The Daily COVID-19 Literature Surveillance Summary

July 27, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Epidemiology

- Authors at Hubei Provincial Hospital of Traditional Chinese Medicine in Wuhan, China conducted a retrospective study of 4,254 cases across 6 types of nucleic acid collection sites and found that the highest proportion SARS-CoV-2 positive individuals at hospital wards (24.71%, n=84), close COVID-19 contact sites had the lowest (0.17%, n=1), and the most afflicted age group was middle-aged to elderly, suggesting a need for continued development in prevention education and safety protocols.
- Researchers modeled the transmission of COVID-19 across Europe from Google and Vodafone data and found a greater drop in local COVID-19 cases in synchronous simulations (each country following the same intervention) compared to unsynchronized ones (elimination rate 5%). While the researchers acknowledge a population bias in the data, they recommend that countries coordinate lockdown efforts to further improve transmission rates.

Understanding the Pathology

- A literature review examining the neuroinvasive potential of SARS-CoV-2 showed potential mechanisms of central nervous system (CNS) infection include blood-brain barrier (BBB) disruption and infection of peripheral nerves leading to trafficking of virions into the CNS, leading authors to believe a government regulated registry to routinely track COVID-19 patients with neurological manifestations may be critical to determine long-term health consequences, and note the possibility of neurodegenerative disorders as seen with other neurotropic RNA viruses.

Transmission & Prevention

- Physicians at Massachusetts General Hospital, Boston, review a recent study by Haver et al. (2020) regarding serosurveillance efforts to measure incidence of COVID-19 and suggest that the minimal herd immunity threshold in the United States is unlikely to be met as uncontrolled cases are increasing every day, in addition to evidence suggesting that acquired immunity may be temporary and short-lived. They propose implementation of active surveillance strategies including mass COVID-19 testing to better drive public health initiatives to contain the pandemic.

Management

- A retrospective cohort study of 398 hospitalized COVID-19 patients with cancer (n=45) and without cancer (n=353) at Beth Israel Deaconess Medical Center, investigated the incidences of thrombotic events at day 28 of hospitalization, and though acknowledging the study's limitation in power, reported no significant differences between active cancer cohort, 14.2% (95% CI, 4.7%-28.7%), and non-cancer cohort, 18.2% (95% CI, 10.2%-27.9%). The researchers believe the overall elevated thrombo-inflammatory state of COVID-19 outcompetes a more moderate hypercoagulable state of cancer.

Adjusting Practice During COVID-19

- A review from authors in India of articles making recommendations on the management of solid tumors, hematologic cancers, and radiation/chemotherapy treatment during the pandemic found highly variable recommendations revealing the importance of examining new literature with scrutiny and also highlighting the need for sharing information to collect high quality and coherent data on COVID-19.
- A population-based cohort study using United Kingdom Biobank data of patients with mental illness, rates of COVID-19 testing, and diagnoses in individuals with and without psychiatric disorders found that patients with psychiatric illnesses were more frequently tested and had lower chances of testing positive than those without - possibly due to higher anxiety about contracting COVID-19, higher frequency of comorbid conditions or somatic symptoms, and increased social isolation.

R&D: Diagnosis and Treatments

- Authors from Geneva, Switzerland assessed the diagnostic accuracy of Augurix COVID-19 IgG rapid diagnostic test (RDT) by analyzing blood samples from 46 confirmed SARS-CoV-2 cases and 45 asymptomatic donors who did not receive testing and found whole blood IgG Augurix RDT had 88% sensitivity, 98% specificity, 97% PPV, and 94% NPV compared to recombinant immunofluorescence assay on plasma with increasing diagnostic accuracy after 14 days post-diagnosis, making IgG Augurix RDT in whole blood a good diagnostic tool for SARS-CoV-2 in high COVID-19 prevalence settings when standard diagnostic serology is unavailable.

Mental Health and Resilience Needs

- Authors at the Department of Neuropsychiatry, Hyogo College of Medicine in Japan conducted a cross sectional study of full remitted (FR, n=24) and partial remitted (PR, n=36) patients with obsessive-compulsive disorder (OCD) and found that compared to pre-pandemic values, Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores in the FR OCD group increased from an average of 5.5 to 5.7 and from 12.2 to 13 in the PR OCD group, while 6.7% of participants (n=4) exhibited additional/renewed OCD symptoms (contamination obsessions or washing compulsions). Authors suggest COVID-19 may induce health-anxiety based symptoms in full and partial remitted OCD patients and lead to acute impact on OCD severity and features.

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CLIMATE

GLOBAL

WHAT WENT WRONG: CORONA AND THE WORLD AFTER THE FULL STOP

Caduff C.. Med Anthropol Q. 2020 Jul 21. doi: 10.1111/maq.12599. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

This author from King's College in London expresses concern for the social and economic impact of worldwide lockdown orders, which he indicates were hastily and inappropriately enacted for some of the following reasons:
- Mathematical modeling with the worst possible outcome was used to guide policy in lieu of clinical evidence
- Media outlets focused attention on articles with the worst predictions, such as those regarding mortality rate, without considering issues with the peer-review process of these articles
- Policy makers failed to recognize the impact that healthcare infrastructure has on COVID-19 and thus generalized scenes of full hospitals in Italy to other countries.

He notes that strict national lockdown measures were implemented instead of strict testing, tracing, and isolating (which were successful in countries like South Korea and Germany) or lockdowns only of specific areas with higher rates of spread, and argues that the response to the pandemic should more carefully examine the potential costs to society by widespread lockdowns.

ABSTRACT

This article examines the global response to the Covid-19 pandemic. It argues that we urgently need to look beyond the virus if we want to understand the real seriousness of what is happening today. How did we end up in a space of thinking, acting, and feeling that has normalized extremes and is based on the assumption that biological life is an absolute value separate from politics? The author suggests that today's fear is fueled by mathematical disease modeling, neoliberal health policies, nervous media reporting, and authoritarian longings.

ANALYSIS OF THE POSITIVE RATE OF 4254 CASES OF COVID-19 NUCLEIC ACID TESTS IN DIFFERENT SITES IN WUHAN, CHINA

Deng K, Li H, Ma X, Yu B, Yi X, Chen Y, Tian B, Zhang Q.. J Med Virol. 2020 Jul 21. doi: 10.1002/jmv.26323. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

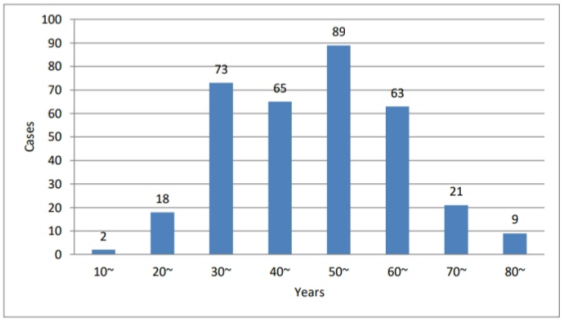
Authors at Hubei Provincial Hospital of Traditional Chinese Medicine in Wuhan, China conducted a retrospective study of 4,254 cases across 6 types of nucleic acid collection sites (Table 1) from 8 February to 7 March 2020 and found the highest proportion SARS-CoV-2 positive individuals (confirmed via reverse transcription polymerase chain reaction [RT-PCR]) at hospital wards (24.71%, n=84) while close COVID-19 contact sites had the lowest (0.17%, n=1), and the most afflicted age group was middle-aged to elderly (Figure 2). Authors highlight these at risk populations, suggesting a need for continued development in prevention education and safety protocols.

ABSTRACT

BACKGROUND: There's an outbreak of COVID-19 since December 2019, first in Wuhan. It has caused huge medical challenges to Hubei Province with currently more than 67 thousand confirmed cases till March 08, 2020. Identification, there is no clinically effective drug. Isolation and masks are essential to limit human-to-human transmission initially. The nucleic acid test (NAT) of COVID-19 currently was the most reliable established laboratory diagnosis method in clinical. METHODS: From February 8th, 2020 to March 7th, 2020, 4254 cases were collected for analysis at six nucleic acid collection sites in the community medical team of Hubei Provincial Hospital of Traditional Chinese Medicine, which cover almost all groups who need NAT in Wuhan. Distribution of positive rates in different sites by genders, ages or occupations were compared. RESULTS: The positive rates of different sites from high to low were: hospital wards (24.71%) > fever clinics (16.57%) > nursing homes (5.51%) > isolation hotels (5.30%) > rehabilitation stations (1.36%) > close contact sites (0.17%). The confirmed patients in isolation hotels, hospital ward and fever clinical were mainly middle-aged and elderly, and most of them were women. The positive rate in isolation hotels and fever clinics gradually decreased over time. There were no significant differences between genders among those six nucleic acid collection sites (P <0.05). CONCLUSIONS: The hospital wards have the highest positive rate; however, close contact sites have lowest one. Patients who are discharged from hospitals may still have potential risks. Middle-aged and older people remain the focus of epidemic prevention and control.

FIGURES

Table 1. The nucleic acid test results of nucleic acid collection sites.



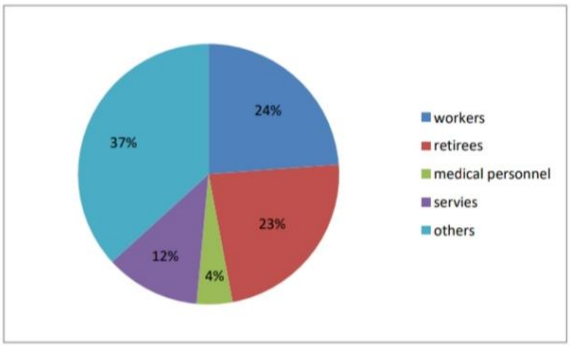


Figure 2. Age distribution of positive patients in hospital wards.

THE COVID-19 PANDEMONIUM CONTINUES: (WITHDRAWAL OF PUBLISHED CLINICAL STUDIES IN LANCET AND N ENGL J MED, 2020)

Woodcock BG.. Int J Clin Pharmacol Ther. 2020 Jul 10. doi: 10.5414/CP203848. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

In this editorial article, the German author discusses the retraction of two literature articles on the effective use of hydroxychloroquine/chloroquine for COVID-19 infection due to the adverse pulmonary and cardiovascular effects. They also make the argument that funding towards investigating this treatment option should have instead been directed towards COVID-19 tracking apps, of which Germany's Corona-Warn-App, is an example of.

MODELING

ASSESSING THE IMPACT OF COORDINATED COVID-19 EXIT STRATEGIES ACROSS EUROPE

Ruktanonchai NW, Floyd JR, Lai S, Ruktanonchai CW, Sadilek A, Rente-Lourenco P, Ben X, Carioli A, Gwinn J, Steele JE, Prosper O, Schneider A, Oplinger A, Eastham P, Tatem AJ.. Science. 2020 Jul 17:eabc5096. doi: 10.1126/science.abc5096. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

Researchers modeled the transmission of COVID-19 across Europe from Google and Vodafone data to conduct simulations such as travel restrictions versus free travel patterns. They found a greater drop in local COVID-19 cases in synchronous simulations (each country following the same intervention) compared to unsynchronous (elimination rate 5%) (Figure 4). While the researchers acknowledge a population bias in the data, they recommend that countries coordinate lockdown efforts to further improve transmission rates.

ABSTRACT

As rates of new COVID-19 cases decline across Europe due to non-pharmaceutical interventions such as social distancing policies and lockdown measures, countries require guidance on how to ease restrictions while minimizing the risk of resurgent outbreaks. Here, we use mobility and case data to quantify how coordinated exit strategies could delay continental resurgence and limit community transmission of COVID-19. We find that a resurgent continental epidemic could occur as many as 5 weeks earlier when well-connected countries with stringent existing interventions end their interventions prematurely. Further, we found that appropriate coordination can greatly improve the likelihood of eliminating community transmission throughout Europe. In particular, synchronizing intermittent lockdowns across Europe meant half as many lockdown periods were required to end community transmission continent-wide.

FIGURES

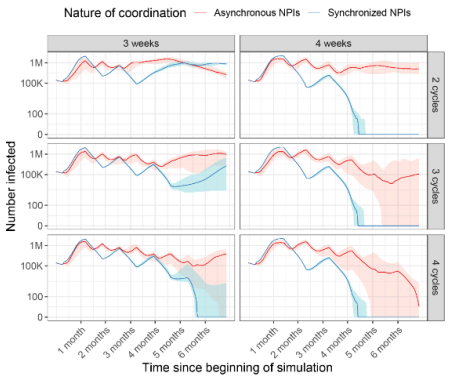


Fig. 4. Cases over time, when NPIs are synchronized and unsynchronized across all European countries. Rows vary the number of on-off cycles that occur, and columns indicate the number of on-off cycles implemented. For example, 4 weeks with 2 cycles (top right) indicates we simulated two cycles of 4 weeks on lockdown, 4 weeks off lockdown for each country. Red: Cases when European countries do not synchronize NPI timing. Blue: Cases when European countries are all synchronized in NPI timing. Shaded areas indicate intervals in which 95% of simulations fell within, over 200 simulations.

SYMPTOMS AND CLINICAL PRESENTATION

ADVANCED AGE

RISK FACTORS INFLUENCING THE PROGNOSIS OF ELDERLY PATIENTS INFECTED WITH COVID-19: A CLINICAL RETROSPECTIVE STUDY IN WUHAN, CHINA

Gao S, Jiang F, Jin W, Shi Y, Yang L, Xia Y, Jia L, Wang B, Lin H, Cai Y, Xia Z, Peng J.. Aging (Albany NY). 2020 Jul 11;12. doi: 10.18632/aging.103631. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

A retrospective cohort study by anesthesiologists from Wuhan, China of COVID-19 patients (n=210, >age of 65) admitted to the hospital between January 23 to February 29, 2020 found significantly higher median C reactive protein (CRP; 125.8 mg/L vs. 9.3 mg/L), lower median lymphocyte counts (0.7×10^9/L vs. 1.1×10^9/L), higher blood urea nitrogen (BUN; 7.2mmol/L vs 4.4mmol/L), and higher frequencies of certain co-morbidities (cardiovascular disease, respiratory disease, etc) in the deceased group (n=35) compared to the discharged group (n=175; Figure 2). Additionally, elevated CRP (>/= 5mg/L) with an abnormal value in either lymphocyte count, BUN, or lactate dehydrogenase was significantly correlated with poor outcomes in this population (Figure 1, Table 3). These findings suggest that high CRP, elevated BUN, lymphopenia, and existing co-morbidities may be associated with increased risk of death from COVID-19 in the elderly population.

ABSTRACT

The mortality rate of elderly patients with Coronavirus Disease 2019 (COVID-19) was significantly higher than the overall mortality rate. However, besides age, leading death risk factors for the high mortality in elderly patients remain unidentified. This retrospective study included 210 elderly COVID-19 patients (aged >= 65 years), of whom 175 patients were discharged and 35 died. All deceased patients had at least one comorbidity. A significantly higher proportion of patients in the deceased group had cardiovascular diseases (49% vs. 20%), respiratory diseases (51% vs. 11%), chronic kidney disease (29% vs. 5%) and cerebrovascular disease (20% vs. 3%) than that in the discharged group. The median levels of C-reactive protein (125.8mg/L vs. 9.3mg/L) and blood urea nitrogen (7.2mmol/L vs. 4.4mmol/L) were significantly higher and median lymphocyte counts (0.7x109/L vs. 1.1x109/L) significantly lower in the deceased group than those in the discharged group. The survival curve analysis showed that higher C-reactive protein (>=5mg/L) plus any other abnormalities of lymphocyte, blood urea nitrogen or lactate dehydrogenase significantly predicted poor prognosis of COVID-19 infected elderly patients. This study revealed that the risk factors for the death in these elderly patients included comorbidities, increased levels of C-reactive protein and blood urea nitrogen, and lymphopenia during hospitalization.

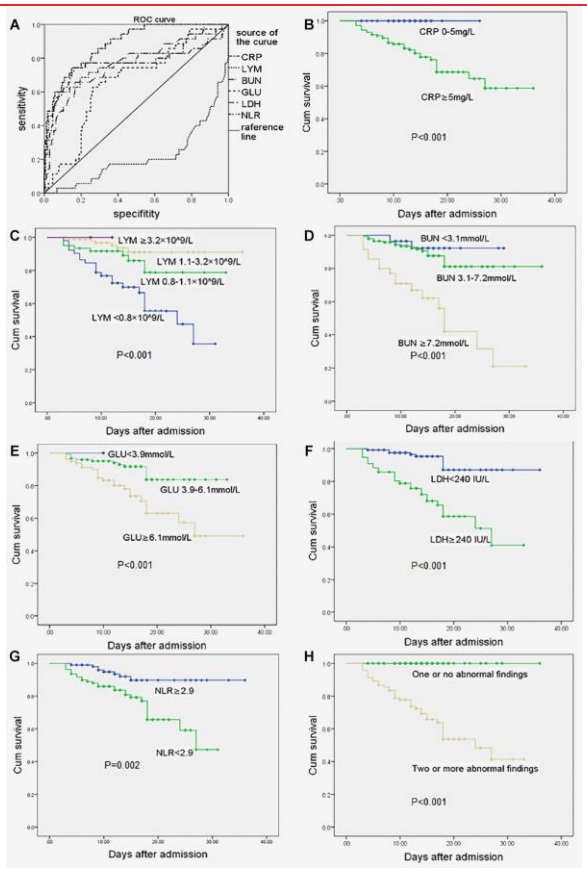


Figure 1."Receiver operating characteristic curve and survival curve. (A) ROC in CRP, LYM, BUN, GLU, LDH, NLR at admission. Survival curves in elderly COVID-19 patients with different levels of CRP (B), LYM(C), BUN (D), GLU (E), LDH (F), NLR (G, NLR value take median value in total patients) at admission. (H) Two or more abnormal values of CRP, LYM, BUN, LDH in the patients at admission can significantly predict poor prognosis of COVID-19 infected elderly patients. Abbreviations: COVID-19, coronavirus disease 2019; ROC, receiver operating curve; CRP, C-reactive protein; LYM, lymphocytes; BUN, blood urea nitrogen; GLU, glucose; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio. P-value reported in each subplot indicates the difference between survival curves by Kaplan-Meier method with log-rank test. P < 0.05 was considered statistically significant."

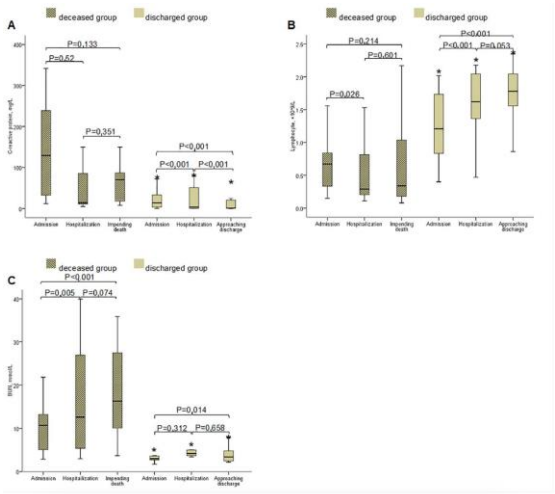


Figure 2. Dynamic Changes of C-reactive protein (A), lymphocyte (B) and BUN (C) within 24 hours at admission, during hospitalization and before discharge or death. Abbreviations: BUN, blood urea nitrogen. The horizontal lines represent the median value in each group. P values indicate differences among admission, hospitalization, impending death between the discharged group and the deceased group. *P<0.05 vs. deceased group. P<0.05 was considered statistically significant.

Test result variable (s)	AUC	highest specificity	highest sensitivity	optimal cut-off values
CRP	0.857	0.85	0.74	63 mg/L
LYM	0.214			
BUN	0.769	0.82	0.66	6.1 mmol/L
GLU	0.660	0.76	0.63	6.5 mmol/L
LDH	0.766	0.79	0.74	265 IU/L
NLR	0.774	0.69	0.60	6.48

Abbreviations: AUC, areas under the curve; BUN, blood urea nitrogen; CRP, C-reactive protein; GLU, glucose; LYM, lymphocytes; NLR, neutrophil-to-lymphocyte ratio.

Table 3. Areas under the curve (AUC) of CRP, LYM, BUN, GLU, LDH, and NLR.

SEVER ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 MAY BE AN UNDERAPPRECIATED PATHOGEN OF THE CENTRAL NERVOUS SYSTEM

Alam SB, Willows S, Kulka M, Sandhu JK.. Eur J Neurol. 2020 Jul 15. doi: 10.1111/ene.14442. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A literature review conducted by Canadian researchers examined the neuroinvasive potential of SARS-CoV-2 and found potential mechanisms of central nervous system (CNS) infection including blood-brain barrier (BBB) disruption (Figure 2) and infection of peripheral nerves leading to trafficking of virions into the CNS (Figure 1). They believe a government regulated registry to routinely track COVID-19 patients with neurological manifestations may be critical to determine long-term health consequences, and note the possibility of neurodegenerative disorders as seen with other neurotropic RNA viruses (see summary).

SUMMARY

Summary of potential neuroinvasive mechanisms of SARS-CoV-2 as follows:

1. Infection of peripheral nerves leading to inflammation and trafficking of virions into the CNS (Figure 1)
-SARS-CoV-2 enters CNS via olfactory receptors by binding ACE2 and Neuropilin1 (NRP1) receptors on olfactory epithelium.
- SARS-CoV-2 enters CNS through vagus nerve from lungs and gut via “lung-gut-brain axis”.
- SARS-CoV-2 binds ACE2 receptors on skeletal muscle and enters CNS via neuromuscular junction by attaching to neural cell adhesion molecule (NCAM) on motor neurons.

2. Disruption of BBB (Figure 2)
- Paracellular transport of SARS-CoV-2 through leaky BBB via loosening of tight junctions by pro-inflammatory cytokines and chemokines.
- Transcellular transport via direct endothelial cell invasion leading to vascular leakage and BBB disruption.
- SARS-CoV-2 binds ACE2 receptors of cerebrovascular endothelial cells and enters CNS via receptor-mediated endocytosis.
- SARS-CoV-2 crosses BBB either by infecting innate cells (monocytes or lymphocytes) or exosome trafficking of viral RNA, known as “a Trojan Horse mechanism”.

Authors hypothesize SARS-CoV-2 infection may lead to development of autoimmune or neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, and multiple sclerosis) as seen in other neurotropic RNA viruses. They suggest a need for routine and long-term tracking of COVID-19 patients with neurological manifestations via neuroimaging and biochemical analysis to map degenerative processes and predict chronic neurological consequences.

ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes a highly contagious respiratory disease referred to as COVID-19. However, emerging evidence indicates that a small, but a growing number of COVID-19 patients also manifest neurological symptoms, suggesting that SARS-CoV-2 may infect the nervous system under some circumstances. SARS-CoV-2 primarily enters the body through the epithelial lining of the respiratory and gastrointestinal tracts, but under certain conditions this pleiotropic virus may also infect peripheral nerves and gain entry into the central nervous system (CNS). The brain is shielded by various anatomical and physiological barriers, most notably the blood-brain barrier (BBB) which functions to prevent harmful substances, including pathogens and pro-inflammatory mediators, from entering the brain. The BBB is composed of highly specialized endothelial cells, pericytes, mast cells and astrocytes that form the neurovascular unit, which regulates BBB permeability and maintains the integrity of the CNS. In this review, we briefly discuss potential routes of viral entry and the possible mechanisms utilized by SARS-CoV-2 to penetrate the CNS, either by disrupting the BBB or infecting the peripheral nerves and using the neuronal network to initiate neuroinflammation. Furthermore, we speculate on the long-term effects of SARS-CoV-2 infection on the brain and in the progression of neurodegenerative diseases known to be associated with other human coronaviruses. Although the mechanisms of SARS-CoV-2 entry into the CNS and neurovirulence are currently unknown, the potential pathways described here might pave the way for future research in this area and enable the development of better therapeutic strategies.

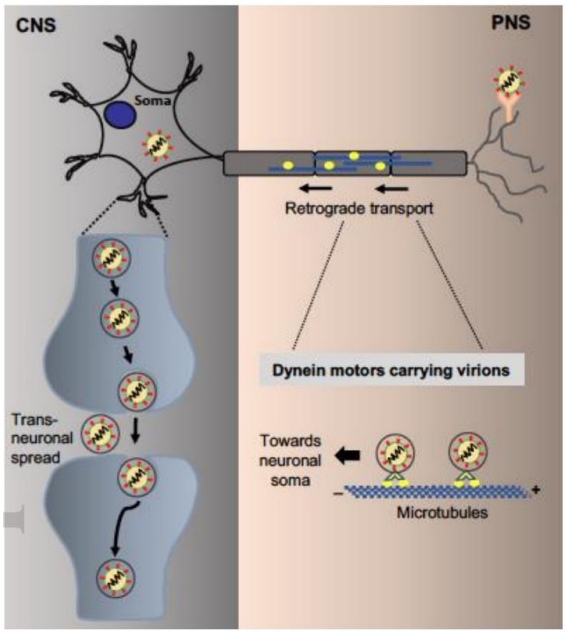


Figure 1. Potential route of SARS-CoV-2 entry from the peripheral nervous system (PNS) into the central nervous system (CNS). The virions bind to the receptors on the peripheral nerves and are then transported via the retrograde transport system using microtubule-associated molecular motor dynein (from + to – end) towards the neuronal cell body (soma). Once inside Accepted Article the soma, the virions undergo transneuronal spread through the synapses to infect the presynaptic neurons.

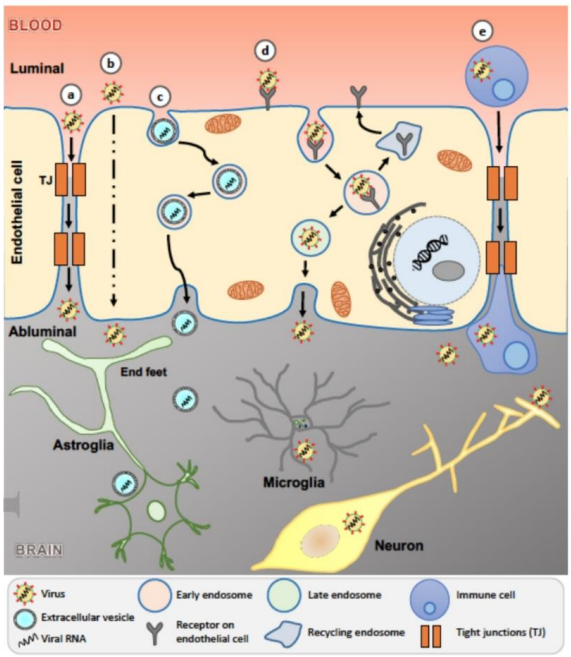


Figure 2. Potential mechanisms of SARS-CoV-2 entry into the central nervous system (CNS). The schematic depicts five routes by which SARS-CoV-2 could traverse across the blood-brain barrier (BBB) to access the CNS. (a) Paracellular transport through leaky BBB due to disrupted tight junctions (TJ), (b) Transcellular transport by direct infection of cerebrovascular endothelial cells, (c) Transport via extracellular vesicles, a form of 'Trojan horse' trafficking, (d) Transport via receptor-mediated endocytosis, (e) Transport via infected peripheral immune cells, another form of "Trojan horse" trafficking.

EXTRAPULMONARY MANIFESTATIONS OF COVID-19

Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, Bikdeli B, Ahluwalia N, Ausiello JC, Wan EY, Freedberg DE, Kirtane AJ, Parikh SA, Maurer MS, Nordvig AS, Accili D, Bathon JM, Mohan S, Bauer KA, Leon MB, Krumholz HM, Uriel N, Mehra MR, Elkind MSV, Stone GW, Schwartz A, Ho DD, Bilezikian JP, Landry DW.. Nat Med. 2020 Jul 10. doi: 10.1038/s41591-020-0968-3. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

American authors conducted a literature review on the extrapulmonary manifestations of COVID-19 based on a multi-organ system description. They highlight the pathophysiology and clinical impact on these organ systems (Figures 1-2) and identify various areas of future research to better understand and manage COVID-19 in extrapulmonary systems.

ABSTRACT

Although COVID-19 is most well known for causing substantial respiratory pathology, it can also result in several extrapulmonary manifestations. These conditions include thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, neurologic illnesses, ocular symptoms, and dermatologic complications. Given that ACE2, the entry receptor for the causative coronavirus SARS-CoV-2, is expressed in multiple extrapulmonary tissues, direct viral tissue damage is a plausible mechanism of injury. In addition, endothelial damage and thromboinflammation, dysregulation of immune responses, and maladaptation of ACE2-related pathways might all contribute to these extrapulmonary manifestations of COVID-19. Here we review the extrapulmonary organ-specific pathophysiology, presentations and management considerations for patients with COVID-19 to aid clinicians and scientists in recognizing and monitoring the spectrum of manifestations, and in developing research priorities and therapeutic strategies for all organ systems involved.

FIGURES

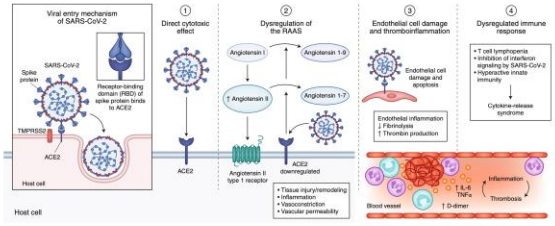


Fig. 1 | Pathophysiology of COVID-19. SARS-CoV-2 enters host cells through interaction of its spike protein with the entry receptor ACE2 in the presence of TMPRSS2 (far left). Proposed mechanisms for COVID-19 caused by infection with SARS-CoV-2 include (1) direct virus-mediated cell damage; (2) dysregulation of the RAAS as a consequence of downregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II; (3) endothelial cell damage and thromboinflammation; and (4) dysregulation of the immune response and hyperinflammation caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of proinflammatory cytokines, particularly IL-6 and TNFα.

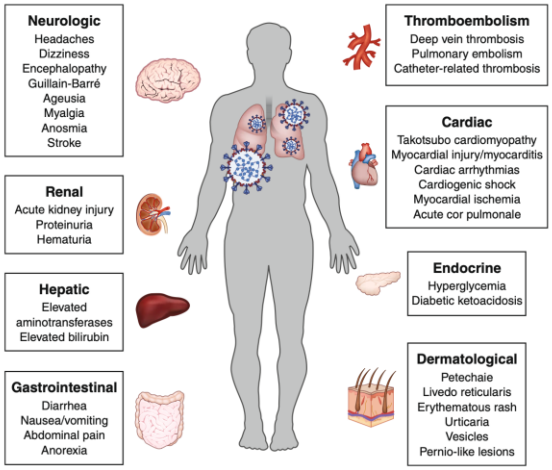


Fig. 2 | Extrapulmonary manifestations of COVID-19. The pulmonary manifestation of COVID-19 caused by infection with SARS-CoV-2, including pneumonia and ARDS, are well recognized. In addition, COVID-19 is associated with deleterious effects on many other organ systems. Common extrapulmonary manifestations of COVID-19 are summarized here.

TRANSMISSION & PREVENTION

DEVELOPMENTS IN TRANSMISSION & PREVENTION

SARS-COV-2 REPLICATING IN NON-PRIMATE MAMMALIAN CELLS PROBABLY HAVE CRITICAL ADVANTAGES FOR COVID-19 VACCINES DUE TO ANTI-GAL ANTIBODIES: A MINIREVIEW AND PROPOSALS

Chen JM.. J Med Virol. 2020 Jul 18. doi: 10.1002/jmv.26312. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A literature review from the College of Veterinary Medicine, Qingdao Agricultural University examines the possibility of designing a COVID-19 vaccine in PK-15 cells or another non-primate mammalian cell line. This would allow for the development of a live or inactivated SARS-CoV-2 vaccine that contains α1,3-galactose (αGal) glycans (Figure 1). Since primates have a natural antibody for this glycan, the authors predict this vaccine could elicit a larger and longer lasting immune response in humans, warranting further research.

ABSTRACT

Glycoproteins of enveloped viruses replicating in non-primate mammalian cells carry alpha1,3-galactose (alphaGal) glycans, and can bind to anti-Gal antibodies which are abundant in humans. The antibodies have protected humans and their ancestors for millions of years, because they inhibit replication of many kinds of microbes carrying alphaGal glycans and aid complements and macrophages to destroy them. Therefore, SARS-CoV-2 replicating in non-primate mammalian cells (e.g., PK-15 cells) carry alphaGal glycans and could be employed as a live vaccine for COVID-19. The live vaccine safety could be further enhanced through intramuscular inoculation to bypass the fragile lungs, like the live unattenuated adenovirus vaccine safely used in US recruits for decades. Moreover, the immune complexes of SARS-CoV-2 and anti-Gal antibodies could enhance the efficacy of COVID-19 vaccines, live or inactivated, carrying aGal glycans. Experiments are imperatively desired to examine these novel vaccine strategies which probably have the critical advantages for defeating the pandemic of COVID-19 and preventing other viral infectious diseases. This article is protected by copyright. All rights reserved.

FIGURES

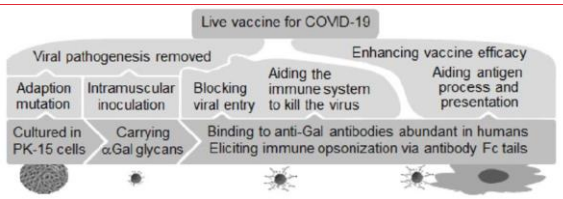


Figure 1. Logic for SARS-CoV-2 replicating in PK-15 cells to be a live COVID-19 vaccine

PREVENTION IN THE COMMUNITY

ABSENCE OF APPARENT TRANSMISSION OF SARS-COV-2 FROM TWO STYLISTS AFTER EXPOSURE AT A HAIR SALON WITH A UNIVERSAL FACE COVERING POLICY - SPRINGFIELD, MISSOURI, MAY 2020

Hendrix MJ, Walde C, Findley K, Trotman R.. MMWR Morb Mortal Wkly Rep. 2020 Jul 17;69(28):930-932. doi: 10.15585/mmwr.mm6928e2.
Level of Evidence: 3 - Local non-random sample

BLUF

An observational study in May, 2020 involving 139 masked clients in Springfield, Missouri exposed to two symptomatic masked hair stylists showed there were no symptomatic secondary cases and that all the clients who tested for SARS-CoV-2

were negative (67/139). These results suggest that proper mask wearing may have played a key factor in protecting clients against the spread of COVID-19.

ABSTRACT

On May 12, 2020 (day 0), a hair stylist at salon A in Springfield, Missouri (stylist A), developed respiratory symptoms and continued working with clients until day 8, when the stylist received a positive test result for SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19). A second hair stylist (stylist B), who had been exposed to stylist A, developed respiratory symptoms on May 15, 2020 (day 3), and worked with clients at salon A until day 8 before seeking testing for SARS-CoV-2, which returned a positive result on day 10. A total of 139 clients were directly serviced by stylists A and B from the time they developed symptoms until they took leave from work. Stylists A and B and the 139 clients followed the City of Springfield ordinance* and salon A policy recommending the use of face coverings (i.e., surgical masks, N95 respirators, or cloth face coverings) for both stylists and clients during their interactions. Other stylists at salon A who worked closely with stylists A and B were identified, quarantined, and monitored daily for 14 days after their last exposure to stylists A or B. None of these stylists reported COVID-19 symptoms. After stylist B received a positive test result on day 10, salon A closed for 3 days to disinfect frequently touched and contaminated areas. After public health contact tracings and 2 weeks of follow-up, no COVID-19 symptoms were identified among the 139 exposed clients or their secondary contacts. The citywide ordinance and company policy might have played a role in preventing spread of SARS-CoV-2 during these exposures. These findings support the role of source control in preventing transmission and can inform the development of public health policy during the COVID-19 pandemic. As stay-at-home orders are lifted, professional and social interactions in the community will present more opportunities for spread of SARS-CoV-2. Broader implementation of masking policies could mitigate the spread of infection in the general population.

SEROSURVEILLANCE AND THE COVID-19 EPIDEMIC IN THE US: UNDETECTED, UNCERTAIN, AND OUT OF CONTROL

Brown TS, Walensky RP.. JAMA. 2020 Jul 21. doi: 10.1001/jama.2020.14017. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

This editorial written by physicians at Massachusetts General Hospital, Boston, review a recent study by Haver et al. (2020) regarding serosurveillance efforts to measure incidence of COVID-19 and suggests that the minimal herd immunity threshold in the United States is unlikely to be met as uncontrolled cases are increasing every day, in addition to evidence suggesting that acquired immunity may be temporary and short-lived. They propose implementation of active surveillance strategies including mass COVID-19 testing to better drive public health initiatives to contain the pandemic.

MANAGEMENT

ACUTE CARE

INCIDENCE OF THROMBOSIS AND HEMORRHAGE IN HOSPITALIZED CANCER PATIENTS WITH COVID-19

Patell R, Bogue T, Bindal P, Koshy A, Merrill M, Aird WC, Bauer KA, Zwicker JI.. J Thromb Haemost. 2020 Jul 21. doi: 10.1111/jth.15018. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cohort study of 398 hospitalized COVID-19 patients with cancer (n=45) and without cancer (n=353) at Beth Israel Deaconess Medical Center, between March-May 2020 investigated the incidences of thrombotic events at day 28 of hospitalization. While the researchers acknowledge the study is limited by the power of the study, they report no significant differences between active cancer cohort, 14.2% (95% CI, 4.7%-28.7%), and non-cancer cohort, 18.2% (95% CI, 10.2%-27.9%). The researchers believe the overall elevated thrombo-inflammatory state of COVID-19 outcompetes a more moderate hypercoagulable state of cancer.

ABSTRACT

BACKGROUND: Coronavirus Disease-2019 (COVID-19) is a recognized prothrombotic state. Patients hospitalized with active cancer are predisposed to thrombosis but whether active cancer further amplifies thrombotic risk with COVID-19 is not known. OBJECTIVES: To evaluate cumulative incidences of thrombotic and hemorrhagic events in hospitalized COVID-19 patients with and without active cancer at 28 days. METHODS: A retrospective cohort analyses of consecutive adults hospitalized with COVID-19 was performed. Active cancer required cancer-directed therapy within last 6 months. The cumulative incidences of thrombosis or hemorrhage were estimated considering death as a competing risk. RESULTS: Patients without cancer (n=353) and active cancer (n=45) were comparable in terms of age, sex, antibiotics administered, length of hospitalization, and critical care. The most common malignancies were lymphoid (17.8%), gastrointestinal (15.6%), lung (13.3%), and genitourinary (13.3%). At day 28, the cumulative incidence of thrombotic events was 18.2% (95% CI, 10.2% to 27.9%) in non-cancer cohort and 14.2% (95% CI, 4.7% to 28.7%) in the cancer cohort. The cumulative incidence of major and fatal bleeding at day 28 was 20.8% (95% CI, 12.1 to 31.0%) in the non-cancer group and 19.5% (95% CI, 5.5% to 39.8%) in the cancer cohort. Three patients experienced fatal bleeds, all of whom were in the non-cancer cohort. Survival was significantly shorter in the group with active cancer (P=0.038). CONCLUSIONS: We observed a similarly high incidence of thrombosis and bleeding among patients admitted with COVID-19 with or without active cancer.

CRITICAL CARE

BLOOD COMPONENT USE IN CRITICAL CARE IN PATIENTS WITH COVID-19 INFECTION: A SINGLE CENTRE EXPERIENCE

Doyle AJ, Danaee A, I Furtado C, Miller S, Maggs T, Robinson SE, Retter A.. Br J Haematol. 2020 Jul 8. doi: 10.1111/bjh.17007. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

This study evaluated the use of blood components in COVID-19 positive patients from March 3 - April 14, 2020 in 30 patients requiring veno-venous extracorporeal membrane oxygenation (vv-ECMO) and 235 patients not requiring vv-ECMO (n=265) (Table 3). Seventeen patients on vv-ECMO (n=17/30, 56.7%) needed blood components compared with 33 patients not on vv-ECMO (n=33/235, 14%) (Table 1). COVID-19 patients in this study qualitatively used less blood products compared with non-COVID patients in similar previous studies.

ABSTRACT

There has been a significant surge in admissions to critical care during the COVID-19 pandemic. At present, the demands on blood components have not been described. We reviewed their use during the first 6 weeks of the outbreak from 3rd March

2020 in a tertiary-level critical care department providing veno-venous extracorporeal membrane oxygenation (vv-ECMO). 265 patients were reviewed - 235 not requiring ECMO and 30 requiring vv-ECMO. In total, 50 patients required blood components during their critical care admission. Red cell concentrates were the most frequently transfused component in COVID-19 infected patients with higher rates of use during vv-ECMO. The use of fresh frozen plasma, cryoprecipitate and platelet transfusions was low in a period prior to the use of convalescent plasma.

FIGURES

Blood Component	No. of units transfused to vv-ECMO patients (number of patients = 33)	No. of units transfused to non-ECMO patients (number of patients =17)
RCC	**95**	**109**
R1 – Acute bleeding	33	12
R2 – Hb ≤70g/L stable patient	11	55
R3 – Hb ≤80g/L if CVD	51	26
R6 – Exchange transfusion	0	16
Platelets	**8**	**15**
P2 – Plt <10-20x10^9/L sepsis	0	9
P3a – Plt <20 x10^9/L CVC insertion	0	1
P4a – Major haemorrhage plt <50x10^9/L	3	2
P5a – DIC pre-procedure or bleeding	5	3
FFP	**16**	**8**
F1 – Major haemorrhage	14	0
F2 – INR >1.5 with bleeding	0	8
F3 - INR >1.5 pre-procedure	2	0
Cryoprecipitate	**8**	**2**
C1 – Significant bleeding and fibrinogen <1.5g/L	8	2

Hb – Haemoglobin, CVD – Cardiovascular disease, Plt – Platelets, CVC – central venous catheter, DIC – disseminated intravascular coagulation, INR – international normalised ratio

Table 1. Clinical characteristics of patients with COVID-19 infections requiring Critical Care support who required blood components

NEUROLOGY

NEUROLOGIC AND NEUROIMAGING FINDINGS IN COVID-19 PATIENTS: A RETROSPECTIVE MULTICENTER STUDY

Kremer S, Lersy F, Anheim M, Merdji H, Schenck M, Oesterlé H, Bolognini F, Messie J, Henri-Feugeas MC, Khalil A, Gaudemer A, Carré S, Alleg M, Lecocq C, Schmitt E, Anxionnat R, Zhu F, Jager L, Nesser P, Mba YT, Hmeydia G, Benzakoun J, Oppenheim C, Ferré JC, Maamar A, Carsin-Nicol B, Comby PO, Ricolfi F, Thouant P, Boutet C, Fabre X, Forestier G, de Beaurepaire I, Bornet G, Desal H, Boulouis G, Berge J, Kazémi A, Pyatigorskaya N, Lecler A, Saleme S, Edjlali-Goujon M, Kerleroux B, Constans JM, Zorn PE, Mathieu M, Baloglu S, Ardellier FD, Willaume T, Brisset JC, Caillard S, Collange O, Mertes M, Schneider F, Fafi-Kremer S, Ohana M, Meziani F, Meyer N, Helms J, Cotton F.. Neurology. 2020 Jul 17:10.1212/WNL.0000000000010112. doi: 10.1212/WNL.0000000000010112. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A multi-center retrospective study of 64 COVID-19 patients with neurologic manifestations conducted in France between March 16 and April 9, 2020 found that 56% of these patients had brain MRI abnormalities such as stroke (n=17), encephalitis (n=8), or leptomeningeal enhancement (n=11, Figures 1-3). These findings suggest that neurological manifestations can occur in COVID-19 patients and show the importance of neurologic examination and follow-up imaging.

ABSTRACT

OBJECTIVE: To describe neuroimaging findings and to report the epidemiological and clinical characteristics of COVID-19 patients with neurological manifestations. METHODS: In this retrospective multicenter study (10 Hospitals), we included 64 confirmed COVID-19 patients with neurologic manifestations who underwent a brain MRI. RESULTS: The cohort included 43 men (67%), 21 women (33%), and the median age was 66 years (range: 20-92). 36 (56%) brain MRIs were considered abnormal, possibly related to SARS-CoV-2. Ischemic strokes (27%), leptomeningeal enhancement (17%), and encephalitis (13%) were the most frequent neuroimaging findings. Confusion (53%) was the most common neurological manifestation, following by impaired consciousness (39%), presence of clinical signs of corticospinal tract involvement (31%), agitation (31%), and headache (16%). The profile of patients experiencing ischemic stroke was different from the other patients with

abnormal brain imaging since the former had less frequently acute respiratory distress syndrome (p=0 006) and more frequently corticospinal tract signs (p=0 02). Patients with encephalitis were younger (p=0 007), whereas agitation was more frequent for patients with leptomeningeal enhancement (p=0 009). CONCLUSIONS: COVID-19 patients may develop a wide range of neurological symptoms, which can be associated with severe and fatal complications, such as ischemic stroke or encephalitis. Concerning the meningoencephalitis involvement, even if a direct effect of the virus cannot be excluded, the pathophysiology rather seems to involve an immune and/or inflammatory process given the presence of signs of inflammation in both cerebrospinal fluid and neuroimaging but the lack of virus in cerebrospinal fluid.

FIGURES

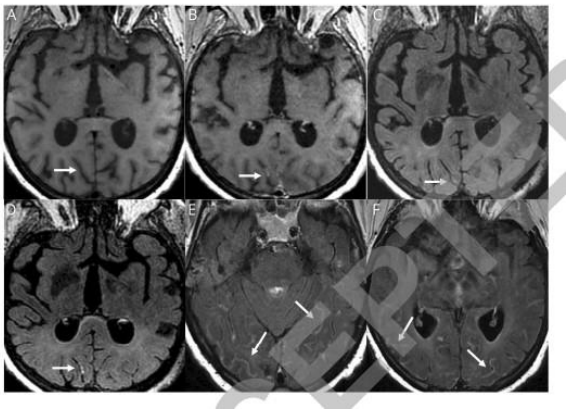


Figure 1 : Leptomeningeal enhancement. Axial T1 before (a) and 5 minutes after contrast (b), axial FLAIR before (c) and immediately after contrast (d), delayed (10 minutes) after contrast axial FLAIR weighted MR images (e,f). Woman aged 77 years : diffuse leptomeningeal linear FLAIR and T1 contrast enhancement (arrows), not visible on pre-contrast T1 and FLAIR (arrows), but better seen on delayed after contrast FLAIR weighted MR images (e,f).

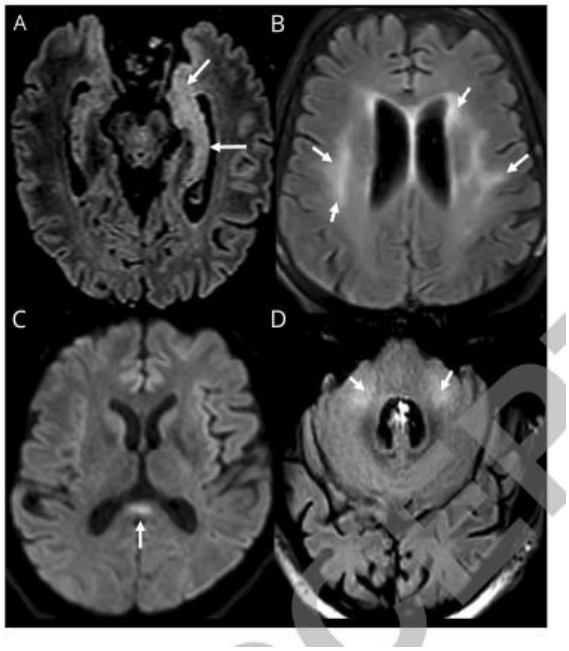


Figure 2: Encephalitis. Axial FLAIR (a,b,d) and diffusion (c) weighted MR images. Man aged 56 years: left hippocampus and amygdala FLAIR hyperintensity (a). Woman aged 71 years: periventricular and subcortical white matter FLAIR confluent hyperintensities (b). Man aged 55 years: corpus callosum splenium diffusion hyperintensity (c). Man aged 64 years: FLAIR middle cerebellar peduncles hyperintensity(d).

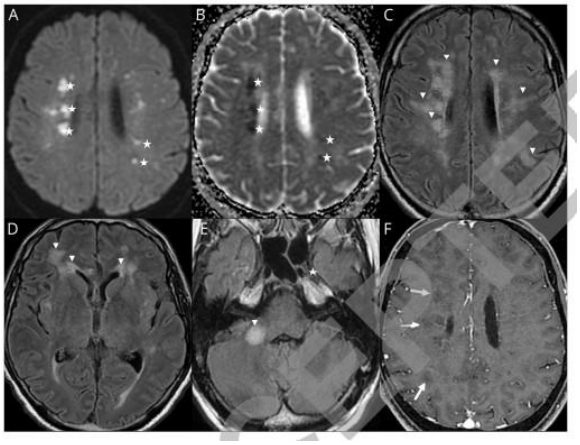


Figure 3: Radiological ADEM. Axial FLAIR (a,e,i), axial diffusion (b,f,j), Apparent diffusion coefficient (ADC) map (c,g,k) and post-contrast T1 (d,h,l) weighted MR images. Man aged 60 years: Subcortical, periventricular, corpus callosum, and posterior fossa white matter FLAIR hyperintensities, without contrast enhancement (arrows). Some lesions appear hyperintense on diffusion-weighted MR images with decreased ADC corresponding to cytotoxic edema (stars). The other lesions present an ADC increase corresponding to vasogenic edema (cross).

ADJUSTING PRACTICE DURING COVID-19

FOR HEALTHCARE PROFESSIONALS

CORTICOSTEROIDS-INDUCED OSTEONECROSIS IN COVID-19: A CALL FOR CAUTION

Zhang B, Zhang S.. J Bone Miner Res. 2020 Jul 22. doi: 10.1002/jbmr.4136. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

In this letter discussing systemic corticosteroid use in COVID-19-induced cytokine storm, authors refer to multiple studies regarding the Severe Acute Respiratory Syndrome (SARS) epidemic in 2003 showing patients at an increased risk of osteonecrosis of the femoral head (ONFH) with prolonged use of systemic steroids. Based on these prior findings, authors suggest use of risk stratification to determine follow-up and management plans, including concurrent use of bisphosphonates and vitamin E with systemic steroids and imaging for early detection of ONFH in patients at increased risk.

SUMMARY

Risk Stratification:

Low risk: Patient received no steroids
Moderate: Steroid duration <1 week and cumulative dose <200mg
High: Steroid duration >1 week, cumaltive dose >2000mg

MEDICAL SUBSPECIALTIES

HEMATOLOGY AND ONCOLOGY

DISCORDANCE OF COVID-19 GUIDELINES FOR PATIENTS WITH CANCER: A SYSTEMATIC REVIEW

Garg PK, Kaul P, Choudhary D, Turaga KK, Singh MP, Tiwari AR, Arora V, Agrawal N, Rau B, Yendamuri S.. J Surg Oncol. 2020 Jul 15. doi: 10.1002/jso.26110. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

This review from authors in India identified 212 articles that met their inclusion/exclusion criteria (Figure 1) for articles making recommendations on the management of solid tumors (e.g., breast, Table 4), hematologic cancers, and radiation/chemotherapy treatment during the pandemic. Overall, these articles demonstrated highly variable recommendations and the authors speculate on the factors that could underlie the lack of agreement (Table 6). The lack of consistent recommendations reveals the importance of examining new literature with scrutiny and also highlights the need for sharing information to collect high quality and coherent data on COVID-19.

ABSTRACT

This review was aimed to systematically evaluate the available literature on the impact of COVID-19 on cancer care and to critically analyze the diagnostic and therapeutic strategies suggested by various healthcare providers, societies, and institutions. Majority guidelines for various types of cancers favored a delay in treatment or a nonsurgical approach wherever feasible. These guidelines are based on a low level of evidence and have significant discordance for the role and timing of surgery, especially in early tumors.

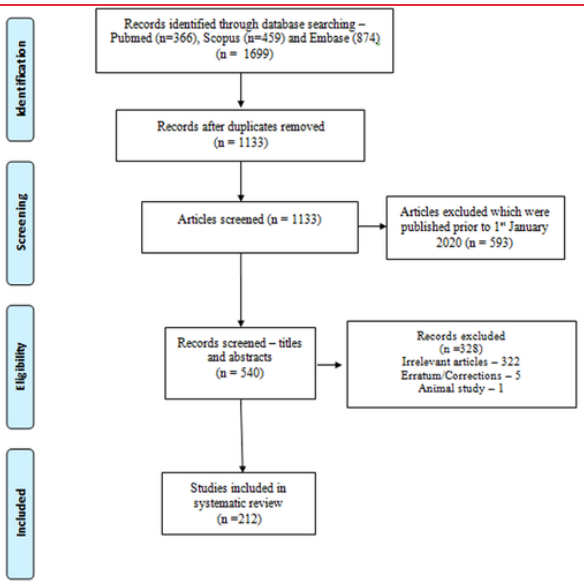


Figure 1. Flowchart of PRISMA.

- A rapid response to the pandemic—various institutional policies were formulated without multicentric discussion.
- Paucity of literature—The outcomes of oncological treatments in form of delaying surgery, chemotherapy/immunotherapy or radiation therapy in the patients with active or latent SARS-CoV-2 infection is currently an unfathomed territory.
- Differences in the national healthcare systems (single-payer system, government-run care, hybrid system, etc), which have a considerable impact while formulating any guidelines.
- Demographic profile of the nation as well as the percentage of population affected by COVID-19 and the relative proportion of healthcare resources available.
- Lack of mental preparedness and unanticipated clinical outcomes of the pandemic.
- All the guidelines/consensus statements are framed in a relatively short period of time without multilevel comprehensive discussions supported by the sufficient evidence.

All the guidelines/consensus statements clearly mention that they can be subjected to constant evolution and dynamism in light of emerging new evidence.

Table 6. Postulated reasons for discordance among the guidelines.

Author/group	Recommendations
Braunstein et al[34]	Different levels of priorities for radiotherapy for patients with breast cancer (a) High—inflammatory breast cancer, residual node positivity after NAC, 4 or more positive nodes (N2), recurrent disease, node-positive TNBC, extensive LVI. (b) Intermediate—ER + with 1-3 positive nodes (N1a), Path N0 after NAC, LVI (NOS), Node-negative TNBC (c) Low—early-stage ER + breast cancer (older patients), DCIS, Otherwise not meeting criteria for high or intermediate priority
Coles et al[35]	International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic 1. Omit RT for patients 65 y and over (or younger with relevant comorbidities), with invasive breast cancer that are up to 30 mm with clear margins, grade 1-2, estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative and node negative, who are planned for treatment with endocrine therapy 2. Deliver RT in 5 fractions only for patients requiring RT with node-negative tumors that do not require a boost. Options include 28-30Gy in once weekly fractions over 5 wk or 26 Gy in 5 daily fractions over 1 wk as per the FAST and FAST Forward trials, respectively. 3. Boost RT should be omitted to reduce fractions and/or complexity in the vast majority of patients unless they 40 years old and under, or over 40 years with significant risk factors for local relapse. 4. Nodal RT can be omitted in postmenopausal women requiring whole breast RT following sentinel lymph node biopsy and primary surgery for T1, ER positive, HER2 negative G1-2 tumors with 1-2 macrometastases. 5. Moderate hypofractionation should be used for all breast/chest wall and nodal RT, for example 40 Gy in 15 fractions over 3 wk
Curigliano et al[36]	Recommendations for triage, prioritization and treatment of breast cancer patients during the COVID-19 pandemicScreening and diagnosis: suspend population mammographic screening, avoid delayed diagnosis [BIRADS 5 (high priority) or BIRADS 4 (medium priority)]Early breast cancer: 1. Surgery: Prefer the most effective minimal surgical procedure with the fastest recovery time 2. Radiation: Postpone RT up to 3 mo for high-risk and up to 6 mo for low-risk patients; Moderate hypofractionation; Omit boost RT in patients with low risk for local relapse; Consider accelerated partial breast RT low-risk patients; consider omission of RT in elderly patients at low risk of recurrence 3. Systemic therapy: Avoid drugs with risk of immunosuppression; limit use of steroids; prefer 3 weekly regimen; recommend anti-HER2 agents for $HER2^+$; follow usual international guidelines for adjuvant endocrine therapy; prefer oral formulations for adjuvant bisphosphonates. Advanced breast cancer: 1. Systemic therapy: consider dose reductions and dose interruptions; consider treatment holidays in prolonged treatments and stable disease; prefer endocrine-based therapy for ER^+/HER2 negative; individualize the use of CDK 4/6 and mTOR inhibitors; prefer oral and liposomal formulations when using chemotherapy; consider use of prophylactic hematopoietic growth factors. 2. Radiation: urgent for spinal cord compression, brain and leptomeningeal metastases, and palliative treatments (eg of bone metastases) not responding to pharmaceutical interventions
Dietz et al,[37] The COVID-19 pandemic breast cancer consortium	Recommendations for prioritization, treatment, and triage of patients with breast cancer during the COVID-19 pandemic.Surgical oncology 1. Priority A (life threatening)—breast abscess in a septic patient, Expanding hematoma in a hemodynamically unstable patient 2. Priority B (not immediately life-threatening conditions but for whom treatment or services should not be indefinitely delayed until the end of the pandemic—most patients with breast cancer; a delay of 6-12 wk is unlikely to impact the overall survival. 3. Priority C (can be indefinitely deferred until the pandemic is over without adversely impacting outcomes)—pre-invasive cancer; breast reconstruction. Medical oncology 1. Priority A (life threatening)—oncologic emergencies requiring immediate treatment (eg febrile neutropenia, intractable pain) 2. Priority B—require systemic therapy but modified therapeutic approaches to minimize patient interactions with healthcare centers, maintain patient safety, and conserve resources while providing effective care 3. Priority C—delay interventions for many months without adverse impact on survival or quality of life. Radiation oncology 1. Priority A—includes patients presenting with symptomatic disease in whom short palliative RT regimens should be utilized 2. Priority B—majority of patients; stratify them based on clinicopathological parameters 3. Priority C—delaying RT does not affect survival outcomes (eg most DCIS, patients ≥ 65–70 y with early stage, node negative, ER + invasive disease)

Table 4

PSYCHIATRY

ASSOCIATIONS BETWEEN PSYCHIATRIC DISORDERS, COVID-19 TESTING PROBABILITY AND COVID-19 TESTING RESULTS: FINDINGS FROM A POPULATION-BASED STUDY

van der Meer D, Pinzón-Espinosa J, Lin BD, Tijdink JK, Vinkers CH, Guloksuz S, Luykx JJ.. BJPsych Open. 2020 Jul 22:1-19. doi: 10.1192/bjo.2020.75. Online ahead of print.
Level of Evidence: 3 - Local and current random sample surveys (or censuses)

BLUF

In this population-based cohort study using United Kingdom Biobank data of patients with mental illness, rates of COVID-19 testing and diagnoses in individuals with and without psychiatric disorders were compared. The study's goal was to understand whether psychiatric patients' face increased susceptibility to infections and complications, stigma, and whether difficulties accessing healthcare were barriers to timely COVID-19 testing. They concluded that patients with psychiatric illnesses were more frequently tested and had lower chances of testing positive than those without - possibly due to higher anxiety about contracting COVID-19, higher frequency of comorbid conditions or somatic symptoms, and increased social isolation (Table 1).

SUMMARY

Additionally, the authors' findings suggest that individuals with neurological disorders exhibit high testing rates, possibly due to overlap with psychiatric symptoms and behavior changes. The study found no significant association between likelihood of testing or outcome and the psychiatric symptoms of depression, mania, anxiety, addiction, psychotic experiences, self-harm, or happiness with previous or current psychiatric diagnoses (Table 2).

FIGURES

Diagnosis	N individuals in UKB	N individuals tested	Ratio tested/in UKB	P-value
Psychiatric disorder	50 506 (10.1%)	344 (23.3%)	2.32	$1.1*10^{-49}$
Neurological	27 950 (5.6%)	187 (12.7%)	2.28	$4.9*10^{-25}$
Metabolic	109 179 (21.7%)	580 (39.3%)	1.81	$8.3*10^{-53}$
Respiratory	88 095 (17.5%)	465 (31.5%)	1.80	$3.8*10^{-39}$
Cardiovascular	178 873 (35.6%)	808 (54.8%)	1.54	$5.1*10^{-51}$
Psychiatric disorder subcategories				
• Depression	20 043 (4.0%)	156 (10.6%)	2.65	$1.7*10^{-27}$
• Substance use	23 911 (4.8%)	173 (11.7%)	2.47	$9.8*10^{-27}$
• Anxiety	11 536 (2.3%)	80 (5.4%)	2.36	$5.5*10^{-12}$

Table 1. Comparison of number of individuals present in the full UKB cohort with those among the COVID-19 tested subset, per diagnostic group, ordered by decreasing ratio. The columns indicate the number of individuals with a specific diagnosis in either the full UKB cohort or in the tested subset, and the resulting ratio. The numbers in brackets indicate the corresponding percentage of individuals. The p-value is determined by Fisher's exact test.

Diagnosis	N individuals in UKB	N individuals tested	Ratio tested/in UKB	P-value
Happiness	86010 (54.7%)	177 (49.6%)	0.91	0.04
Depression	89034 (56.6%)	225 (63%)	1.11	0.01
Mania	42499 (27%)	109 (30.5%)	1.13	0.14
Anxiety	55199 (35.1%)	142 (39.8%)	1.13	0.07
Self-harm	30418 (19.3%)	87 (24.4%)	1.26	0.02
Addiction	9382 (6.0%)	30 (8.4%)	1.41	0.06
Psychotic experiences	7803 (5.0%)	29 (8.1%)	1.64	0.01
Excluded individuals with a psychiatric disorder				
Happiness	86010 (54.7%)	149 (49.2%)	0.90	0.06
Anxiety	55199 (35.1%)	111 (36.6%)	1.04	0.59
Mania	42499 (27%)	87 (28.7%)	1.06	0.52
Depression	89034 (56.6%)	185 (61.1%)	1.08	0.12
Psychotic experiences	7803 (5.0%)	17 (5.6%)	1.13	0.59
Addiction	9382 (6.0%)	22 (7.3%)	1.22	0.33
Self-harm	30418 (19.3%)	73 (24.1%)	1.25	0.06

(bottom half).

Table 2. Comparison of number of individuals in the full UKB cohort and those among the COVID-19 tested subset, per mental health questionnaire category. The columns indicate the number of individuals with an affirmative response to specific category in either the full UKB cohort, or among the tested subset, and the resulting ratio. The numbers in brackets indicate the corresponding percentage of individuals. The p-value is determined by Fisher's exact test. Top half indicates numbers across everyone, bottom half numbers after excluding individuals with a psychiatric disorder diagnosis.

SURVEILLANCE FOR PROBABLE COVID-19 USING STRUCTURED DATA IN THE ELECTRONIC MEDICAL RECORD

Burke PC, Shirley RB, Faiman M, Boose EW, Jones RW, Merlino A, Gordon SM, Fraser TG.. Infect Control Hosp Epidemiol. 2020 Jul 23:1-10. doi: 10.1017/ice.2020.359. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

Authors at the Cleveland Clinic developed a novel standardized clinical note template that surveyed and reported probable COVID-19 infections to local public health through their electronic medical record. Probable cases were identified by assessing known exposures and clinical symptoms based on COVID-19's case definition from the Council for State and Territorial Epidemiologists (Table). Using this template, the authors found a 62% increase in their report of previously undetected COVID-19 cases, suggesting the need for more widespread testing and surveillance of probable positive cases.

ABSTRACT

We developed an electronic medical record structured note template including features of Council for State and Territorial Epidemiologists' case definition for COVID-19. We found 218 probable COVID-19 cases in one week, increasing our reports to public health by 62%. Only 10% of patients who would have been probable COVID-19 but were tested for SARS-CoV-2, tested positive.

FIGURES

Table - Clinical and epidemiologic characteristics of patients seen by Cleveland Clinic virtual visit for COVID-19 concern who did and did not meet the CSTE case definition for probable COVID-19, April 15 – April 21, 2020

	Probable COVID-19 N = 218	Not Probable COVID-19* N = 106
	N (%)	N (%)
Major Clinical Criteria		
Cough	160 (74)	34 (32)
Shortness of Breath	80 (37)	8 (8)
Difficulty Breathing	39 (18)	5 (5)
Minor Clinical Criteria		
Fever (measured or subjective)	87 (40)	14 (13)
Chills	120 (55)	11 (10)
Rigors**	-	-
Myalgia	114 (52)	17 (16)
Headache	119 (55)	30 (28)
Sore throat	96 (44)	27 (25)
New olfactory and taste disorder(s)	37 (17)	2 (2)
Epidemiologic Link		
Travel to or residence in an area with sustained, ongoing community transmission of SARS-CoV-2	218 (100)	106 (100)
Close contact with a confirmed or probable case of COVID-19 disease	79 (36)	17 (16)

*patients that did not meet the probable COVID-19 case definition and no SARS-Cov-2 test was performed before April 26, 2020

** symptom not included in COVID-19 Smart Data Elements

DEVELOPMENTS IN DIAGNOSTICS

DIAGNOSTIC ACCURACY OF AUGURIX COVID-19 IGG SEROLOGY RAPID TEST

Andrey DO, Cohen P, Meyer B, Torriani G, Yerly S, Mazza L, Calame A, Arm-Vernez I, Guessous I, Stringhini S, Roux-Lombard P, Fontao L, Agoritsas T, Stirnemann J, Reny JL, Siegrist CA, Eckerle I, Kaiser L, Vuilleumier N; Geneva Center for Emerging Viral Diseases.. Eur J Clin Invest. 2020 Jul 21:e13357. doi: 10.1111/eci.13357. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

Authors from Geneva, Switzerland assessed the diagnostic accuracy of Augurix COVID-19 IgG rapid diagnostic test (RDT) by analyzing blood samples from 46 RT-PCR confirmed SARS-CoV-2 cases and 45 asymptomatic donors who did not receive RT-PCR testing. Whole blood IgG Augurix RDT was found to have 88% sensitivity, 98% specificity, 97% PPV, and 94% NPV compared to recombinant immunofluorescence assay on plasma with increasing diagnostic accuracy after 14 days post-diagnosis (Table 3), making IgG Augurix RDT in whole blood a good diagnostic tool for SARS-CoV-2 in high COVID-19 prevalence settings when standard diagnostic serology is unavailable.

ABSTRACT

AIMS: To validate the diagnostic accuracy of the Augurix SARS-CoV-2 IgM/IgG rapid immunoassay diagnostic test (RDT) for COVID-19. METHODS: In this unmatched 1:1 case-control study, blood samples from 46 real-time RT-PCR-confirmed SARS-

CoV-2 hospitalized cases and 45 healthy donors (negative controls) were studied. Diagnostic accuracy of the IgG RDT was assessed against both an in-house recombinant spike-expressing immunofluorescence assay (rIFA), as an established reference method (primary endpoint), and the Euroimmun SARS-CoV2 IgG enzyme-linked immunosorbent assays (ELISA) (secondary endpoint). RESULTS: COVID-19 patients were more likely to be male (61% versus 20%; p=0.0001) and older (median 66 versus 47 years-old; p<0.001) than controls. Whole blood IgG-RDT results showed 86% and 93% overall Kendall concordance with rIFA and IgG ELISA, respectively. IgG RDT performances were similar between plasma and whole blood. Overall, RDT sensitivity was 88% (95% confidence interval [95%CI]: 70-96), specificity 98% (95%CI: 90-100), PPV 97% (95%CI: 80-100) and NPV 94% (95%CI: 84-98). The IgG-RDT carried out from 0 to 6 days, 7 to 14 days and >14 days after the SARS-CoV-2 RT-PCR test displayed 30%, 73% and 100% positivity rates in the COVID-19 group, respectively. When considering samples taken >14 days after RT-PCR diagnosis, NPV was 100% (95%CI:90-100), and PPV was 100% (95%CI:72-100). CONCLUSIONS: The Augurix IgG-RDT done in whole blood displays a high diagnostic accuracy for SARS-CoV-2 IgG in high COVID-19 prevalence settings, where its use could be considered in the absence of routine diagnostic serology facilities.

FIGURES

Table. 3

	SE % (95%CI)	SP % (95%CI)	PPV% (95%CI)	NPV% (95%CI)
All cases (n=91), IgG rIFA seropositivity 35%				
IgG RDT (WB) vs rIFA	88 (70-96)	98 (90-100)	97 (80-100)	94 (84-98)
IgG RDT (WB) vs ELISA	96 (80-100)	97 (88-99)	93 (76-99)	98 (90-100)
DPD 0-6 and controls (N= 65), IgG rIFA seropositivity 15%				
IgG RDT (WB) vs rIFA	70 (35-92)	100 (92-100)	100 (56-100)	95 (85-99)
IgG RDT (WB) vs ELISA	86 (42-99)	98 (90-100)	86 (42-99)	98 (90-100)
DPD 7-14 and controls (N= 59), IgG rIFA seropositivity 18%				
IgG RDT (WB) vs rIFA	91 (57-100)	98 (88-100)	91 (57-100)	98 (57-100)
IgG RDT (WB) vs ELISA	100 (66-100)	98 (88-100)	91 (57-100)	100 (91-100)
DPD >14 and controls (N= 57), IgG rIFA seropositivity 23%				
IgG RDT (WB) vs rIFA	100 (72-100)	100 (90-100)	100 (72-100)	100 (90-100)
IgG RDT (WB) vs ELISA	100 (72-100)	100 (90-100)	100 (72-100)	100 (90-100)

RDT, Augurix rapid diagnostic test ; SE, sensibility; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; rIFA, recombinant immunofluorescence assays

DETECTION OF COVID-19 INFECTION FROM ROUTINE BLOOD EXAMS WITH MACHINE LEARNING: A FEASIBILITY STUDY

Brinati D, Campagner A, Ferrari D, Locatelli M, Banfi G, Cabitza F.. J Med Syst. 2020 Jul 1;44(8):135. doi: 10.1007/s10916-020-01597-4.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Italian experts in chemistry, and information and laboratory medicine present a feasibility study on two machine learning models Logistic Regression and Random Forest (Figure 1) with comparable performance to rRT-PCR to detect SARS-CoV-2 using blood values from routine exams (Figure 2). The authors suggest the Decision Tree model (Figure 3) as a simple decision-making tool for identifying suspected cases of COVID-19 using other hematological lab results (Figure 2 and 3) and believe this method may circumvent the shortcomings of rRT-PCR.

SUMMARY

Two machine learning models are developed to detect COVID-19 using hematological parameters from routine blood samples to overcome the shortcoming of current rRT-PCR.

The authors analyzed the blood values from a dataset of 279 patients admitted at San Raffaele Hospital, Italy with COVID-19 symptoms from the end of Feb to mid-March, 2020. rRT-PCR from these patients showed 177 positive and 102 negatives for SARS-CoV-2.

The parameters included in the best performing model were analyzed for Feature importance scores with AST having the highest score (Figure 2).

Different machine learning classifiers were compared (Figure 1). The performance of the LR and RF model was well comparable with less than 1% difference. But, RF model turned out to be the best with high accuracy, sensitivity, specificity, PPV, and AUC.
TWRF - "accuracy=86%, sensitivity=95%, PPV=86%, specificity=75%, coverage=70%".

Since the RF model is the average of Decision Trees, the authors developed DT model to enable simple decision-making for COVID-19 suspect patients using the blood values. (Figure 3).

ABSTRACT

The COVID-19 pandemia due to the SARS-CoV-2 coronavirus, in its first 4 months since its outbreak, has to date reached more than 200 countries worldwide with more than 2 million confirmed cases (probably a much higher number of infected), and almost 200,000 deaths. Amplification of viral RNA by (real time) reverse transcription polymerase chain reaction (rRT-PCR) is the current gold standard test for confirmation of infection, although it presents known shortcomings: long turnaround times (3-4 hours to generate results), potential shortage of reagents, false-negative rates as large as 15-20%, the need for certified laboratories, expensive equipment and trained personnel. Thus there is a need for alternative, faster, less expensive and more accessible tests. We developed two machine learning classification models using hematochemical values from routine blood exams (namely: white blood cells counts, and the platelets, CRP, AST, ALT, GGT, ALP, LDH plasma levels) drawn from 279 patients who, after being admitted to the San Raffaele Hospital (Milan, Italy) emergency-room with COVID-19 symptoms, were screened with the rRT-PCR test performed on respiratory tract specimens. Of these patients, 177 resulted positive, whereas 102 received a negative response. We have developed two machine learning models, to discriminate between patients who are either positive or negative to the SARS-CoV-2: their accuracy ranges between 82% and 86%, and sensitivity between 92% e 95%, so comparably well with respect to the gold standard. We also developed an interpretable Decision Tree model as a simple decision aid for clinician interpreting blood tests (even off-line) for COVID-19 suspect cases. This study demonstrated the feasibility and clinical soundness of using blood tests analysis and machine learning as an alternative to rRT-PCR for identifying COVID-19 positive patients. This is especially useful in those countries, like developing ones, suffering from shortages of rRT-PCR reagents and specialized laboratories. We made available a Web-based tool for clinical reference and evaluation (This tool is available at https://covid19-blood-ml.herokuapp.com/).

FIGURES

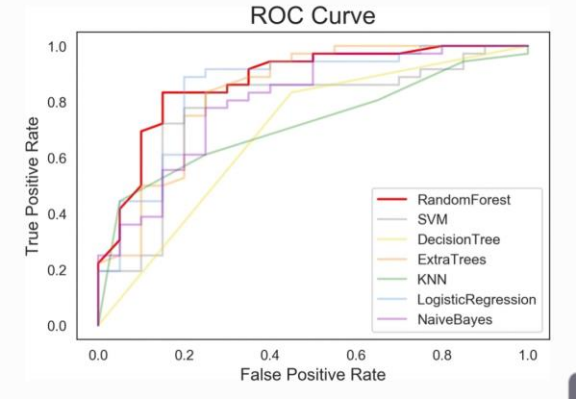


Figure 1: The sensitivity and specificity curve (i.e., sensitivity /positive predictive value curve or, equivalently true positive rate / false positive rate as depicted in the Figure) of the evaluated models. The best performing algorithm, Random Forest, is highlighted.

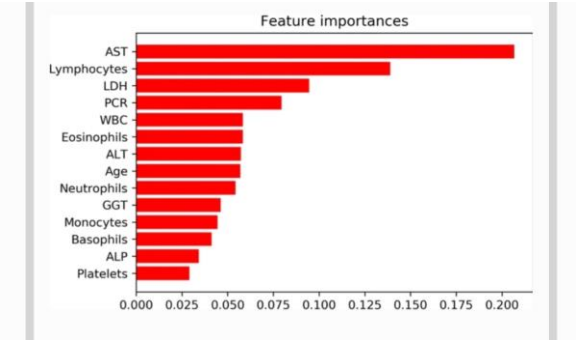


Figure 2: Feature importance scores for the best performing model.

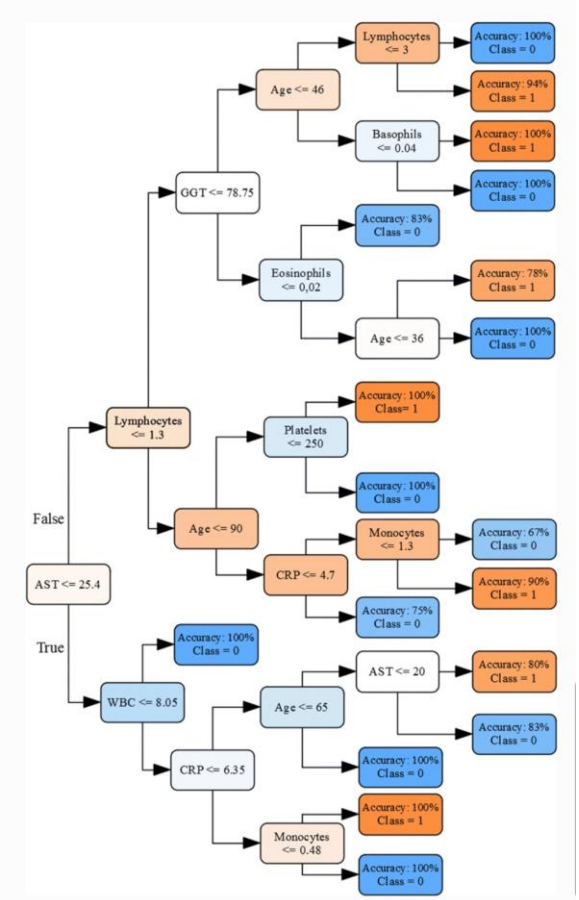


Figure 3: An interpretable Decision Tree, developed in order to support the interpretation of the predictions from the other models. Color gradients denote predictivity for either classes (shades of blue correspond to COVID-19 negativity, shades of orange to positivity)

THE ROLE OF SPIRITUALITY IN THE COVID-19 PANDEMIC: A SPIRITUAL HOTLINE PROJECT

Ribeiro MRC, Damiano RF, Marujo R, Nasri F, Lucchetti G.. J Public Health (Oxf). 2020 Jul 22:fdaa120. doi: 10.1093/pubmed/fdaa120. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A letter to the editor by associates of São Paulo Medical Spiritist Association in Brazil discussed the use of a spiritual care hotline run by specially trained psychiatrists and psychologists that began on 29 May 2020 and found widespread support by both health professionals and participants (108 appointments from 107 Brazilian states), suggesting utility of spiritual support platforms to provide holistic care, support mental health and address patients' spiritual needs as they cope with stressful conditions (i.e. isolation, closed churches, and deaths) during the COVID-19 pandemic.

ABSTRACT

Recent correspondence letters to the editor of this journal pointed out to the need of implementing psychological support during the pandemic and post-pandemic period to both general and frontline workers. Especially, they highlighted the importance of religious/spiritual interventions in order to provide an integral and holistic care. In this perspective, an important consequence of the social isolation is the closure of churches and the suspension of religious meetings in order to avoid agglomeration and contagion. However, although this is a very important approach in terms of public health, a question is raised: how to promote spiritual care and help spiritual/religious individuals to cope with their problems while maintaining compliance with social isolation? To address this question, we report the Spiritual Hotline Project, a project designed by many Brazilian healthcare workers intended to give spiritual and religious assistance to people with different cultural background. So far, the hotline was able to assist people from different parts of the world, including Brazil and Portugal as well as with different religious affiliation, in order to provide a spiritual comfort and care during this public health crisis.

DEBATE: FACING UNCERTAINTY WITH(OUT) A SENSE OF CONTROL - CULTURAL INFLUENCE ON ADOLESCENTS' RESPONSE TO THE COVID-19 PANDEMIC

Zhu N, O J, Lu HJ, Chang L.. Child Adolesc Ment Health. 2020 Jul 17. doi: 10.1111/camh.12408. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Authors within the fields of psychology and applied social sciences argue that uncertainty towards COVID-19-related restrictions may undercut adolescents' sense of control in an individualistic culture while increasing the sense of control of those in a collectivist culture due to their different learning styles (individual learning-focused problem-solving vs. social learning-oriented problem-solving). Further, adolescents from individualistic societies may practice risky behaviors (i.e. violations, substance use, etc) due to feeling a low sense of control in the context of restrictions on personal freedoms. The authors suggest that implementing creative, social learning approaches to portray the importance of societal restrictions may help adolescents mitigate uncertainties during the COVID-19 pandemic.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has brought about healthcare, economic, and psychological crises around the world. The psychological impact on adolescents is likely going to be uneven across different societies, as cultures vary in terms of their dominant learning style that may influence how people cope with uncertainty and perceive their sense of control. We postulate that for adolescents in individualistic cultures where individual learning prevails, their sense of control might be undermined by societal disease-control regulations that restrict personal freedoms, while adolescents' sense of control might increase via participating in societal preventive efforts in collectivistic cultures where social learning is more prevalent. Individual differences regarding one's sense of control would, in turn, have implications for adolescents' short-term adjustments to COVID-19-related challenges and their future development.

THE ACUTE IMPACT OF THE PANDEMIC OF COVID-19 ON THE PHENOMENOLOGICAL FEATURES IN THE FULL OR PARTIAL REMITTED PATIENTS WITH OBSESSIVE-COMPULSIVE DISORDER (OCD)

Matsunaga H, Mukai K, Yamanishi K.. Psychiatry Clin Neurosci. 2020 Jul 22. doi: 10.1111/pcn.13119. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Authors at the Department of Neuropsychiatry, Hyogo College of Medicine in Japan conducted a cross sectional study of full remitted (FR, n=24) and partial remitted (PR, n=36) patients with obsessive-compulsive disorder (OCD) between 7 April and 2 May 2020 and found compared to pre-pandemic values, Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores in the FR OCD group increased from an average of 5.5 to 5.7 and from 12.2 to 13 in the PR OCD group, while 6.7% of participants (n=4) exhibited additional/renewed OCD symptoms (contamination obsessions or washing compulsions). Authors suggest COVID-19 may induce health-anxiety based symptoms in full and partial remitted OCD patients and lead to acute impact on OCD severity and features.

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