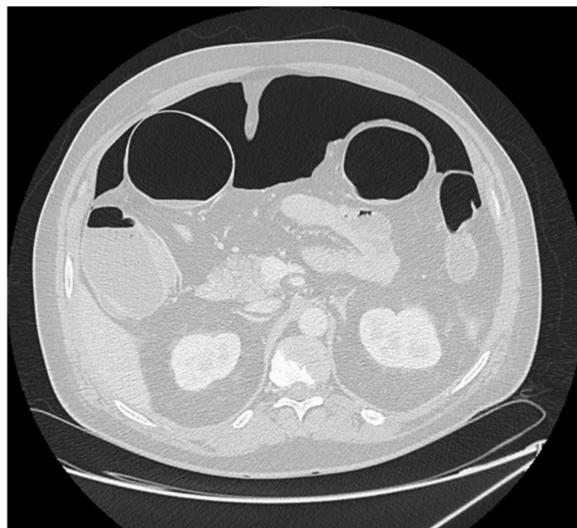
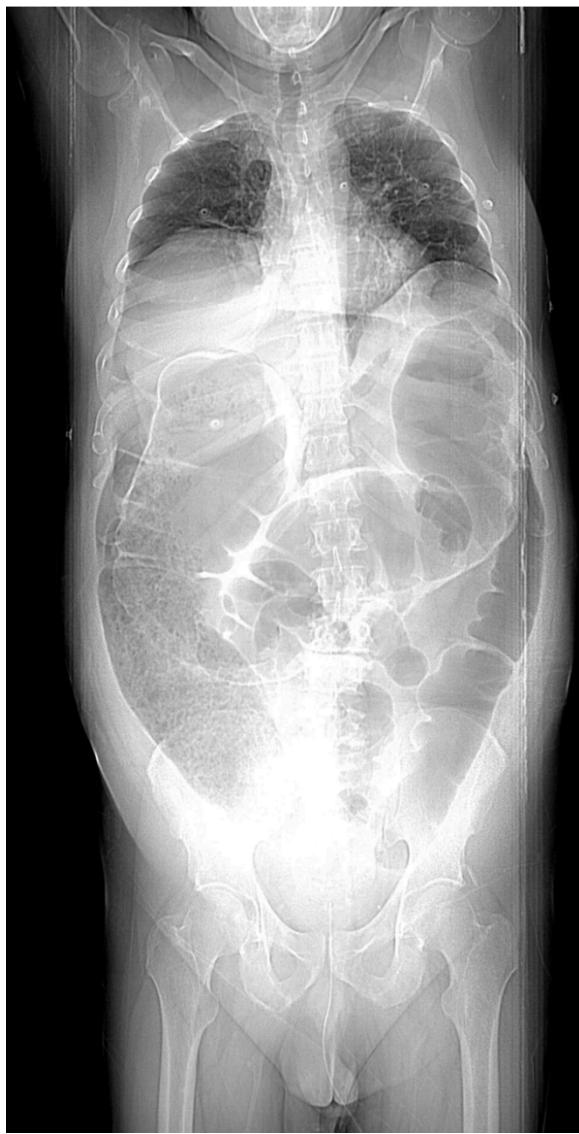


Figure 2: A high-resolution computed tomography of the abdomen showing free air in the abdominal cavity, axial view



HEMATOLOGY AND ONCOLOGY

COVID-19 IN A MELANOMA PATIENT UNDER TREATMENT WITH CHECKPOINT-INHIBITION

Schmidle P, Biedermann T, Posch C.. J Eur Acad Dermatol Venereol. 2020 May 26. doi: 10.1111/jdv.16661.
Online ahead of print.

Level of Evidence: Other

BLUF

A case review of a 47 year old patient on adjuvant immunotherapy for fully resected melanoma who contracted COVID-19. The patient had mild to moderate symptoms and did not develop respiratory symptoms. Immunotherapy was withheld as a precautionary measure. Two weeks after onset she was found to have developed COVID-19 IgG antibodies with complete resolution of symptoms. Authors conclude that it remains unclear if checkpoint inhibition positively affects disease course.

ABSTRACT

SARS-CoV-2 poses new challenges in all aspects of healthcare. Patients with preexisting cardio-vascular conditions are at higher risk of developing severe symptoms and worse outcome. Data also suggest that cancer

patients are particularly vulnerable, but differences between tumor entities and cancer treatments may exist. Little is known how cancer treatment engaging immune checkpoints affects the course of COVID-19.

ADJUSTING PRACTICE DURING COVID-19

FOR HEALTHCARE PROFESSIONALS

THE POTENTIAL LONG-TERM IMPACT OF THE COVID-19 OUTBREAK ON PATIENTS WITH NON-COMMUNICABLE DISEASES IN EUROPE: CONSEQUENCES FOR HEALTHY AGEING

Palmer K, Monaco A, Kivipelto M, Onder G, Maggi S, Michel JP, Prieto R, Sykara G, Donde S.. Aging Clin Exp Res. 2020 May 26. doi: 10.1007/s40520-020-01601-4. Online ahead of print.

Level of Evidence: Other

BLUF

This narrative review shares how the COVID-19 pandemic has the potential to impact non-communicable disease (NCD) management and affect patient outcomes across Europe. The authors speculate that SARS-CoV-2 infection may affect progression of NCDs due to limitations in physical activity levels, reduced social networks, impaired immune function, and poor adherence to medications amid the pandemic.

ABSTRACT

The early stages of the COVID-19 pandemic have focused on containing SARS-CoV-2 infection and identifying treatment strategies. While controlling this communicable disease is of utmost importance, the long-term effect on individuals with non-communicable diseases (NCD) is significant. Although certain NCDs appear to increase the severity of COVID-19 and mortality risk, SARS-CoV-2 infection in survivors with NCDs may also affect the progression of their pre-existing clinical conditions. Infection containment measures will have substantial short- and long-term consequences; social distancing and quarantine restrictions will reduce physical activity and increase other unhealthy lifestyles, thus increasing NCD risk factors and worsening clinical symptoms. Vitamin D levels might decrease and there might be a rise in mental health disorders. Many countries have made changes to routine management of NCD patients, e.g., cancelling non-urgent outpatient visits, which will have important implications for NCD management, diagnosis of new-onset NCDs, medication adherence, and NCD progression. We may have opportunities to learn from this unprecedented crisis on how to leverage healthcare technologies and improve procedures to optimize healthcare service provision. This article discusses how the COVID-19 outbreak and related infection control measures could hit the most frail individuals, worsening the condition of NCD patients, while further jeopardizing the sustainability of the healthcare systems. We suggest ways to define an integrated strategy that could involve both public institutional entities and the private sector to safeguard frail individuals and mitigate the impact of the outbreak.

ACUTE CARE

CRITICAL CARE

THERAPEUTIC ALTERNATIVES AND STRATEGIES FOR DRUG CONSERVATION IN THE INTENSIVE CARE UNIT DURING TIMES OF DRUG SHORTAGE: A REPORT OF THE ONTARIO COVID-19 ICU DRUG TASK FORCE

Kanji S, Burry L, Williamson D, Pittman M, Dubinsky S, Patel D, Natarajan S, MacLean R, Huh JH, Scales DC, Neilipovitz D; Ontario COVID-19 ICU Drug Task Force (Appendix).. Can J Anaesth. 2020 May 26. doi: 10.1007/s12630-020-01713-5. Online ahead of print.

Level of Evidence: Other

BLUF

The Ontario COVID-19 ICU Drug Task Force provides recommendations for drug conservation strategies and essential drug alternatives, with a focus on drugs at a risk of shortage in the intensive care unit (ICU) during the COVID-19 pandemic.

SUMMARY

Key recommendations from the Ontario COVID-19 ICU Drug Task Force include:

- **Sedatives:** Employ an escalation strategy starting with intermittent enteral agents, followed by intermittent intravenous (IV) agents and, if required, continuous infusions.
- **Opioid Analgesics:** Employ an escalation strategy where enteral agents are preferred over intermittent IV agents, followed by continuous IV infusions if required. Use a step-wise, multi-modal approach to pain management by employing non-opioid adjunctive therapy to reduce opioid requirements.
- **Neuromuscular Blocking Agents:** Use the lowest effective dose for the shortest time possible by including dose titration according to train-of-four monitoring and observed respiratory effort.
- **Vasopressors/Inotropes:** Efforts to conserve vasopressors should target using a lower level of sedation in eligible patients.

ABSTRACT

During the coronavirus disease (COVID-19) global pandemic, urgent strategies to alleviate shortages are required. Evaluation of the feasibility, practicality, and value of drug conservation strategies and therapeutic alternatives requires a collaborative approach at the provincial level. The Ontario COVID-19 ICU Drug Task Force was directed to create recommendations suggesting drug conservation strategies and therapeutic alternatives for essential drugs at risk of shortage in the intensive care unit during the COVID-19 pandemic. Recommendations were rapidly developed using a modified Delphi method and evaluated on their ease of implementation, feasibility, and supportive evidence. This article describes the recommendations for drug conservation strategies and therapeutic alternatives for drugs at risk of shortage that are commonly used in the care of critically ill patients. Recommendations are identified as preferred and secondary ones that might be less desirable. Although the impetus for generating this document was the COVID-19 pandemic, recommendations should also be applicable for mitigating drug shortages outside of a pandemic. Proposed provincial strategies for drug conservation and therapeutic alternatives may not all be appropriate for every institution. Local implementation will require consultation from end-users and hospital administrators. Competing equipment shortages and available resources should be considered when evaluating the appropriateness of each strategy.

NEUROLOGY

CATASTROPHIC INTRACRANIAL HEMORRHAGE IN TWO CRITICALLY ILL PATIENTS WITH COVID-19

Carroll E, Lewis A.. Neurocrit Care. 2020 May 26. doi: 10.1007/s12028-020-00993-5. Online ahead of print.
Level of Evidence: 4

BLUF

This case series conducted at NYU Langone Medical Center during March 2020 presents two patients diagnosed with COVID-19 who developed devastating neurological complications, emphasizing the importance of performing frequent neurologic assessments in patients with COVID-19. Should patients' pulmonary function deteriorate severely, necessitating sedation and intubation, the authors recommend daily monitoring of pupillary reflexes at a minimum.

SUMMARY

Current literature has documented an association of increased risk of coagulopathy and venous thromboemboli (VTE) in patients with COVID-19. Provided that both patients had elevated D-dimers, empiric anticoagulation therapy (enoxaparin or heparin titrated to a low therapeutic anti-Xa goal of 0.3–0.5 U/mL) was initiated. Despite maintaining therapeutic levels, the patients developed fatal catastrophic bleeds. This demonstrates a need for future research to identify which patients with COVID-19 will benefit from anticoagulation therapy, in addition to identifying risk factors that may predispose patients to severe brain injuries and exploration of preventative measures.

FIGURES

	Patient #1 mean (range)	Patient #2 mean (range)
Vital signs		
Systolic blood pressure (BP) while on heparin (mmHg)	113 (70–197)	117 (47–204)
Diastolic BP while on heparin (mmHg)	67 (40–104)	58 (29–112)
Oxygen saturation	94% (66–100%)	94% (71–100%)
Coagulation/hematologic labs		
Anti-Xa (U/mL)	0.42 (0.23–0.73)	0.30 (0.01–0.62)
D-dimer (ng/mL)	2997 (460–> 10,000)	1608 (677–4488)
White blood cell count (WBC) ($\times 10^3/\mu\text{L}$)	7.75 (4.7–17.4)	9.7 (4.6–18.3)
Platelets ($\times 10^3/\mu\text{L}$)	175 (123–216)	385 (210–518)
Metabolic panels		
Sodium (mmol/L)	142 (137–148)	148 (130–167)
BUN (mg/dL)	67.6 (10–157)	48 (11–80)
Creatinine (mg/dL)	5.71 (0.75–12.36)	1.33 (0.73–1.69)
Inflammatory markers		
C-reactive protein (CRP) (mg/L)	165 (22–370)	232 (121–415)
Ferritin (ng/mL)	3072 (103–5227)	8530 (2477–40,000)
Procalcitonin (ng/mL)	7.8 (0.28–23.33)	2.12 (0.39–8)

Table 1: Blood pressure and laboratory results

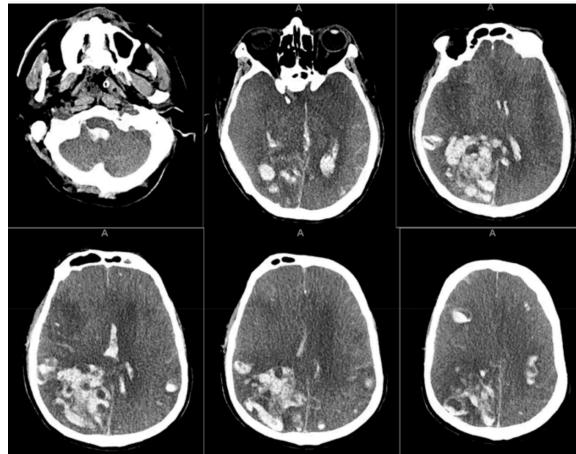
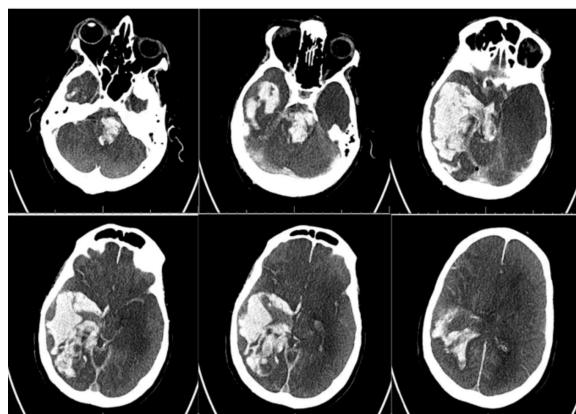


Figure 1: Patient #1 NCHCT. NCHCT obtained on HD #13, demonstrating multifocal intraparenchymal hemorrhage with intraventricular extension, mass effect, and evidence of global anoxic injury, cerebral edema, and downward herniation of the cerebellar tonsils



DERMATOLOGY

THE COVID-19 OUTBREAK IN DERMATOLOGIC SURGERY: RESETTING CLINICAL PRIORITIES

Rossi E, Trakatelli M, Giacomelli L, Ferrari B, Francomano M, Pellacani G, Magnoni C.. J Eur Acad Dermatol Venereol. 2020 May 26. doi: 10.1111/jdv.16672. Online ahead of print.

Level of Evidence: Other

BLUF

A commentary written by a group of dermatologists in Italy describes changes to their dermatology practice during the COVID-19 pandemic, highlighting the rapid change towards new triage guidelines for dermatological surgery and changes to protective equipment protocols. Authors recommended mandatory use of high protection masks (FFP3) during surgery on the face, strict triage protocols for elective dermatological surgeries, and the use of standardized consent forms for possible SARS-CoV-2 infection risk to promote transparency (Figure 1).

ABSTRACT

Emilia-Romagna was one of the Italian regions mostly affected by the COVID-19 pandemic and lockdown measures were taken to slow the COVID-19 outbreak. All routine activities in Modena hospitals were suspended; however, urgent procedures were still to be performed. Setting the priority of procedures in oncological dermatology in the COVID-19 era is challenging.

FIGURES



Figure 1: Reset of clinical priorities after the COVID-19 pandemic for dermatologic surgery planning.

CONSIDERATIONS FOR SAFETY IN THE USE OF SYSTEMIC MEDICATIONS FOR PSORIASIS AND ATOPIC DERMATITIS DURING THE COVID-19 PANDEMIC

Ricardo JW, Lipner SR.. Dermatol Ther. 2020 May 27. doi: 10.1111/dth.13687. Online ahead of print.

Level of Evidence: Other

BLUF

A literature review by two Cornell dermatologists investigated safety of psoriasis and atopic dermatitis medications during the COVID-19 pandemic. Due to the immunomodulatory nature of such medications, the authors believe that in patients who have an active infection, systemic conventional medications, the JAK inhibitor tofacitinib, and biologics for psoriasis should be halted. Patients without infection should continue medication, however if a safer agent is available this should be considered. Data suggests that use of IL-17 and IL-23 inhibitors are safer than TNF-blockers, while apremilast, acitretin, and dupilumab appear safe and can continue to be used. The authors provide treatment algorithms (figures 1 and 2) and suggest following these guidelines until more conclusive data is obtained.

ABSTRACT

Coronavirus disease 2019 (COVID-19), is responsible for at least 2,546,527 cases and 175,812 deaths as of April 21, 2020. Psoriasis and atopic dermatitis are common, chronic, inflammatory skin conditions, with immune dysregulation as a shared mechanism; therefore, mainstays of treatment include systemic immunomodulating therapies. It is unknown whether these therapies are associated with increased to COVID-19 susceptibility or worse outcomes in infected patients. In this review, we discuss overall infection risks of non-biologic and biologic systemic medications for psoriasis and atopic dermatitis, and provide therapeutic recommendations. In summary, in patients with active infection, systemic conventional medications, the JAK inhibitor tofacitinib, and biologics for psoriasis should be temporarily held until there is more data; in uninfected patients switching to safer alternatives should be considered. Interleukin (IL)-17, IL-12/23 and IL-23 inhibitors are associated with low infection risk, with IL-17 and IL-23 favored over IL-12/23 inhibitors. Pivotal trials and postmarketing data also suggest that IL-17 and IL-23 blockers are safer than TNF-blockers. Apremilast, acitretin and dupilumab, have favorable safety data, and may be safely initiated and continued in uninfected patients. Without definitive COVID-19 data, these recommendations may be useful in guiding treatment of psoriasis and atopic dermatitis patients during the COVID-19 pandemic. This article is protected by copyright. All rights reserved.

FIGURES

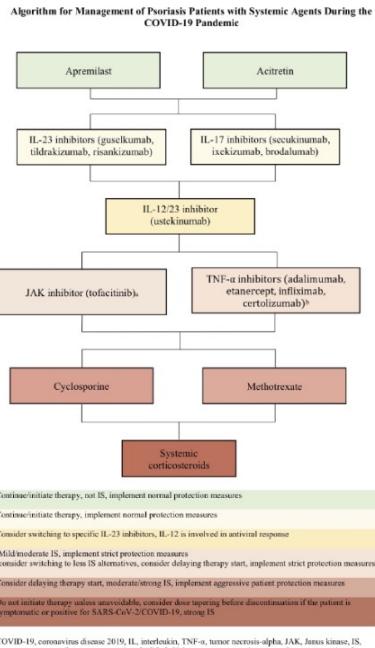


Figure 1. Proposed treatment algorithm of systemically-treated psoriasis patients during the COVID-19 pandemic. In case the patient is positive or symptomatic for SARS-CoV-2/COVID-19, all immunomodulating medications must be discontinued

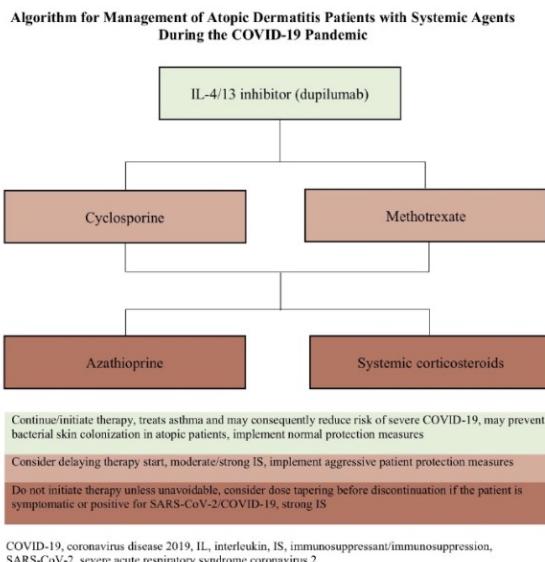


Figure 2. Proposed treatment algorithm of systemically-treated atopic dermatitis patients during the COVID-19 pandemic. In case the patient is positive or symptomatic for SARS-CoV-2/COVID-19, all immunomodulating medications must be discontinued

RESTRUCTURING AN ACADEMIC DERMATOLOGY PRACTICE DURING THE COVID-19 PANDEMIC
Sheriff T, Murrell OG, Murrell DF.. Dermatol Ther. 2020 May 27. doi: 10.1111/dth.13684. Online ahead of print.

Level of Evidence: Other

BLUF

This article details strategies implemented by a dermatology clinic in Australia in order to treat patients needing urgent care or evaluation while also minimizing spread. Strategies included staggering appointments, transitioning to telemetry medicine whenever possible with the use of video conferences, and risk assessment for COVID-19 exposure with incoming patients.

ABSTRACT

SARS-CoV-2 is a highly virulent positive-sense single stranded RNA virus that spreads rapidly via respiratory droplets, causing severe acute respiratory syndromes with significant mortality and morbidity. Currently 210 countries and territories are affected around the world with a reported 2.6 million confirmed cases.¹ The COVID 19 pandemic has changed the way patients attend their specialist appointments and receive medical care. Whilst some specialist clinics have closed we have implemented strategies and restructured our academic practice in Australia to minimize the spread of disease whilst treating patients who need urgent care. We hope to share these strategies in the hope they may be useful to the dermatology community.

CARDIOLOGY

RHYTHM BLUES IN THE TIME OF CORONAVIRUS DISEASE 2019 (COVID-19): HOW THE CARDIAC ELECTROPHYSIOLOGIST ADAPTS TO A VIRAL PANDEMIC IN SINGAPORE

Level of Evidence: Other

BLUF

Authors from Tan Tock Seng Hospital in Singapore discuss the effect of the COVID-19 pandemic on the cardiac electrophysiology and pacing (EP) service. Thus far, the cardiac EP service has seen only one case of arrhythmia due to COVID-19 (Figure 1). The authors additionally note steps taken at this institution to protect healthcare workers which include:

- Separating workers into two teams with separate clinical roles and responsibilities
- Limiting cross-institutional movement
- Postponing elective procedures
- Specifying management of patients pre-operatively (figure 2).

FIGURES

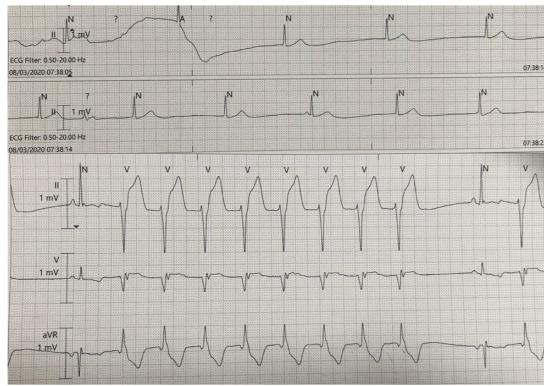
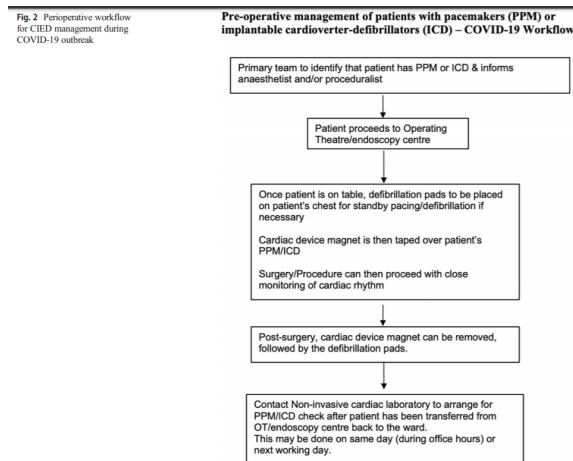


Fig. 1 Electrocardiography strips showing intermittent junctional bradycardia and non-sustained ventricular tachycardia in a confirmed COVID-19 patient



HEMATOLOGY AND ONCOLOGY

MANAGEMENT OF OUTPATIENT WARFARIN THERAPY AMID COVID-19 PANDEMIC: A PRACTICAL GUIDE

Level of Evidence: Other

BLUF

Authors from Malaysia and the United Kingdom discuss the management of patients on warfarin during the COVID-19 pandemic, recommending the following strategies to reduce adverse outcomes such as bleeding and thromboembolism (figure 1):

- Reevaluate the need for continued use of warfarin
- Switch to direct oral anticoagulants (DOAC) or, if not possible, to low molecular weight heparin (LMWH)/fondaparinux.
- Self-monitor INR at home
- If unable to self-monitor INR at home, then increase interval between in-clinic INR monitoring (if stable)

ABSTRACT

Many healthcare resources have been and continue to be allocated to the management of patients with COVID-19. Therefore, the ongoing care of patients receiving oral anticoagulation with warfarin is likely to be compromised amid this unprecedented crisis. This article discusses a stepwise algorithm for the management of outpatient warfarin therapy. Alternative management strategies are presented and discussed, including alternative pharmacological therapy options and self-monitoring. Our algorithm aims to help clinicians safely optimize the treatment of patients requiring anticoagulation therapy in the context of the global response to the current pandemic.

FIGURES

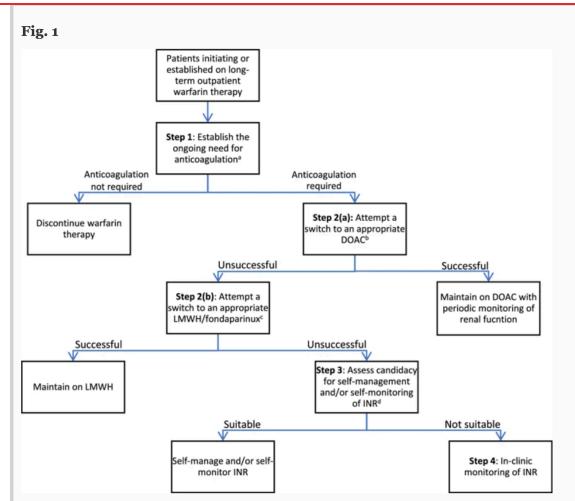


Figure 1. A proposed stepwise algorithm for the management of outpatient warfarin therapy. DOAC direct oral anticoagulant, INR international normalized ratio, LMWH low-molecular-weight heparin. a - Consider appropriateness of indication for warfarin therapy and current bleeding risk. b - Consider contraindications, indications where DOACs might not be suitable, availability of DOACs in the formulary, and cost issues. c - Only for patients with venous thromboembolism. Consider personal preference, renal function, suitability for injection, and cost issues. d - Consider suitability for self-managed and/or self-monitored INR, a requirement for training prior to self-managed and/or self-monitored INR, local resources, and cost issues

GYNECOLOGIC ONCOLOGY AT THE TIME OF COVID-19 OUTBREAK

Bogani G, Brusadelli C, Guerrisi R, Lopez S, Signorelli M, Ditto A, Raspagliesi F.. J Gynecol Oncol. 2020 May 27. doi: 10.3802/jgo.2020.31.e72. Online ahead of print.
Level of Evidence: Other

BLUF

Researchers in Italy provide guidelines for adjusting clinical practice in gynecologic oncology including management of ovarian, endometrial, and cervical cancer (figures 1-3). They highlight the prioritization of less invasive procedures in order to reduce the length of postoperative hospitalization, the preference for minimally invasive techniques over laparoscopic procedures in order to reduce the risk of the care team's exposure during the procedure, and the importance of properly distributing resources.

ABSTRACT

The World Health Organization (WHO) classified the novel coronavirus (i.e., coronavirus disease 2019 [COVID-19]) as a global public health emergency. COVID-19 threatens to curtail patient access to evidence-based treatment. Medicine is changing, basically due to the limited available resources. In the field of gynecologic oncology, we have to re-design our treatments' paradigm. During COVID-19 pandemic outbreak, the highest priority is to achieve the maximum benefit from less demanding procedures. Extensive procedures should be avoided, in order to reduce hospitalization and postoperative events that might increase the in-hospital spread of the virus. There are ongoing concerns on the use of laparoscopic procedures, related to the possible contamination of the staff working in the operation room. Other minimally invasive techniques, including, vaginal surgery as well as robotic-assisted and isobaric procedures would be preferred over laparoscopy. A fair allocation of resources is paramount adequate treatments.

FIGURES

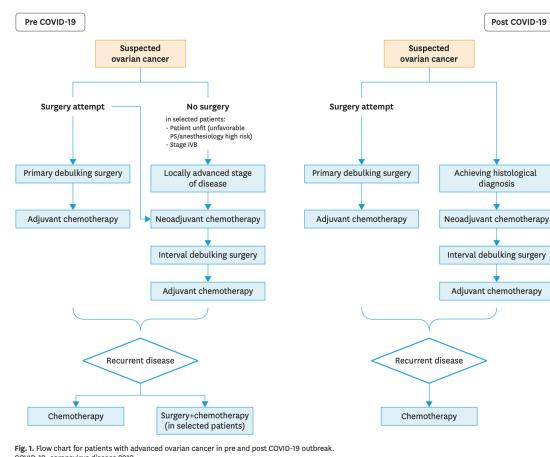


Fig. 1. Flow chart for patients with advanced ovarian cancer in pre and post COVID-19 outbreak.
COVID-19, coronavirus disease 2019.

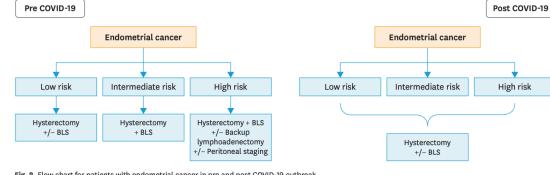
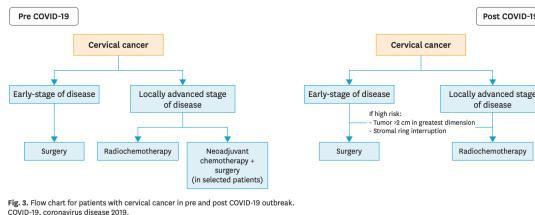


Fig. 2. Flow chart for patients with endometrial cancer in pre and post COVID-19 outbreak.
COVID-19, coronavirus disease 2019; BLS, bilateral salpingo-oophorectomy.



NEPHROLOGY

SAFETY AND EFFICACY OF BEDSIDE PERITONEAL DIALYSIS CATHETER PLACEMENT IN THE COVID-19 ERA: INITIAL EXPERIENCE AT A NEW YORK CITY HOSPITAL

Vigiola Cruz M, Bellorin O, Srivatana V, Afaneh C.. World J Surg. 2020 May 26. doi: 10.1007/s00268-020-05600-4. Online ahead of print.

Level of Evidence: 4

BLUF

To address a shortage of hemodialysis (HD), surgeons at an academic hospital in New York City present a protocol and case series of short-term results of bedside peritoneal catheter placement and dialysis on both critically-ill, intubated patients with COVID-19 (n=8) and asymptomatic untested ambulatory patients (n=3) with acute or chronic kidney disease (Figure 1). They note advantages of minimal necessary personnel (two physicians) and minimal resources (only local anesthetic) without any compromise to dialysis efficacy compared to HD, though they acknowledge that further long-term study is warranted.

SUMMARY

Inpatients were selected based on limited or no past abdominal surgical history, persistent hypotension limiting HD use, and “repeated thrombosis of dialysis lines or circuits.” Outpatients were selected on criteria of surgical adequacy, as well as willingness and ability to participate.

- All selected patients were screened for adequacy based on well-documented surgical history and, for outpatients with chronic kidney disease, dialysis urgency. See Table 2 for additional patient characteristics.
- Catheters inserted just lateral to midline in the right upper quadrant, and patients were provided pre- and 24h-postoperative prophylaxis with a first generation cephalosporin. They also received preoperative oxycodone and local anesthesia for placement, and 10/11 received anticoagulative therapy.
- Guidelines are included for managing leakage and flow dysfunction in dialysis.
- Catheters were all successfully placed, and outflow dysfunction was reported in one patient with a BMI of 37.6 kg/m² and a history of open appendectomy.
- On postoperative day 3, one patient had sanguineous dialysate and a 1g/dL drop in serum hemoglobin while on anticoagulants over 36h, which resolved with cessation of heparin for 24h.
- “The quality of dialysis was evaluated daily by the nephrology team and was, on average, calculated to be equivalent to C3 days of hemodialysis per week for all patients, which is considered physiologically adequate.”

ABSTRACT

INTRODUCTION: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is common in critically ill patients with COVID-19. Unparalleled numbers of patients with AKI and shortage of dialysis

machines and operative resources prompted consideration of expanded use of urgent-start peritoneal dialysis (PD) and evaluation of the safety and efficacy of bedside surgical placement of PD catheters.

STUDY DESIGN: Bedside, open PD catheter insertions were performed in early April 2020, at a large academic center in New York City. Patients with SARS-CoV-2 infection and AKI and ambulatory patients with chronic kidney disease and impending need for RRT were included. Detailed surgical technique is described.

RESULTS: Fourteen catheters were placed at the bedside over 2 weeks, 11 in critically ill COVID-19 patients and three in ambulatory patients. Mean patient age was 61.9 years (43-83), and mean body mass index was 27.1 (20-37.6); four patients had prior abdominal surgery. All catheters were placed successfully without routine radiographic studies or intraoperative complications. One patient (7%) experienced primary nonfunction of the catheter requiring HD. One patient had limited intraperitoneal bleeding while anticoagulated, which was managed by mechanical compression of the abdominal wall and temporarily holding anticoagulation. All other catheters had an adequate function at 3-18 days of follow-up.

CONCLUSIONS: Bedside placement of PD catheters is safe and effective in ICU and outpatient clinic settings. Our surgical protocols allowed for optimization of critical hospital resources, minimization of hazardous exposure to healthcare providers and a broader application of urgent-start PD in selected patients. Long-term follow-up is warranted.

FIGURES

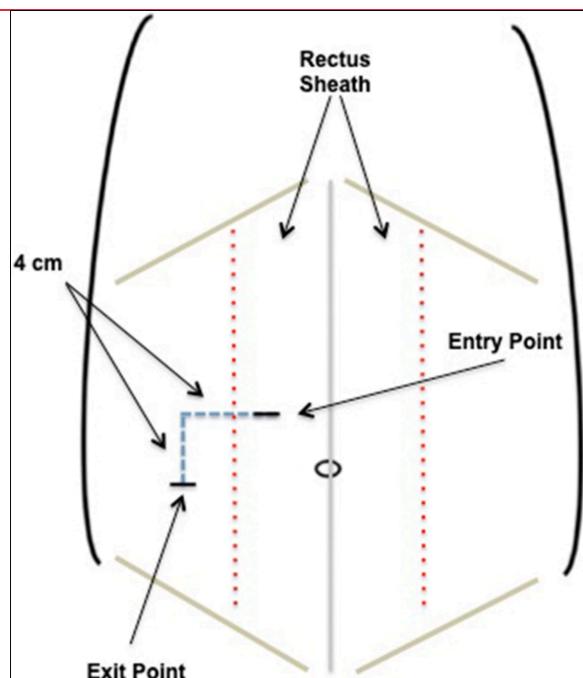


Figure 1. Anatomic landmarks. Catheter entry site incision in the right upper quadrant, approximately 2–3 cm lateral to the midline and tunneled toward the exit site at 4 cm inferior and 4 cm lateral to the introduction site

Patient	Age	Sex	COVID-19 status	ASA	BMI	Baseline CKD	Prior abd. surgery	Ongoing HD and/or PEEP>10	FiO2>50 and/or PEEP>10	Active vasopressors	Therapeutic anticoagulation	Bedside location	HD# at procedure	Complications
1	43	F	UNK	3	20.0	Y						Clinic	N/A	
2	43	M	UNK	3	34.2	Y					Y	Clinic	N/A	
3	68	M	UNK	3	30.7	Y						Clinic	N/A	
4	74	M	(+)	4	30.1	Y						ICU	2	
5	65	M	(+)	4	22.9						Y	ICU	16	
6	77	M	(+)	4	23.6	Y					Y	ICU	16	Bleeding*
7	77	M	(+)	4	22.6					Y	Y	ICU	7	
8	50	M	(+)	4	37.6		Y	Y	Y	Y	Y	ICU	7	Nonfunction ^b
9	83	F	(+)	4	33.9					Y	Y	ICU	4	
10	49	M	(+)	4	26.0		Y		Y	Y	Y	ICU	2	
11	61	M	(+)	4	23.9	Y					Y	ICU	12	
12	52	M	(+)	4	23.1		Y		Y	Y	Y	ICU	6	
13	59	M	(+)	4	26.4			Y		Y	Y	ICU	20	
14	66	M	(+)	4	25.0						Y	ICU	28	

Table 2. Relevant patient characteristics. Relevant demographic and clinical characteristics of patients undergoing bedside catheter placement

RHEUMATOLOGY

CARE FOR PATIENTS WITH RHEUMATIC DISEASES DURING COVID-19 PANDEMIC: A POSITION STATEMENT FROM APLAR

Tam LS, Tanaka Y, Handa R, Chang CC, Cheng YK, Isalm N, Li M, Lorenzo JP, Song YW, Yamamoto K, Zeng X, Haq SA.. Int J Rheum Dis. 2020 May 27. doi: 10.1111/1756-185X.13863. Online ahead of print.

Level of Evidence: Other

BLUF

A task-force from the Asia Pacific League of Associations for Rheumatology (APLAR) developed guidelines on the treatment of rheumological diseases during the COVID-19 pandemic based on evidence reported up to 26 April 2020. They found that immunosuppressive drugs used to treat rheumatic diseases did not increase patient susceptibility to COVID-19, and suggest rheumatoid treatments should continue as normal. In the case of infection, however, treatment should be reconsidered and deescalated or discontinued if necessary. The authors conclude by emphasizing these recommendations may change as new data emerges.

SUMMARY

Their key findings and recommendations are summarized here:

Potential risk factors for SARS-COV-2 infection in patients with rheumatic diseases

- On immunosuppressive agents
- Chronic kidney disease, eg lupus nephritis
- With lung involvement, eg interstitial lung disease
- Elderly patients
- Frequently visiting medical clinic
- With underlying health conditions, such as smoking, obesity, hypertension and diabetes
- Pregnancy

Medication for patients with rheumatic diseases

- Continue current treatment if disease is stable, and contact your doctor for suitable medicine if disease has flared
- Use of hydroxychloroquine (HCQ) and sulphasalazine (SLZ) should be continued and should not increase the risk of infection
- Use of other conventional synthetic disease-modifying drugs (csDMARDs, eg methotrexate, leflunomide) and immunosuppressants (eg cyclophosphamide, azathioprine, mycophenolate mofetil, tacrolimus) should be continued
- Corticosteroid use can be continued
- A new prescription of immunosuppressant or increase in dose of an ongoing immunosuppressant would need to be carefully discussed in epidemic areas
- Use of all biologic DMARDs should be continued if possible
- If infliximab infusion is not accessible, switching to other anti-tumor necrosis factor injection at home is encouraged

- Targeted synthetic DMARDs (Janus-activated kinase [JAK] inhibitors) including tofacitinib/baricitinib/upadacitinib can be continued

Surgery

- Postpone elective surgery, eg joint replacement surgery
- Screening for COVID-19 (symptoms suggestive of COVID-19, complete blood count, nasopharyngeal swab and chest X-ray or chest computed tomography according to local recommendation) before emergency surgery

Patients with rheumatic disease and fever

- Contact your rheumatologist about potential option to visit fever outpatient clinic with personal protection provisions if temperature continues over 38°C
- Patients must not suddenly stop prednisolone
- Suspend the use of immunosuppressants and biological agents after consultation with your rheumatologist, and follow appropriate local guidance for suspected COVID-19 if COVID-19 cannot be ruled out
- Patients can continue HCQ and SLZ if they are infected with COVID-19.

SURGICAL SUBSPECIALTIES

THE RISK OF COVID-19 TRANSMISSION BY LAPAROSCOPIC SMOKE MAY BE LOWER THAN FOR LAPAROTOMY: A NARRATIVE REVIEW

Mintz Y, Arezzo A, Boni L, Baldari L, Cassinotti E, Brodie R, Uranues S, Zheng M, Fingerhut A.. Surg Endosc. 2020 May 26. doi: 10.1007/s00464-020-07652-y. Online ahead of print.

Level of Evidence: Other

BLUF

Surgeons in Europe and Asia conducted a literature review to determine if laparoscopy or laparotomy would be safer in terms of SARS-CoV-2 containing surgical aerosol/smoke production. While they found no literature demonstrating SARS-CoV-2 transmission through surgical smoke, they conclude that laparoscopy may have lower risk than laparotomy for possible transmission through surgical smoke. Current evidence suggests that surgical smoke may be easier to contain in the closed environment of laparoscopy.

ABSTRACT

BACKGROUND: Surgical smoke is a well-recognized hazard in the operating room. At the beginning of the COVID-19 pandemic, surgical societies quickly published guidelines recommending avoiding laparoscopy or to consider open surgery because of the fear of transmission of SARS-CoV-2 through surgical smoke or aerosol. This narrative review of the literature aimed to determine whether there are any differences in the creation of surgical smoke/aerosol between laparoscopy and laparotomy and if laparoscopy may be safer than laparotomy.

METHODS: A literature search was performed using the Pubmed, Embase and Google scholar search engines, as well as manual search of the major journals with specific COVID-19 sections for ahead-of-print publications.

RESULTS: Of 1098 identified articles, we critically appraised 50. Surgical smoke created by electrosurgical and ultrasonic devices has the same composition both in laparoscopy and laparotomy. SARS-CoV-2 has never been found in surgical smoke and there is currently no data to support its virulence if ever it could be transmitted through surgical smoke/aerosol.

CONCLUSION: If laparoscopy is performed in a closed cavity enabling containment of surgical smoke/aerosol, and proper evacuation of smoke with simple measures is respected, and as long as laparoscopy is not

contraindicated, we believe that this surgical approach may be safer for the operating team while the patient has the benefits of minimally invasive surgery. Evidence-based research in this field is needed for definitive determination of safety.

DECREASED MORTALITY OF COVID-19 WITH RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS THERAPY IN PATIENTS WITH HYPERTENSION: A META-ANALYSIS

Guo X, Zhu Y, Hong Y.. Hypertension. 2020 May 27. doi: 10.1161/HYPERTENSIONAHA.120.15572.

Online ahead of print.

Level of Evidence: 2

BLUF

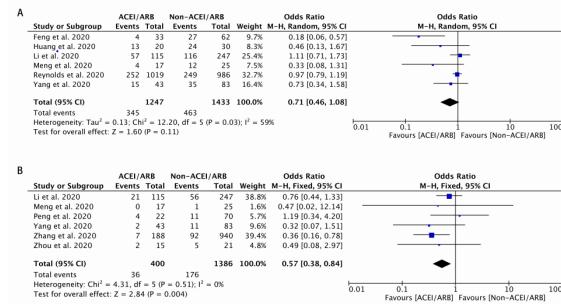
This article details a meta-analysis of 9 studies comprising of 3,936 patients which determined whether patients with hypertension and concurrent COVID-19 infection might benefit from angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) therapy. The results indicated that "ACEI/ARB therapy did not aggravate disease severity of COVID-19" (figure A) and that ACEI/ARB can actually "decrease the mortality of COVID-19" (figure B) in COVID-19 patients with concurrent hypertension.

ABSTRACT

The coronavirus disease 2019 (COVID-19) is caused by the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), having gradually developed into a pandemic and endangered global health. The continued use of angiotensin converting enzyme inhibitor (ACEIs) and angiotensin II receptor blockers (ARBs) which are part of renin-angiotensin-aldosterone system (RAAS) inhibitors in COVID-19 patients with hypertension has become controversial. We conducted a meta-analysis by searching Pubmed, Web of Science, Scopus and Embase up to 13 May 2020. Data analyses were performed by the Cochrane Collaboration's Review Manager 5.3 software. Finally, we included 9 studies comprising 3936 patients with hypertension and COVID-19 infection. Compared with non-ACEI/ARB treatment, ACEI/ARB treatment was not associated with disease severity (OR 0.71, 95 % CI 0.46-1.08, P 0.11, I² 59%) but was related to lower mortality of COVID-19 in patients with hypertension (OR 0.57, 95 % CI 0.38-0.84, P 0.004, I² 0). In summary, ACEI/ARB therapy did not aggravate disease severity of COVID-19. Besides, ACEI/ARB therapy can decrease the mortality of COVID-19. Current evidence suggested that RAAS inhibitors should be continued in COVID-19 patients with hypertension. Future well-designed randomized controlled trials are needed to confirm these findings.

FIGURES

Figure. Forest plots of **A** disease severity and **B** mortality in the ACEI/ARB versus the non-ACEI/ARB groups in COVID-19 patients with hypertension



CURRENT DIAGNOSTICS

MOLECULAR, SEROLOGICAL, AND BIOCHEMICAL DIAGNOSIS AND MONITORING OF COVID-19: IFCC TASKFORCE EVALUATION OF THE LATEST EVIDENCE

Bohn MK, Lippi G, Horvath A, Sethi S, Koch D, Ferrari M, Wang CB, Mancini N, Steele S, Adeli K..

Clin Chem Lab Med. 2020 May 27:/j/cclm.ahead-of-print/cclm-2020-0722/cclm-2020-0722.xml. doi:

10.1515/cclm-2020-0722. Online ahead of print.

Level of Evidence: Other

BLUF

A collective review of the latest evidence on molecular, serological, and biochemical testing for COVID-19 was conducted by the International Federation of Clinical Chemistry and Laboratory Medicine Task Force.

Laboratory diagnostics remain crucial for understanding infectivity, monitoring disease progression, and guiding therapy.

- Molecular testing: Nucleic acid amplification tests are currently the gold-standard for diagnosing suspected cases of COVID-19, of which real-time reverse-transcriptase polymerase chain reaction is most commonly employed.
- Pre-analytical considerations: Both upper and lower respiratory tract specimens are suitable for collection. Testing should be employed when viral load is potentially at its peak. For throat swabs, viral load is maximal in first 5 days after symptom onset.
- Analytical considerations: Viral recombination or mutation may affect accuracy of testing.
- Serology testing: Includes analyses of plasma, serum, or whole blood for detecting antibodies specific to SARS-CoV-2 antigens. Common methods include disposable immunochromatographic lateral flow assays, enzyme-linked immunosorbent assays, or chemiluminescent immunoassays.
- Pre-analytical considerations: Seroconversion occurs between 7 and 14 days after symptom onset. Sensitivity of tests may differ considerably among different clinical populations.
- Analytical considerations: Cross-reactivity is high among SARS-CoV-2 samples.
- Biochemical monitoring: Biochemical, hemotological, and immunohistochemical laboratory testing is routinely employed to monitor disease progression and severity and guide treatment. Inflammatory, cardiac, hepatic, and renal biomarkers are monitored to evaluate organ function and immune response.

ABSTRACT

The global coronavirus disease 2019 (COVID-19) has presented major challenges for clinical laboratories, from initial diagnosis to patient monitoring and treatment. Initial response to this pandemic involved the development, production, and distribution of diagnostic molecular assays at an unprecedented rate, leading to minimal validation requirements and concerns regarding their diagnostic accuracy in clinical settings. In addition to molecular testing, serological assays to detect antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are now becoming available from numerous diagnostic manufacturers. In both cases, the lack of peer-reviewed data and regulatory oversight, combined with general misconceptions regarding their appropriate use, have highlighted the importance of laboratory professionals in robustly validating and evaluating these assays for appropriate clinical use. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Task Force on COVID-19 has been established to synthesize up-to-date information on the epidemiology, pathogenesis, and laboratory diagnosis and monitoring of COVID-19, as well as to develop practical recommendations on the use of molecular, serological, and biochemical tests in disease diagnosis and management. This review summarizes the latest evidence and status of molecular, serological, and biochemical testing in COVID-19 and highlights some key considerations for clinical laboratories operating to support the global fight against this ongoing pandemic. Confidently this consolidated information provides a useful resource to laboratories and a reminder of the laboratory's critical role as the world battles this unprecedented crisis.

FIGURES

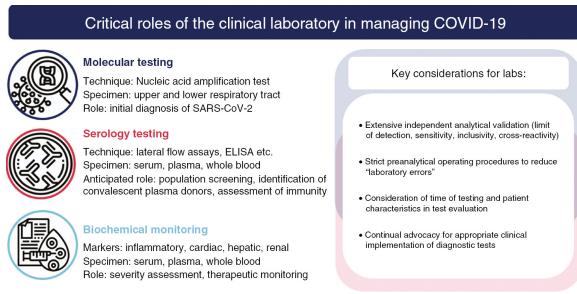


Figure 1. Overview of the key roles of the clinical laboratory in managing COVID-19.

DEVELOPMENTS IN DIAGNOSTICS

DIAGNOSTIC PERFORMANCE OF IMMUNOCHROMATOGRAPHY ASSAY FOR RAPID DETECTION OF IGM AND IGG IN CORONAVIRUS DISEASE 2019

Choe JY, Kim JW, Kwon HH, Hong HL, Jung CY, Jeon CH, Park EJ, Kim SK.. J Med Virol. 2020 May 26. doi: 10.1002/jmv.26060. Online ahead of print.

Level of Evidence: 3

BLUF

A prospective cohort study of 149 subjects (70 positive, 79 negative for COVID-19 via reverse transcriptase [RT]-PCR) conducted in Daegu, Republic of Korea found that a specific immunochromatography-based assay for COVID-19 had a sensitivity and specificity for IgM or IgG antibodies of 92.9% (95% Confidence Interval [CI] 84.1–97.6) and 96.2% (95% CI 89.3–99.2), respectively, with 95.6% PPV and 93.8% NPV. This data indicates that this rapid COVID-19 IgM/IgG assay would be a useful and practical diagnostic assay for COVID-19.

ABSTRACT

Serologic assays have been developed to detect infection with coronavirus disease 2019 (COVID-19). This study was conducted to evaluate the diagnostic performance of an immunochromatography-based assay of human serum for COVID-19. The present study enrolled 149 subjects who had been tested by real-time reverse transcription-polymerase chain reaction (RT-PCR) for COVID-19 and were classified into two groups: 70 who were positive for COVID-19 and 79 who were negative for COVID-19 based on RT-PCR. An immunochromatography-based COVID-19 IgG/IgM rapid test on the sera of the study population was applied to measure the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) curve compared to RT-PCR, with a 95% confidence interval (CI). IgM or IgG antibodies were detected in 65 subjects (92.9%) classified as positive for COVID-19 and in 3 subjects (3.8%) classified as negative for COVID-19. The sensitivity and specificity percentages for IgM or IgG antibodies were 92.9% (95% CI 84.1 - 97.6) and 96.2% (95% CI 89.3 - 99.2), respectively, with 95.6% PPV and 93.8% NPV. The PPV rapidly improved with increasing disease prevalence from 19.8% to 96.1% in the presence of either IgM or IgG, while the NPV remained high with a change from 99.9% to 93.1%. The area under the ROC curve was 0.945 (95% CI 0.903 - 0.988) for subjects with either IgM or IgG positivity. In conclusion, the immunochromatography-based COVID-19 IgG/IgM rapid test is a useful and practical diagnostic assay for detection of COVID-19, especially in the presence of IgM or IgG antibodies. This article is protected by copyright. All rights reserved.

FIGURES

Table 3. Comparison of diagnostic values for immunoassay

Immunochromatography					
	IgM or IgG		IgM and IgG		
	Values	95% CI	Values	95% CI	
Sensitivity	92.9%	84.1 to 97.6	65.7%	53.4 to 76.7	
Specificity	96.2%	89.3 to 99.2	100.0%	95.4 to 100.0	
Positive Predictive Value	95.6%	87.7 to 98.5	100.0%		
Negative Predictive Value	93.8%	86.7 to 97.3	76.7%	70.4 to 82.0	

Table 3: Comparison of diagnostic values for immunoassay

EVALUATING THE USE OF POSTERIOR OROPHARYNGEAL SALIVA IN A POINT-OF-CARE ASSAY FOR THE DETECTION OF SARS-COV-2

Chen JH, Yip CC, Poon RW, Chan KH, Cheng VC, Hung IF, Chan JF, Yuen KY, To KK.. Emerg Microbes Infect. 2020 May 27:1-14. doi: 10.1080/22221751.2020.1775133. Online ahead of print.
Level of Evidence: 3

BLUF

This study, by researchers at Queen Mary Hospital in Hong Kong, compared point-of-care RT-PCR (Xpert Xpress) assay performance on posterior oropharyngeal saliva samples versus nasopharyngeal swabs (NPS) collected from 58 COVID-19 positive patients. They found no significant difference in the detection rate between NPS and saliva samples, suggesting a potential for use of saliva specimens for SARS-CoV-2 detection.

ABSTRACT

During the Coronavirus disease 2019 (COVID-19) pandemic, logistic problems associated with specimen collection limited the SARS-CoV-2 testing especially in the community. In this study, we assessed the use of posterior oropharyngeal saliva as specimens for the detection of SARS-CoV-2 in an automated point-of-care molecular assay. Archived nasopharyngeal swab (NPS) and posterior oropharyngeal saliva specimens of 58 COVID-19 patients were tested with the Xpert Xpress SARS-CoV-2 assay. SARS-CoV-2 was detected in either NPS or saliva specimens of all patients. Among them, 84.5% (49/58) tested positive in both NPS and saliva, 10.3% (6/58) tested positive in NPS only, and 5.2% (3/58) tested positive in saliva only. No significant difference in detection rate was observed between NPS and saliva (McNemar's test $p=0.5078$). The detection rate was slightly higher for N2 (NPS 94.8% and Saliva 93.1%) than that of the E gene target (Saliva:89.7% vs 82.8%) on both specimen types. Significant earlier median Ct value was observed for NPS comparing to that of saliva on both E (26.8 vs 29.7, $p=0.0002$) and N2 gene target (29.3 vs 32.3, $p=0.0002$). The median Ct value of E gene target was significantly earlier than that of the N2 gene target for both NPS (26.8 vs 29.3, $p<0.0001$) and saliva (29.7 vs 32.3, $p<0.0001$). In conclusion, posterior oropharyngeal saliva and NPS were found to have similar detection rates in the point-of-care test for SARS-CoV-2 detection. Due to the easy collection of posterior oropharyngeal saliva, the use of saliva as an alternative specimen type for SARS-CoV-2 detection is recommended.

DEVELOPMENTS IN TREATMENTS

A HUMAN NEUTRALIZING ANTIBODY TARGETS THE RECEPTOR BINDING SITE OF SARS-COV-2

Shi R, Shan C, Duan X, Chen Z, Liu P, Song J, Song T, Bi X, Han C, Wu L, Gao G, Hu X, Zhang Y, Tong Z, Huang W, Liu WJ, Wu G, Zhang B, Wang L, Qi J, Feng H, Wang FS, Wang Q, Gao GF, Yuan Z, Yan J.. *Nature*. 2020 May 26. doi: 10.1038/s41586-020-2381-y. Online ahead of print.

Level of Evidence: 5

BLUF

In this basic science research article, the authors identified two human monoclonal antibodies, isolated from a COVID-19 patient, with neutralizing activity against the SARS-CoV-2 S-protein receptor binding domain. The authors then sequenced, biochemically characterized, and performed in vitro and in vivo SARS-CoV-2 infection experiments with these antibodies and found they were both effective in limiting SARS-CoV-2 infection in multiple experimental models. While the results are limited in their direct translatability to human treatment for COVID-19, the structural and biochemical data provided will be enormously useful in furthering development of antibody therapy for COVID-19.

ABSTRACT

An outbreak of the coronavirus disease 2019 (COVID-19)1-3, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)4 spread globally. Countermeasures are needed to treat and prevent further dissemination of the virus. In this study, we report the isolation of 2 specific human monoclonal antibodies (MAbs) from a convalescent COVID-19 patient. CA1 and CB6 demonstrated potent SARS-CoV-2-specific neutralization activity in vitro against SARS-CoV-2. In addition, CB6 inhibited SARS-CoV-2 infection in rhesus monkeys at both prophylactic and treatment settings. Further structural studies revealed that CB6 recognizes an epitope that overlaps with angiotensin converting enzyme 2 (ACE2)-binding sites in SARS-CoV-2 receptor binding domain (RBD), thereby interfering with the virus/receptor interactions by both steric hindrance and direct interface-residue competition. Our results suggest CB6 deserves further clinical translation.

REMDESIVIR FOR TREATMENT OF COVID-19: COMBINATION OF PULMONARY AND IV ADMINISTRATION MAY OFFER ADDITIONAL BENEFIT

Sun D.. *AAPS J*. 2020 May 26;22(4):77. doi: 10.1208/s12248-020-00459-8.

Level of Evidence: 5

BLUF

An analysis of remdesivir therapy in COVID-19 by Duxin Sun from the University of Michigan suggests that a study on the combination of pulmonary delivery, specifically nebulizer inhalation, and IV administration of remdesivir should be performed for possible increased efficacy. This suggestion was posed while considering two main observations from reviewing current monkey model studies:

1. Plasma concentrations of the remdesivir, a prodrug of nucleoside monophosphate, and its active metabolites (monophosphate, alanine metabolite, nucleoside) may not be associated to its effectiveness as a clinical therapy (Table 1)
2. The concentrations of remdesivir and its metabolites are unlikely to be sufficient enough to eliminate the COVID-19 virus in the lungs with the currently utilized IV doses (Table 3)

ABSTRACT

Remdesivir is one of the most promising drugs to treat COVID-19 based on the following facts: remdesivir has a broad-spectrum antiviral mechanism of action; it demonstrated in vitro activity against SARS-CoV-2 and in

vivo efficacy in animal models against the similar coronavirus MERS-CoV; its safety profile has been tested in Ebola patients and in compassionate use in COVID-19 patients. Currently, remdesivir is being investigated in ten randomized controlled trials against COVID-19. The dose regimen of remdesivir is an IV loading dose of 200 mg on day 1 followed by daily IV maintenance doses of 100 mg for 5-9 days. Based on our data analysis, however, remdesivir with IV administration alone is unlikely to achieve excellent clinical efficacy. This analysis is based on the following observations: plasma exposures of remdesivir and its active metabolite are unlikely to be correlated with its clinical efficacy; remdesivir and its active metabolites are unlikely to be adequate in the lung to kill the SARS-CoV-2 virus. Even if remdesivir demonstrates benefits in the current randomized controlled trials, its efficacy may be limited. We suggest that a combination of an IV and pulmonary delivery dose regimen should be studied immediately to realize a potentially more effective antiviral therapy against COVID-19. Graphical abstract.

FIGURES

	Remdesivir (inactive) plasma	Alanine metabolite (inactive) plasma	Nucleoside (Nuc) (active) plasma	Nucleoside triphosphate (Nuc-TP) (active) plasma	Nucleoside triphosphate (Nuc-TP) (active) PBMC
0.5 h	~1 μM ~0.1 μM	<2 μM <0.5 μM	~1 μM ~1 μM	ND	ND
2 h	ND	<0.5 μM	~1 μM	ND	30–40 μM
8 h	ND	<0.2 μM	~0.4 μM	ND	20–30 μM
24 h	ND	ND	<0.2 μM	ND	20–30 μM

ND, not detected

Table I. Drug and Metabolite Concentrations in Plasma And PBMCs 2–24 h After an IV 10-mg/kg Dose in Monkey [1]

	Remdesivir (inactive) plasma	Alanine metabolite (inactive) plasma	Nucleoside (Nuc) (active) plasma	Nucleoside triphosphate (Nuc-TP) (active) plasma	Nucleoside triphosphate (Nuc-TP) (active) PBMC
0.5 h	~1 μM ~0.1 μM	<2 μM <0.5 μM	~1 μM ~1 μM	ND	ND
2 h	ND	<0.2 μM	~0.4 μM	ND	30–40 μM
8 h	ND	ND	<0.2 μM	ND	20–30 μM
24 h	ND	ND	<0.2 μM	ND	20–30 μM

ND, not detected

Table III. Concentrations of Remdesivir and Its Active Metabolite in Monkey Lung Following an IV 10-mg/kg Dose [1] and Predicted Concentration in the Human Lung After an IV 200-mg Dose

	2 h		24 h		Human lung tissue	Human lung intracellular	IC ₅₀	IC ₅₀
	Monkey lung tissue	Monkey lung intracellular	Monkey lung tissue	Monkey lung intracellular				
Remdesivir	ND	ND	ND	ND	ND	ND	0.77 μM	1.76 μM
Nuc-TP	1.5 μM μM (estimate)	3.3 μM (estimate)	0.8 μM μM (estimate)	1.7 μM (estimate)	~2–5 μM (estimate)	~4–10 μM (estimate)	7.7 μM (estimate)	17.5 μM (estimate)

ND, not determined; Nuc-TP, nucleoside triphosphate

Table III. Concentrations of Remdesivir and Its Active Metabolite in Monkey Lung Following an IV 10-mg/kg Dose [1] and Predicted Concentration in the Human Lung After an IV 200-mg Dose

LYMPHOPENIA IN COVID-19: THERAPEUTIC OPPORTUNITIES

Fathi N, Rezaei N.. Cell Biol Int. 2020 May 27. doi: 10.1002/cbin.11403. Online ahead of print.

Level of Evidence: 5

BLUF

In this literature review, authors from Tehran, Iran highlight the role of hypercytokinemia, T cell and NK cell lymphopenia, exhausted lymphocytes, and apoptosis of T and NK cells in COVID-19 and their association with disease severity. The authors also identify promising drug therapies for COVID-19 currently used to treat viruses with similar pathophysiology profiles as SARS-CoV-2 (Table 1).

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is uncontrollably spread all over the world. The host immune responses strongly try to confront it with all the potential cells and cytokines. With chronically condition of SARS-CoV-2, NK cells and T cells become exhausted and decreasing their count leads to lymphopenia. Inability to eradicate the infected organ makes hyper-initiation of the immune system, which

releases the excessive inflammatory cytokines to compensate the exhausted one as well as the low lymphocytes counts; it consequently lead to the cytokine storm syndrome. These mechanisms and the potential therapeutic targeting are discussed in this paper. This article is protected by copyright. All rights reserved.

FIGURES

Table 1. Promising therapies that used for other viruses with distinctive pathobiology condition.

	Drugs, Biological or chemical modifiers
Hypercytokinemia	NSAIDs (Bozza et al., 2008; Carter, 2007), Janus kinase (JAK) inhibition, IL-1 and IL-6 receptor antagonist, SIP1R agonists (Oldstone & Rosen, 2014), p38 and MAPK inhibitors (Johnson et al., 2014), Zanamivir + COX-2 inhibitors (Walsh et al., 2011), IVIG
T cell and NK cell lymphopenia	Cyclophosphamide followed by fludarabine (Cooley, June, Schoenberger, & Miller, 2007), IL-1 receptor antagonist, IL-7 agonists, HSCT
Exhausted lymphocytes	Histone deacetylase(iv) (Zhang et al., 2014), Blockade PD-1 and or PD-L1 (Yi, Cox, & Zajac, 2010), TIM-3, CTLA-4, LAG-3, 2B4, BTLA and TRAIL, Blocking NKG2a or its ligand (HLA-E)
Apoptosis of T and NK cells	Resveratrol, Coenzyme Q10, Flavopiridol, Roscovitine, Simvastatin, Flurbiprofen, Rosiglitazone, Minocycline (X Sureda et al., 2011), PD1/PD-L1 inhibitors

NSAID: Non-steroidal anti-inflammatory drug; iv: in vitro study; HSCT: hematopoietic stem cell transplantation; IVIG: intravenous immunoglobulin

Table 1. Promising therapies that used for other viruses with distinctive pathobiology condition.

MENTAL HEALTH & RESILIENCE NEEDS

IMPACT ON PUBLIC MENTAL HEALTH

COVID-19-RELATED ANXIETY PREDICTS SOMATIC SYMPTOMS IN THE UK POPULATION

Shevlin M, Nolan E, Owczarek M, McBride O, Murphy J, Gibson Miller J, Hartman TK, Levita L, Mason L, Martinez AP, McKay R, Stocks TVA, Bennett KM, Hyland P, Bentall RP.. Br J Health Psychol. 2020 May 27. doi: 10.1111/bjhp.12430. Online ahead of print.

Level of Evidence: 1

BLUF

In this cross-sectional study, the authors surveyed 2,025 people representative of the general UK population from March 23 to 28, 2020 to determine if there was a relationship between increased anxiety from the COVID-19 pandemic and somatic symptoms. Analysis of the survey concluded that there was a positive correlation with anxiety and all somatic symptoms surveyed using the Patient Health Questioner (PHQ-15; Tables 1-2), suggesting possible additional public health strains that may result from this pandemic.

ABSTRACT

This study aimed to estimate the association between anxiety associated with COVID-19 and somatic symptoms, using data from a large, representative sample ($N = 2,025$) of the UK adult population. Results showed that moderate to high levels of anxiety associated with COVID-19 were significantly associated with general somatic symptoms and in particular with gastrointestinal and fatigue symptoms. This pattern of associations remained significant after controlling for generalized anxiety disorder (GAD), pre-existing health problems, age, gender, and income. This is the first evidence that anxiety associated with COVID-19 makes a unique contribution to somatization, above and beyond the effect of GAD.

FIGURES

Table 1. Descriptive statistics and correlations for all study variables											
	Age	Gender (Female)	Income	Health Problem	GAD-7 ≥ 10	COVID-19 Anxiety	PHQ: Pain	PHQ: Gastro	PHQ: Cardio	PHQ: Fatigue	PHQ total
Gender (female)	.261***										
Income	.008*	.158***									
Health problem	-.112**	-.040	-.072*								
GAD-7 ≥ 10	-.237***	.104***	-.119***	.032**							
COVID-19 Anxiety	.064**	.113***	.053*	.085*	.260***						
PHQ: Pain	.125***	.125***	.125***	.125***	.289***	.136***					
PHQ: Gastro	-.242***	.097***	-.090***	.135***	.340***	.072**	.642***				
PHQ: Cardio	-.197***	-.069*	-.050*	.135***	.340***	.072**	.642***	.704***			
PHQ: Fatigue	-.143***	.137***	-.088***	.139***	.384***	.166***	.552***	.614***	.495***		
PHQ total	.240***	.205***	-.098***	.155***	.411***	.160***	.552***	.614***	.495***	.700***	
Mean(N)	45.446	1.047	347	438	67.724	942	1.140	634	1.001	3.718	
SD(%)	15.901	(51.9%)		(17.1%)	(21.6%)	24.596	1.337	1.693	1.431	1.182	4.767

Note. * $p < .05$; ** $p < .01$; *** $p < .001$.

Table 2. Unstandardized regression coefficients from models predicting PHQ-15 Scale and Subscale Scores

	Pain	Gastro	Cardio	Fatigue	Total scale
<i>Model 1</i>					
COVID-19 anxiety					
Quintile 1	—	—	—	—	—
Quintile 2	0.140	0.339**	0.231	0.178*	0.889***
Quintile 3	0.189*	0.340***	0.119	0.281***	0.931***
Quintile 4	0.181*	0.289**	0.064	0.267**	0.801*
Quintile 5	0.427***	0.594***	0.251*	0.590***	1.863***
R ²	.011*	.012**	.004	.027***	.013**
<i>Model 2</i>					
COVID-19 anxiety					
Quintile 1	—	—	—	—	—
Quintile 2	0.103	0.249*	0.164	0.122	0.637*
Quintile 3	0.141	0.251*	0.058	0.196**	0.647*
Quintile 4	0.121	0.230*	0.014	0.179*	0.544
Quintile 5	0.232*	0.327**	0.058	0.337***	0.954**
Control variables					
Age	-.0004*	-.019***	-.013***	-.005**	-.041***
Gender (female)	-.074	0.021	-.305***	0.123*	-.024
Income	-.065***	-.052*	-.022	-.028	-.017*
Health problem	0.262**	0.395***	0.360***	0.238**	1.255***
GAD-7 ≥ 10	0.858***	1.243***	1.059***	0.971***	4.131***
R ²	.103***	.172***	.152***	.169***	.198***

Note. * $p < .05$; ** $p < .01$; *** $p < .001$.

FLATTENING THE MENTAL HEALTH CURVE: COVID-19 STAY-AT-HOME ORDERS ARE ASSOCIATED WITH ALTERATIONS IN MENTAL HEALTH SEARCH BEHAVIOR IN THE UNITED STATES

Jacobson N, Lekkas D, Price G, Heinz MV, Song M, O'Malley AJ, Barr PJ.. JMIR Ment Health. 2020 May 26. doi: 10.2196/19347. Online ahead of print.

Level of Evidence: Other

BLUF

Dartmouth College researchers analyzing public Google Trends search data from March 16 to March 23, 2020 discovered that stay-at-home orders were associated with a significant "flattening of the curve" for mental-health related searches related to suicidal ideation, anxiety, negative thoughts, and sleep disturbances (Table 2 and Figure 4). Their analysis suggests the COVID-19 pandemic may be associated with increasing mental health concerns, which then leveled-off after the implementation of state-wide stay-at-home orders.

ABSTRACT

BACKGROUND: COVID-19 has led to dramatic changes globally in persons' everyday lives. To combat the pandemic, many governments have implemented social distancing, quarantine, and stay-at-home orders. There is limited research on the impact of such extreme measures on mental health.

OBJECTIVE: The goal of the present study was to examine whether stay-at-home orders produced differential changes in mental health symptoms using internet search queries at a national scale.

METHODS: In the United States, individual states vary in their adoption of measures to reduce the spread of COVID-19; as of March 23, 2020, eleven of the fifty states had issued stay-at-home orders. The staggered rollout of stay-at-home measures across the U.S. allows us to investigate whether these measures impact mental health by exploring variations in mental health search queries across the states. The current manuscript examines the changes in mental health search queries on Google between March 16-23, 2020 across each state and Washington D.C. Specifically, the current manuscript examines differential change in mental health searches based on patterns of search activity following issuance of stay-at-home orders in these states compared to all other states. Participants included all persons who searched mental health terms in Google between March 16-23. Between March 16-23, eleven states underwent stay-at-home orders to prevent the transmission of COVID-19. Outcomes included search terms measuring anxiety, depression, obsessive-compulsive, negative thoughts, irritability, fatigue, anhedonia, concentration, insomnia, and suicidal ideation.

RESULTS: Analyzing over 10 million search queries using generalized additive mixed models, the results suggested that the implementation of stay-at-home orders are associated with a significant flattening of the curve for searches for suicidal ideation, anxiety, negative thoughts, and sleep disturbances with the most prominent flattening associated with suicidal ideation and anxiety.

CONCLUSIONS: These results suggest that, despite decreased social contact, mental health search queries increased rapidly prior to the issuance of stay-at-home orders, and these changes dissipated following the announcement and enactment of these orders. Although more research is needed to examine sustained effects, these results suggest mental health symptoms were associated with an immediately leveling off following the issuance of stay-at-home orders.

FIGURES

Search Term	edf	Ref.df	F	p-value
anxiety	3.969	3.999	12.846	<.001*
depression	1.788	2.073	2.765	0.061
ocd	1.000	1.000	0.189	0.664
hopeless	3.791	3.955	14.519	<.001*
angry	2.612	2.830	1.775	0.189
afraid	4.000	4.000	16.192	<.001*
apathy	1.000	1.000	23.870	<.001*
worthless	3.888	3.985	4.349	0.002*
worried	1.000	1.000	1.292	0.256
restless	3.905	3.985	4.314	0.002*
irritable	3.450	3.687	4.108	0.002*
tense	1.000	1.000	0.399	0.528
scattered	1.046	1.077	16.123	<.001*
tired	1.000	1.000	9.113	0.003*
avoiding	2.672	2.865	5.301	<.001*
procrastinate	1.556	1.800	7.057	0.005*
insomnia	3.916	3.993	10.209	<.001*
suicidal	3.970	3.999	13.446	<.001*
suicide	3.996	4.000	20.314	<.001*

Table 2. Changes in search behavior related to stay-at-home orders. This table corresponds to the test of the term s2 in the model (which estimates the effects of the stay-at-home policy intervention as a deviation from the state-specific counterfactual trend that would have occurred had there not been a stay-at-home order issued). Significant values represent the difference between what would have happened in a state with a stay-at-home policy intervention and what would have happened in the absence of that intervention. EDF stands for the model estimated residual degrees of freedom, where 1 corresponds to a linear deviation from the time trend.

Ref.df refers to the number of model data minus the model degrees of freedom

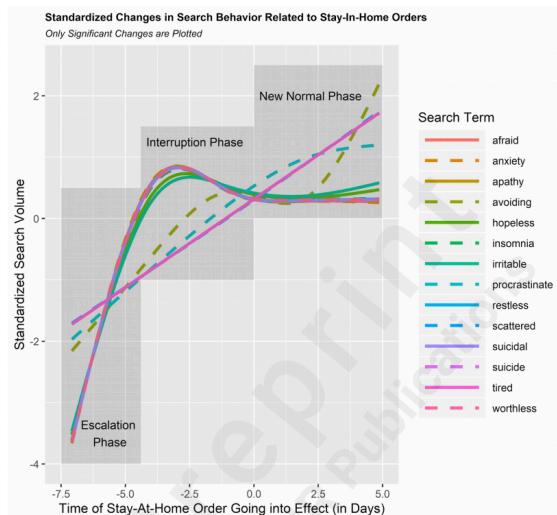


Figure 4. This plot depicts the standardized changes in search patterns relative to the orders going into effect. Values are normalized to reflect the relative change in these searches across time. Negative time of stay-at-home values reflect the time before the stay-at-home orders go into effect, and positive values reflect the time following the order going into effect. Values are standardized to show the relative pattern of the effect. The escalation phase designates approximately 4 days prior to the stay-at-home orders going into effect. The interruption phase spans between approximately 4 days and 0 days before the order

RESOURCES

COVID-19 PANDEMIC - AN AFRICAN PERSPECTIVE

Lone SA, Ahmad A.. *Emerg Microbes Infect.* 2020 May 27;1-28. doi: 10.1080/22221751.2020.1775132.

Online ahead of print.

Level of Evidence: Other

BLUF

This review done by infectious disease experts in South Africa analyzed 54 articles published between January 1 and April 18, 2020 provides an overview of etiology, epidemiology, vulnerability, and economic impact of the COVID-19 pandemic in African countries, urging for global support in various areas to combat this pandemic.

SUMMARY

General Information:

- African continents contributed 90 genomic sequences of SARS-CoV-2 out of 7,700 genomic sequences collected worldwide. More data needs to be submitted in order to help develop vaccines that will address African-specific strains.
- By April 18th, there were a total of 19,895 confirmed cases in Africa with a mortality rate of 5.1%, and cases were seen in all countries of Africa except for Lesotho and Comoros. South Africa, Egypt, Morocco, Algeria, and Cameroon are most affected so far.

Vulnerability:

- Infectious disease burden (HIV, HBV, and HCV) and noncommunicable disease burden are already very high, placing the African population at relatively immunocompromised states
- Weak healthcare sectors involving infrastructures and trained workforce place additional challenges
- Seasonal respiratory viruses are anticipated to circulate from May through September, 2020

Preparedness:

- By March 6,2020, only 43 African countries were able to test for COVID-19
- Many African countries have low capacity in managing the disease burden, but options to learn from other countries and some financial support from various agencies was scheduled

Economic Impact:

- Inflation of the African markets due to reduction of importation from China
- Countries relying on crude oil price were hit by reduced oil consumption globally
- Global travel restrictions and port closures reduced the demand and investment for the mining industry
- Reduced tourism

ABSTRACT

The recently emerged novel coronavirus, "severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)", caused a highly contagious disease called coronavirus disease 2019 (COVID-19). The virus was first reported from Wuhan city in China in December, 2019, which in less than three months spread throughout the globe and was declared a global pandemic by the World Health Organization (WHO) on 11th of March, 2020. So far, the ongoing pandemic severely damaged the world's most developed countries and is becoming a major threat for low- and middle-income countries. The poorest continent, Africa with the most vulnerable populations to infectious diseases, is predicted to be significantly affected by the ongoing COVID-19 outbreak. Therefore, in this review we collected and summarised the currently available literature on the epidemiology, etiology, vulnerability, preparedness and economic impact of COVID-19 in Africa, which could be useful and provide

necessary information on ongoing COVID-19 pandemics in the continent. We also briefly summarised the concomitance of the COVID-19 pandemic and global warming.

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