The Daily COVID-19 Literature Surveillance Summary

July 22, 2020

COVID-19 LST

DISCLAIMER

This free and open source document represents a good faith effort to provide real time, distilled information for guiding best practices during the COVID-19 pandemic. This document is not intended to and cannot replace the original source documents and clinical decision making. These sources are explicitly cited for purposes of reference but do not imply endorsement, approval or validation.

This is not an official product or endorsement from the institutions affiliated with the authors, nor do the ideas and opinions described within this document represent the authors' or their affiliated institutions' values, opinions, ideas or beliefs. This is a good faith effort to share and disseminate accurate summaries of the current literature.

NOW LIVE!

Daily audio summaries of the literature in 10 minutes or less.
https://www.covid19lst.org/podcast/

COVID-19 LST

COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table
OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653
** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

CLIMATE:

- A retrospective observational study of 336 severely or critically ill COVID-19 patients in Wuhan, China found that decreased lymphocyte ratios (<8.615%), elevated blood urea nitrogen levels (≥5.95 mmol/l), and raised D-dimer levels (≥1.56 µg/ml) at admission were associated with increased mortality. Using these three laboratory indicators, the authors created a model for predicting clinical outcome in critically ill COVID-19 patients.
- Italian authors propose a mathematical model to predict the rapidly evolving trends of the pandemic on a short and long-term basis considering two important variables - ICU beds and official deaths. They believe these models may facilitate planned decision-making and emergency preparedness.

EPIDEMIOLOGY:

- Biologists from Spain propose a pathophysiological mechanism for the "cytokine storm" seen in severe COVID-19 disease. They suggest that SARS-CoV-2 has an effect on macrophage activation by reducing cell surface ACE2 expression, causing an imbalance of increased pro-inflammatory Ang-II and decreased anti-inflammatory Ang1-7. As a result, the lungs release IL-6 cytokines which have been strongly implicated in this hyperinflammatory state, suggesting that modulation of this pathway may be a key aspect of potential target for COVID-19 treatment.
- Authors from the Imperial College in London discuss how T cell response may be a critical aspect of long-lasting immunity to SARS-CoV-2 infection. This theory is supported by evidence of the well-documented finding of lymphopenia in severe disease, the cross reactive immunity of memory T cells to among other coronaviruses, and the basic principle that CD8+ (T cells) are critical in combating both acute and chronic viral infections via the CD8 receptor to MHC-1 interaction with antigen presenting cells. Authors suggest that, while the focus has been on the role of neutralizing antibodies in immunity, T cell response should be strongly considered in vaccine development and measuring herd immunity.

TRANSMISSION AND PREVENTION:

- A cohort study from China of 182 recovered COVID-19 patients under isolation found that 20 (10.99%) of these patients were repeat positives upon testing for SARS-CoV-2 RNA, despite showing no clinical symptoms and having SARS-CoV-2 antibodies. These patients tended to be younger (less than or equal to 18 years old) and have experienced only mild disease during their initial infection ($p < 0.05$). These results further complicate policy decisions such as reopening of schools and highlight the importance of widespread testing to detect reduce asymptomatic spread.

MANAGEMENT:

- This case series from Switzerland describes encephalopathy in five patients intubated for COVID-19 acute respiratory distress syndrome (ARDS). Patients' Glasgow Coma Scores (GCSs) ranged from 4-9, and researchers noted the presence of type IV oligoclonal bands in the patients' cerebrospinal fluid (CSF) and abnormal contrast enhancement in the intracerebral vascular walls on MRI without evidence of arterial stenosis, inflammatory plaques, or leptomeningeal enhancement (Figure 1). The patients were started on a course of IV methylprednisolone, which resulted in positive clinical outcomes, with improved GCSs in all patients and extubation of three of the five patients. These findings point to the potential utility of corticosteroid treatment for COVID-19 associated encephalopathy.

R&D DIAGNOSIS AND TREATMENT:

- A retrospective study of 134 COVID-19 patients compared overall clinical improvement, mortality, ICU stay, and adverse effects between patients administered hydroxychloroquine plus azithromycin and a control group that did not receive treatment. The study showed no statistically significant clinical improvement by day seven of treatment between the two groups, but a higher incidence of QT prolongation ($p=0.028$), mortality ($p=0.03$), and ICU transfer ($p=0.16$) in the treatment group compared to the control group. The authors use these findings to illustrate the potentially hazardous effects of adopting therapeutics without adequate scientific study and peer review.

MENTAL HEALTH AND RESILIENCE:

- Researcher from Seoul, Korea investigated the psychological impacts of mandatory quarantine of 72 caregivers due to contact with a COVID-19 patient in a children's hospital. The highest reported were worrying (94.4%) and nervousness (90.3%), there were some reports of suicidal (4.2%) and homicidal (1.4%) ideations, and fear of infection of the patient (91.7%) and fear of infection of oneself (86.1%) were the most frequently reported stressors (Table 1). Authors emphasize the need to balance carefully the benefits of mandatory quarantine against its psychological costs to patients and caregivers when making decisions.

TABLE OF CONTENTS

EPIDEMIOLOGY

MODELING

LABORATORY FINDINGS AND A COMBINED MULTIFACTORIAL APPROACH TO PREDICT DEATH IN CRITICALLY ILL PATIENTS WITH COVID-19: A RETROSPECTIVE STUDY

Liu Q, Song NC, Zheng ZK, Li JS, Li SK.. Epidemiol Infect. 2020 Jun 30:1-26. doi: 10.1017/S0950268820001442. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

Authors of a retrospective observational study of 336 severely or critically ill COVID-19 patients conducted in Wuhan, China found that decreased lymphocyte ratios (<8.615%), elevated blood urea nitrogen levels (≥5.95 mmol/l), and raised D-dimer levels (≥1.56 μg/ml) at admission were related to death outcomes and subsequently used these three laboratory indicators to create a model for predicting clinical outcome in critically ill COVID-19 patients (Table 3).

SUMMARY

A single-center, retrospective, observational study of 336 patients who developed severe or critically ill COVID-19 infection compared patients' laboratory parameters between survivor and non-survivors at admission, when mechanically ventilated, and before death in order to develop a clinical outcome prediction model. A multivariable regression analysis indicated that decreased lymphocyte ratios, elevated BUN, and elevated D-dimer levels at admission were closely related to death. The logistic regression model and ROC curves evaluated the efficiency of these three laboratory parameters and their use in a prediction model (Table 3). The authors found no statistical difference when comparing these three laboratory indicators between admission, when ventilated, and before death. Based on this, they suggest that these indicators may not change over the patient's clinical course and existing treatments may not significantly change the disease's course (Table 4). Elevated D-dimer levels indicate that severe infection or sepsis is a major cause of death in COVID-19 patients, while lower lymphocyte ratio suggests that the virus suppresses cellular immune function through lymphocyte apoptosis, and that elevated BUN related to acute kidney injury may be due viral invasion, insufficient oxygen supply, and shock.

FIGURES

Table 3. AUC of meaningful factors predicting death

	AUC (95% CI)	Cut-off value	Sensitivity	Specificity	PPV	NPV
Lymr (%)	0.980 (0.961–0.999)	8.615	0.941	0.972	0.800	0.993
BUN (mmol/l)	0.853 (0.755–0.951)	5.950	0.765	0.948	0.634	0.973
DD (μg/ml)	0.951 (0.916–0.987)	1.560	0.912	0.941	0.646	0.990
PRE	0.994 (0.979–0.999)	0.115	1.000	0.972	0.810	1.000

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; Lymr, lymphocyte ratio; BUN, blood urea nitrogen; DD, D-dimer; PRE, a combined predictive factor with the three factors above.

Table 3: AUC of meaningful factors predicting death. AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; Lymr, lymphocyte ratio; BUN, blood urea nitrogen; DD, D-dimer; PRE, a combined predictive factor with the three factors above.

Table 4. Meaningful indicators of patients who died at different time points

	On admission	Mechanical ventilation	Before death	*P*-value
Lymr (%)	4.20 (2.50–7.11)	4.50 (2.38–8.08)	4.45 (1.95–12.4)	0.568
BUN (mmol/l)	9.79 (5.83–12.08)	9.71 (5.28–14.90)	10.65 (8.75–11.87)	0.361
DD (μg/ml)	4.02 (2.34–9.84)	8.16 (6.43–10.02)	6.45 (3.03–9.87)	0.121

Lymr, lymphocyte ratio; BUN, blood urea nitrogen; DD, D-dimer.
Notes: 95% confidence interval in brackets.

Table 4: Meaningful indicators of patients who died at different time points. Lymr, lymphocyte ratio; BUN, blood urea nitrogen; DD, D-dimer

A SIMPLIFIED MATH APPROACH TO PREDICT ICU BEDS AND MORTALITY RATE FOR HOSPITAL EMERGENCY PLANNING UNDER COVID-19 PANDEMIC

Manca D, Caldiroli D, Storti E.. Comput Chem Eng. 2020 Sep 2;140:106945. doi: 10.1016/j.compchemeng.2020.106945. Epub 2020 Jun 4.
Level of Evidence: Other - Modeling

BLUF

Italian authors propose simplified math models (Figures 2, 6 and 7) to predict evolution trends of the COVID-19 pandemic on a short and long-term basis considering two important variables - ICU beds and official deaths. They believe these models may facilitate planned decision-making and emergency preparedness.

SUMMARY

Three mathematical models - Exponential Modified Gaussian (EMG), Logistics, and Gompertz (Figures 2, 6, 7) are proposed to predict COVID-19 evolution trends in Italy and Lombardy considering two variables - ICU beds and official deaths.

Figure 1 depicts the exponential growth of ICU beds in Italy where linear trend progresses gradually towards quadratic behavior justifying EMG.

Figure 2 describes the ICU patients in Lombardy - logistic and Gompertz model describes the uphill trend (day 1-32), EMG depicts the plateau and downhill trends (from day 32). The reverse logistic and Gompertz describe the downhill trend from the maximum plateau (from day 41). On extrapolating to the long-term horizon, the bottom horizontal red line shows 10% of the maximum value and the time when most of the ICU wards would be empty.

Figure 3 depicts deaths in Italy showing inflection and halfway points. Gompertz model predicted the total expected death of which 98% attained on day 111. On day 130, "Gompertz predicts 99.17% of the whole phenomenon is manifested". The Gompertz is the only reliable model over long-term horizons.

RMSE(Root mean square errors), MAE, MEDAE (Mean and Median absolute errors) predict the performances of these three models.

ABSTRACT

The different stages of Covid-19 pandemic can be described by two key-variables: ICU patients and deaths in hospitals. We propose simple models that can be used by medical doctors and decision makers to predict the trends on both short-term and long-term horizons. Daily updates of the models with real data allow forecasting some key indicators for decision-making (an Excel file in the Supplemental material allows computing them). These are beds allocation, residence time, doubling time, rate of renewal, maximum daily rate of change (positive/negative), halfway points, maximum plateaus, asymptotic conditions, and dates and time intervals when some key thresholds are overtaken. Doubling time of ICU beds for Covid-19 emergency can be as low as 2-3 days at the outbreak of the pandemic. The models allow identifying the possible departure of the phenomenon from the predicted trend and thus can play the role of early warning systems and describe further outbreaks.

FIGURES

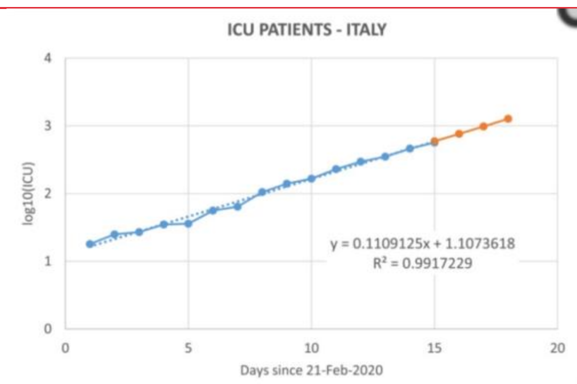


Figure 2: Linear trend in semilog coordinates of ICU patients in Italy in the first 15 days of pandemic. Cyan line with dots reports real data. Orange line with dots shows extrapolated values. Dashed line is the linear trend line that evidences the exponential growth of the phenomenon.

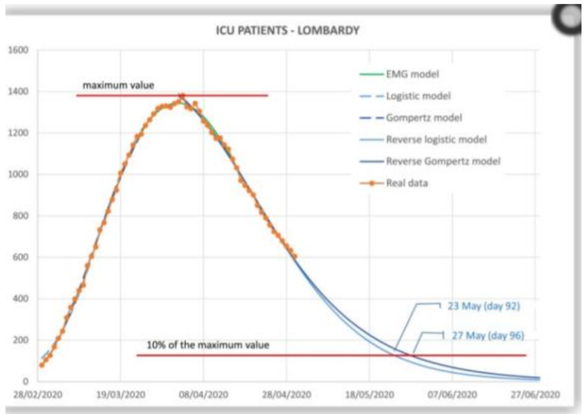


Figure 6: Extrapolation of ICU patients in Lombardy over a long-term horizon. The red horizontal bottom line shows the 10% threshold respect to the maximum measured value and identifies the times when most of the ICU wards should be empty. Last available real data on 30-Apr.

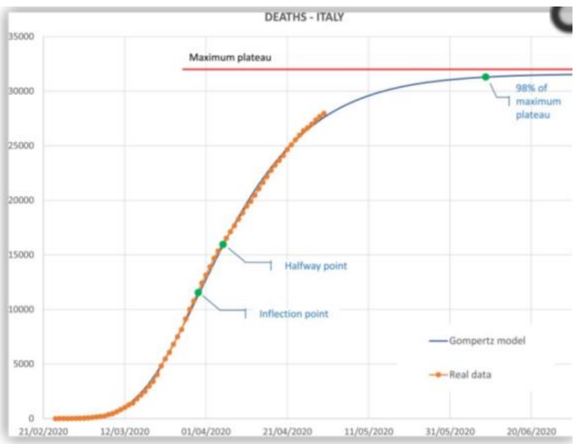


Figure 6: Extrapolation of ICU patients in Lombardy over a long-term horizon. The red horizontal bottom line shows the 10% threshold respect to the maximum measured value and identifies the times when most of the ICU wards should be empty. Last available real data on 30-Apr.

SARS-COV-2 INFECTION-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Prilutskiy A, Kritselis M, Shevtsov A, Yambayev I, Vadlamudi C, Zhao Q, Kataria Y, Sarosiek SR, Lerner A, Sloan JM, Quillen K, Burks EJ.. Am J Clin Pathol. 2020 Jul 18:aqaa124. doi: 10.1093/ajcp/aqaa124. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

Researchers from Boston, MA conducted autopsies of four patients who died of COVID-19 and found multiple signs of hemophagocytic lymphohistiocytosis (HLH); a condition in which excess immune cells are generated (Figure 1, summarized below). The authors suggest identifying HLH in the setting of SARS-CoV-1 infections can help optimize therapeutic strategies against COVID-19's hyperinflammatory clinical phenotype.

SUMMARY

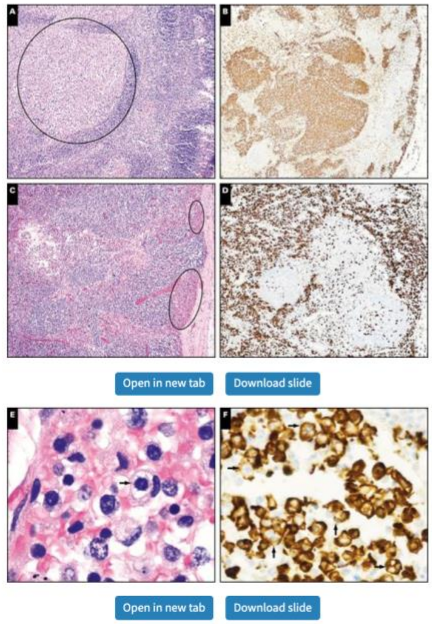
Findings suggestive of HLH included:
(1) diffuse alveolar damage, (2) histologic evidence (via H&E stain and immunohistochemical staining for CD163) of hemophagocytosis within the lymph nodes surrounding the lungs, (3) hemophagocytosis in the spleen, and (4) diagnostic features of HLH (H-score of 217).

ABSTRACT

OBJECTIVES: A subset of coronavirus disease 2019 (COVID-19) patients exhibit clinical features of cytokine storm. However, clinicopathologic features diagnostic of hemophagocytic lymphohistiocytosis (HLH) have not been reported. We studied the reticuloendothelial organs of 4 consecutive patients who died of COVID-19 and correlated with clinical and laboratory parameters to detect HLH. METHODS: Autopsies were performed on 4 patients who died of COVID-19. Routine H&E staining and immunohistochemical staining for CD163 were performed to detect hemophagocytosis. Clinical and laboratory results from premortem blood samples were used to calculate H-scores. RESULTS: All 4 cases demonstrated diffuse alveolar damage within the lungs. Three of the 4 cases had histologic evidence of hemophagocytosis within pulmonary lymph nodes. One case showed hemophagocytosis in the spleen but none showed hemophagocytosis in liver or bone marrow. Lymphophagocytosis was the predominant form of hemophagocytosis observed. One patient showed diagnostic features of HLH with an H-score of 217, while a second patient likely had HLH with a partial H-score of 145 due to a missing triglyceride level. The remaining 2 patients had H-scores of 131 and 96. CONCLUSIONS: This is the first report of severe acute respiratory syndrome coronavirus 2-associated HLH. Identification of HLH in a subset of patients with severe COVID-19 will inform clinical trials of therapeutic strategies.

FIGURES

Image 1



Hemophagocytosis in pulmonary hilar and mediastinal lymph nodes. H&E (**A**) and CD163 immunohistochemical (**B**) stains of lymph node from patient 1 showing distended cortical and subcortical sinusoids filled with histiocytes exhibiting focal necrosis (circled area). (×40). H&E (**C**) and CD163 immunohistochemical (**D**) stains of a lymph node from patient 2 showing a lesser degree of sinusoidal expansion, predominantly filling the subcapsular sinuses (circled areas) (×40). Hemophagocytosis consisted predominantly of lymphophagocytosis (arrow) in all cases and seen on H&E stain (**E**, ×1,000) and highlighted with CD163 immunohistochemical stain where numerous histiocytes phagocytosing 1 to several lymphocytes were apparent (arrows) (**F**, ×400).

SARS-COV-2 AS A FACTOR TO DISBALANCE THE RENIN-ANGIOTENSIN SYSTEM: A SUSPECT IN THE CASE OF EXACERBATED IL-6 PRODUCTION

Franco R, Rivas-Santisteban R, Serrano-Marín J, Rodríguez-Pérez AI, Labandeira-García JL, Navarro G.. J Immunol. 2020 Jul 17:ji2000642. doi: 10.4049/jimmunol.2000642. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Biologists from Spain suggest that SARS-CoV-2 has an effect on macrophage activation by reducing cell surface ACE2 expression causing an imbalance of increased pro-inflammatory Ang-II and decreased anti-inflammatory Ang1-7 (Figure 4 and 5). As a result, the lungs release IL-6 cytokines and thus potentially correlating to COVID-19 severity, suggesting a potential target for COVID-19 treatment.

ABSTRACT

Fever in infections correlates with inflammation, macrophage infiltration into the affected organ, macrophage activation, and release of cytokines involved in immune response, hematopoiesis, and homeostatic processes. Angiotensin-converting enzyme 2 (ACE2) is the canonical cell surface receptor for SARS-CoV-2. ACE2 together with angiotensin receptor types 1 and 2 and ACE2 are components of the renin-angiotensin system (RAS). Exacerbated production of cytokines, mainly IL-6, points to macrophages as key to understand differential COVID-19 severity. SARS-CoV-2 may modulate macrophage-mediated inflammation events by altering the balance between angiotensin II, which activates angiotensin receptor types 1 and 2, and angiotensin 1-7 and alamandine, which activate MAS proto-oncogene and MAS-related D receptors, respectively. In addition to macrophages, lung cells express RAS components; also, some lung cells are able to produce IL-6. Addressing how SARS-CoV-2 unbalances RAS functionality via ACE2 will help design therapies to attenuate a COVID-19-related cytokine storm.

FIGURES

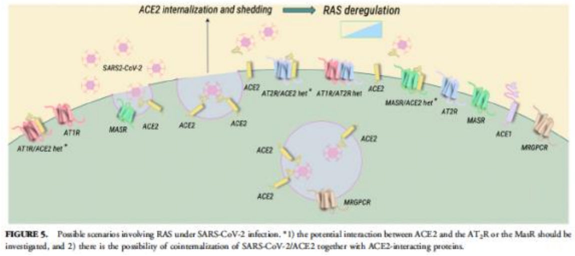
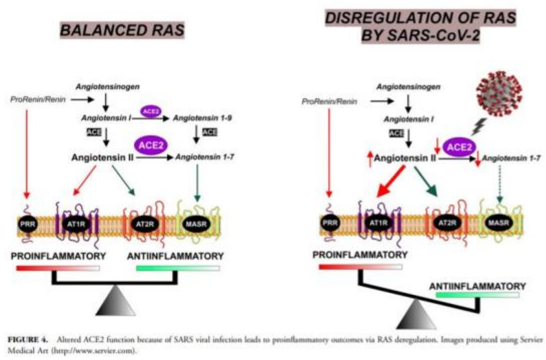


FIGURE 5. Possible scenarios involving RAS under SARS-CoV-2 infection. *1) the potential interaction between ACE2 and the AT2R or the MasR should be investigated, and 2) there is the possibility of cointernalization of SARS-CoV-2/ACE2 together with ACE2-interacting proteins.



SARS-COV-2 T CELL IMMUNITY: SPECIFICITY, FUNCTION, DURABILITY, AND ROLE IN PROTECTION

Altmann DM, Boyton RJ.. Sci Immunol. 2020 Jul 17;5(49):eabd6160. doi: 10.1126/sciimmunol.abd6160.
Level of Evidence: Other - Review / Literature Review

BLUF

A perspective article by authors at Imperial College in London, UK analyze T cell immunity to SARS-CoV-2 (Table 1) by presenting hypothetical interactions (Figure 1) while also discussing observations including lower CD8 levels in bronchoalveolar lavage (BAL) with overt lymphopenia in severe/critical disease (Liao et al, 2020), viral adaptions predisposing for T cell activation phenotype despite elevated co-expression of exhaustion markers (PD-1 and TIM-3), and cross-reactive immune memory from prior human coronaviruses (HCoVs) infection. Authors suggest T cell profiles may be more reliable adaptive immunity markers than antibodies but acknowledge a need for further research of T cell immunology to gain a detailed understanding of COVID-19 pathogenesis.

ABSTRACT

In efforts to synthesize a clear understanding of SARS-CoV-2 protective immunity, antibody analysis has been paralleled by T cell studies across asymptomatic, mild and severe COVID-19. Defining CD4 and CD8 effector functions in protection is important considering that antibody responses appear short-lived and T cell memory is potentially more durable. To fully understand population level immunity, screening for both antibody and T cell immunity using standardized testing methods would be beneficial.

FIGURES

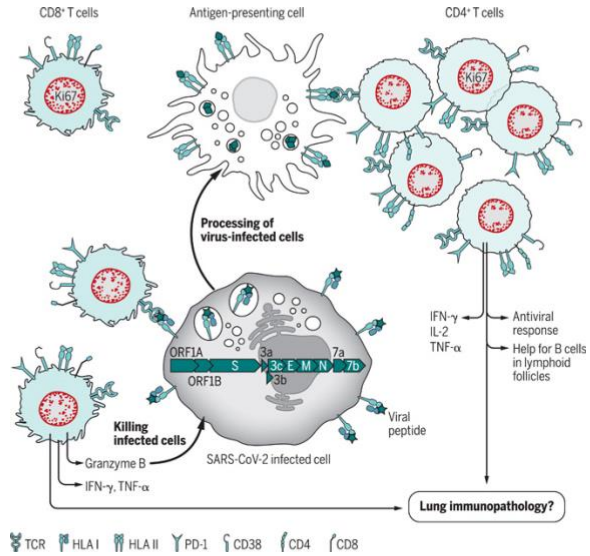


Figure 1. Hypothetical interactions between SARS-CoV-2 infected cells, antigen-presenting cells, CD4 and CD8 T cells. Viral peptides (shown in dark green) will be processed from all parts of the SARS-CoV-2 proteome and presented to the TCR repertoire in the grooves of HLA I molecules on the infected cell, and by HLA II molecules of antigen-presenting cells that have taken up debris from infected cells. SARS-CoV-2-reactive CD4 cells appear to be largely Th1-like, secreting IFN-γ, TNF-α and IL-2. CD8 cells can secrete a similar cytokine profile but also lyse infected target cells. We are unaware of data at present clearly indicating a role of CD4 or CD8 T cells in lung immunopathology, but illustrate here the hypothetical likelihood of this.

Manuscript	Methods	Cohort	T cell subsets, features	Antigen hierarchy	Epitope data	Cytokine/Effector function	Cross-reactivity evidence
Braun *et al.* (*15*)	Spike peptide panel; AIM	Mild, severe, ICU COVID-19	CD38⁺HLA-DR⁺ activated T cells	Analysis limited to Spike	nd	nd	Yes: a third of HC responded to C-terminal peptides from Spike
Thieme *et al.* (*7*)	Peptide panels; ICS	Moderate, severe, ICU COVID-19	• CD4 response detected in 95% • CD8 response in 77%	M>S>N	nd	CD4 response: IFN-γ, IL-2, TNF-α; Higher frequency of polyfunctional cells in patients with greater severity	nd
Sekine *et al.* (*3*)	Peptide panels; ICS; AIM, tetramers.	Moderate to severe COVID-19; exposed family members	• CD4: CD38⁺CD69⁺ Ki67⁺ PD-1⁺ • CD8: CD38⁺ CD39⁺ CD69⁺ CTLA-4⁺ HLA-DR⁺ Ki67⁺ LAG 3⁺ TIM-3⁺ 'activated-cycling' phenotype	M>N	Several predicted HLA-A and HLA-B predicted binders from the full proteome used to make tetramers	CD4 response: IFN-γ, IL-2, TNF-α; Th1-skewed response CD8 response: IFN-γ, TNF-α, CD107a	Yes: cross-reactive recognition of Spike and M
Peng *et al.* (*8*)	Peptide pools (not ORF1); ICS; ELISpot; pentamers; T cell lines	Recovered from mild to severe COVID-19	Higher magnitude and broader breadth of T cell responses in severe cases in comparison with mild cases	S>M>ORF3a	Spike: 18 peptides N: 10 peptides M: 6 peptides ORF3a: 4 peptides ORF7a: 3 peptides	IFNγ, IL-2, and TNF-α polyfunctional response in both CD4 and CD8, mild and severe cases	No: none observed in n=16
Grifoni *et al.* (*9*)	Mega-pools; AIM; ICS	Mild to severe COVID-19, and pre-2019 samples	Patients were convalescent and showed no evidence of lymphopenia	S>M>N	Antigen mega-pools not resolved to the level of individual epitopes	CD4 response mainly IFN-γ; CD8 is IFN-γ, TNF-α, and granzyme B	Half of HC showed cross-reactivity with RBD from HCoV OC43 or NL63
LeBert *et al.* (*16*)	Peptide pools from N, ORF3 NSP-7 and NSP-13	Mild to severe COVID-19 convalescent	Response in 100% to N epitopes	Study focus on N	N: 7 peptides	nd	All SARS-CoV patients showed cross-reactive response to SARS-CoV-2 NP. Half of HC show cross-reactivity with epitopes in ORF-1 NSP-7 and -13
Gallais *et al.* (*4*)	Peptide pools; ELISpot.	Household contacts of 7 PCR+ cases	Response in 100% of index cases and in seronegative contacts	S=M=N co-dominant	nd	nd	nd
Weiskopf *et al.* (*13*)	Mega-pools; AIM	ICU ARDS including fatal cases	• T cell lymphopenia • Majority of responder cells were Tcm based on CD45RA and CCR7 expression	S>'remainder of proteome mega-pool'	Antigen mega-pools not resolved to the level of individual epitopes	T cell culture supernatants contained: IFN-γ, TNF-α, IL-2, IL-5, IL-13, IL-10, IL-9, IL-17A, IL-17F and IL-22	Cross-reactivity in 2/10 HC.
Oja *et al.* (*2*)	Peptide pools; AIM; ICS; used PBMC and BAL	Mild, severe, ICU COVID-19	• T cell lymphopenia • PD-1 highest in most severe	S>N>M>ORF3a. Spike response seen in BAL. Reduced response to Spike and N in ICU cases	nd	Mainly IFN-γ and TNF-α. IFN-γ response significantly lower in ICU cases	No cross-reactivity found to Spike peptides from S299E, S-OC43

Table 1. Summary of published studies analyzing T cell responses to SARS-CoV-2. Abbreviations: AIM=activation-induced marker; ARDS=acute respiratory distress syndrome; BAL=bronchoalveolar lavage; HC=healthy control; ICS=intracellular cytokine staining; ICU=intensive care unit; nd=not done; M=membrane antigen; N=nucleocapsid antigen; ORF=open reading frame; S=spike antigen; Tcm=central memory T cells

DEVELOPMENTS IN TRANSMISSION & PREVENTION

RECURRENCE OF POSITIVE SARS-COV-2 VIRAL RNA IN RECOVERED COVID-19 PATIENTS DURING MEDICAL ISOLATION OBSERVATION

Yuan B, Liu HQ, Yang ZR, Chen YX, Liu ZY, Zhang K, Wang C, Li WX, An YW, Wang JC, Song S.. Sci Rep. 2020 Jul 17;10(1):11887. doi: 10.1038/s41598-020-68782-w.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A cohort study by researchers at the Science and Education Department at Shenzhen Samii Medical Center (Guandong Province, China) consisting of 182 recovered COVID-19 patients under isolation found that 20 (10.99%) of these patients were repeat positives upon testing for SARS-CoV-2 RNA, despite showing no clinical symptoms and having SARS-CoV-2 antibodies. These patients tended to be younger (less than or equal to 18 years old) and did not have severe infection during their initial clinical course (p less than 0.05 for all, Table 1). These results suggest that it is important to perform regular clinical testing of recovered COVID-19 patients to understand their infectivity risk and manage their removal from isolation.

ABSTRACT

Recently, the recurrence of positive SARS-CoV-2 viral RNA in recovered COVID-19 patients is receiving more attention. Herein we report a cohort study on the follow-up of 182 recovered patients under medical isolation observation. Twenty (10.99%) patients out of the 182 were detected to be SARS-CoV-2 RNA positive (re-positives), although none showed any clinical symptomatic recurrence, indicating that COVID-19 responds well to treatment. Patients aged under 18 years had higher re-positive rates than average, and none of the severely ill patients re-tested positive. There were no significant differences in sex between re-positives and non-re-positives. Notably, most of the re-positives turned negative in the following tests, and all of them carried antibodies against SARS-CoV-2. This indicates that they might not be infectious, although it is still important to perform regular SARS-CoV-2 RNA testing and follow-up for assessment of infectivity. The findings of this study provide information for improving the management of recovered patients, and for differentiating the follow-up of recovered patients with different risk levels.

FIGURES

	Re-positive (n = 20)	Non-re-positive (n = 162)	*P* value
Epidemiological information			
Total (n = 182)	20 (10.99%)	162	/
Severe cases (n = 39)	0**	39	0.014
Wuhan exposure (n = 75)	5	70	0.120
Time from onset to admission	5.1 ± 4.8	4.5 ± 4.0	0.766
Time from admission to discharge	20.8 ± 7.1*	25.6 ± 7.6	0.02
Comorbidity			
Hypertension	3	26	0.907
Diabetes	0	12	0.211
Hyperlipemia	0	2	0.627
Cardiovascular disease	2	10	0.520
Malignant tumor	0	5	0.432
Hepatopathy	1	7	0.894
Lung disease	0	3	0.547
Sex			
Male (n = 84)	7 (8.3%)	77	0.294
Female (n = 98)	13 (13.3%)	85	
Age (years)			
Median age (range)	41.5 (1–72)	49 (1–81)	/
Average age	39.9 ± 20.1	47.2 ± 16.6	0.073
Under 18 years old (n = 13)	4 (30.8%)*	9	0.018
Over 18 years old (n = 169)	16 (9.5%)	153	

Table 1. Basic information of recovered COVID-19 patients. All data were analyzed using the Mann–Whitney U test. *less than 0.05, **less than 0.01 versus the non-re-positive group.

IMPACT OF HEALTHCARE WORKER SHIFT SCHEDULING ON WORKFORCE PRESERVATION DURING THE COVID-19 PANDEMIC

Kluger DM, Aizenbud Y, Jaffe A, Parisi F, Aizenbud L, Minsky-Fenick E, Kluger JM, Farhadian S, Kluger HM, Kluger Y.. Infect Control Hosp Epidemiol. 2020 Jul 20:1-15. doi: 10.1017/ice.2020.337. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

A modeling study using a Monte Carlo simulation of healthcare worker (HCW) shift schedules conducted by researchers from Yale University found that the optimal arrangement to reduce the spread of COVID-19 from infected patients to HCWs would be an arrangement where:
1. All HCWs work at least 3 consecutive days,
2. Nurses take 12 hour shifts as opposed to 8 hour shifts, and
3. The number of staggered shifts between HCWs is minimized (Figure 2).

These results suggest that simple scheduling optimizations can be used to preserve the physician and nursing workforce during the pandemic.

ABSTRACT

Reducing SARS-COV-2 infections among healthcare workers is critical. We ran Monte Carlo simulations modeling the spread of SARS-CoV-2 in non-COVID wards, and found that longer nursing shifts and scheduling designs in which teams of nurses and doctors co-rotate no more frequently than every three days, can lead to fewer infections.

FIGURES

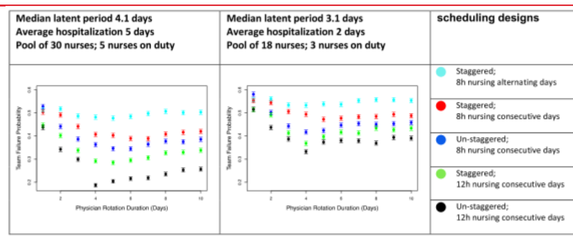


Figure 2. Probability of team failure vs. physician rotation duration. Team failure probability is based on Monte Carlo simulations plotted by duration of physician rotation, modeled for a team caring for patients with five-day average hospitalizations with fewer patients per nurse, such as internal medicine wards (left) or for patients with two-day average hospitalizations and more patients per nurse, such as maternity wards (right.) The plots compare the probability of team failure for five different scheduling designs. The designs simulated vary by whether they are staggered versus un-staggered, whether they have 8-hour nurse shifts versus 12-hour nurse shifts, and whether nurses work consecutive days versus work alternating days. Note that in our simulations with nurses working consecutive days, when the physician rotations are sufficiently short, the nurses work the same number of consecutive days as the physician do; however, if the physician rotations are too long, the nurses are scheduled to work as many consecutive days as possible without exceeding 48 hours of work in the span of one week, and without exceeding 36 hours/week on average. Of note, due to unknown variables in the model, these plots do not suggest that the actual probability of team failure lies in the 20-60% range, but rather the plots are intended to demonstrate the relative improvement of various staff scheduling changes. From the plots above, and from similar plots that we generated with varying choices of the unknown parameters, we observe that scheduling designs with un-staggered rotations, 12-hour nursing shifts over consecutive days are favorable, and further, the probability of team failure is lower when all HCWs work at least 3-4 consecutive days.

MANAGEMENT

EARLY OUTPATIENT TREATMENT OF SYMPTOMATIC, HIGH-RISK COVID-19 PATIENTS

Korman TM.. Am J Epidemiol. 2020 Jul 20:kwaa154. doi: 10.1093/aje/kwaa154. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

An Australian author critiques Risch 2020 "Early outpatient treatment of symptomatic, high-Risk Covid-19 patients" by analyzing the risk vs benefit of treating symptomatic COVID-19 patients early with hydroxychloroquine, azithromycin, and remdesivir. Risch concludes that early intervention must be promoted immediately for COVID-19 patients. However, this author suggests that since current studies have shown minimal benefit to early treatment with these medications, the risks may not yet outweigh the benefits and providers should use caution if prescribing these for COVID-19 outpatients.

ACUTE CARE

GASTROINTESTINAL AND HEPATIC ABNORMALITIES IN PATIENTS WITH CONFIRMED COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Zarifian A, Bidary MZ, Arekhi S, Rafiee M, Gholamalizadeh H, Amiriani A, Ghaderi MS, Khadem-Rezaiyan M, Amini M, Ganji A.. J Med Virol. 2020 Jul 18. doi: 10.1002/jmv.26314. Online ahead of print.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Authors from Mashhad University of Medical Sciences in Iran performed a meta-analysis of 67 studies on gastrointestinal and hepatic characteristics of patients with confirmed COVID-19 (n=13,251). After adjusting for chronic pre-existing illnesses, diarrhea (8.7%), anorexia (8.0%), and nausea (5.1%) were found to be the three most common gastrointestinal symptoms; mild reduction in albumin (49.3%) and elevations in ALT (19.4%) and AST (15.2%) were the most common liver function abnormalities (Table 3). Additionally, they found a higher prevalence of gastrointestinal and liver abnormalities among severe COVID-19 cases. These findings may help clinicians be aware of such gastrointestinal and hepatic manifestations when evaluating patients of suspected COVID-19.

ABSTRACT

BACKGROUND AND AIM: Although not common, gastrointestinal and liver symptoms have reportedly been the initial presentation of COVID-19 in a large group of patients. Therefore, knowing the frequency and characteristics of these manifestations of COVID-19 is important for both clinicians and health policymakers. A systematic review and meta-analysis of the available data on the gastrointestinal and liver manifestations of COVID-19 patients was performed. METHODS: PubMed and Scopus databases and Google Scholar search engine were searched for published and unpublished preprint articles up to April 10, 2020. Original studies providing information on clinical digestive symptoms or biomarkers of liver function in patients with polymerase chain reaction confirmed diagnosis of COVID-19 were included. After quality appraisal, data were extracted. Prevalence data from individual studies were pooled using a random-effects model. RESULTS: Overall, 67 studies were included in this systematic review and meta-analysis, comprising a pooled population of 13,251 patients with confirmed COVID-19. The most common gastrointestinal symptoms were anorexia (10.2%, 95%CI=6.2-16.4%), diarrhea (8.4%, 95%CI=6.2-11.2%), and nausea (5.7%, 95%CI=3.7-8.6%), respectively. Decreased albumin levels (39.8%, 95%CI=15.3-70.8%), increased aspartate aminotransferase (22.8%, 95%CI=18.1-28.4%) and alanine aminotransferase (20.6%, 95%CI=16.7-25.1%) were common hepatic findings. After adjusting for pre-existing gastrointestinal (5.9%) and liver diseases (4.2%), the most common gastrointestinal findings were diarrhea (8.7%, 95%CI=5.4-13.9%), anorexia (8.0%, 95%CI=3.0-19.8%), and nausea (5.1%, 95%CI=2.2-14.3%). CONCLUSIONS: Gastrointestinal and liver manifestations are not rare in patients with COVID-19, but their prevalence might be affected by pre-existing diseases. Diarrhea and mild liver abnormalities seem to be relatively common in COVID-19, regardless of comorbidities.

FIGURES

Table 3. Pooled prevalence of gastrointestinal and liver symptoms in COVID-19 patients, after adjustment for pre-existing diseases

Findings	All studies (Published and Pre-print)					Published studies				
	N Patients	N Studies	Point estimate (%)	95% CI (%)	I-squared	N Patients	N Studies	Point estimate (%)	95% CI (%)	I-squared
Gastrointestinal symptoms										
Diarrhea	5104	23	8.7	5.4-13.9	94.62	2308	15	9.9	6.5-14.9	85.90
Anorexia	2515	5	8.0	3.0-19.8	97.21	1438	3	20.0	9.5-37.2	95.97
Nausea	2458	7	5.1	2.3-11.0	88.63	1349	4	8.1	4.0-15.6	70.30
Vomiting	2513	6	3.7	1.6-8.3	85.29	1577	5	5.8	3.3-10.2	71.67
Abdominal pain	1400	3	3.7	2.8-4.8	<0.01	1400	3	3.7	2.8-4.8	<0.01
Abdominal distension	1020	2	0.7	0.0-18.9	89.22	84	1	3.6	1.2-10.5	0.00
Liver function abnormalities										
Decreased albumin	136	2	49.3	34.4-64.4	48.41	136	2	49.3	34.4-64.4	48.41
Elevated ALT	426	3	19.4	9.9-34.3	88.68	364	2	20.8	8.3-43.4	93.71
Elevated AST	311	3	15.2	9.3-23.8	59.98	311	3	15.2	9.3-23.8	59.98

Table 3

CI: Confidence Interval, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

continuation of Table 3

CRITICAL CARE

EVALUATION AND MANAGEMENT OF SHOCK IN PATIENTS WITH COVID-19

Fox S, Vashisht R, Siuba M, Dugar S.. Cleve Clin J Med. 2020 Jul 17. doi: 10.3949/ccjm.87a.ccc052. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Four Critical Care attendings at the Cleveland Clinic perform a literature review evaluating the 4 different types of shock (ie., distributive, cardiogenic, obstructive, and hypovolemic) in the setting of COVID-19 and their common etiologies, characteristics, and management. They note that shock is developed in 67% of patients with SARS-CoV-2 requiring ICU admission and accounts for 7% of COVID-19 deaths (Tables 1 & 2). From this they make management recommendations, summarized below.

SUMMARY

The authors recommend COVID-19-associated shock management, including norepinephrine as the preferred vasopressor agent, targeting mean arterial pressures between 60 to 65 mmHg in distributive shock, assessing for acute cardiac injury such as right and left ventricular failure to prevent cardiogenic shock, preventing and treating thrombotic events with anticoagulation, and maintaining hemoglobin levels above 7 mg/dL and providing IV fluids in hypovolemic shock.

ABSTRACT

Shock is common in critically ill patients with COVID-19, developing in up to 67% of patients in intensive care (5% to 10% overall) and is associated with high mortality. Optimal management requires prompt recognition with precise evaluation and differentiation. Correcting hypoperfusion and treating the underlying process are fundamental aspects of treatment. Undifferentiated shock may be treated initially with norepinephrine to optimize perfusion while additional evaluation is performed to categorize the shock pathophysiology. Physical examination, bedside echocardiography, hemodynamic monitoring, lactate and venous oxygen saturation are important components of the patient evaluation.

FIGURES

TABLE 1

Key parameters in the evaluation of shock

Physical examination
Capillary refill
Mental status
Extremity temperature
Urine output
Focused echocardiography
LV systolic function
RV size and function
LVOT VTI
Pericardial effusion
Mitral, aortic, and tricuspid valve assessment
Regional wall motion abnormality
Laboratory studies
Mixed venous oxygen saturation
Central venous oxygen saturation
Lactate

LV = left ventricle; LVOT VTI = left ventricular outflow tract velocity time integral; RV = right ventricle

TABLE 2

Common shock etiologies and differentiation strategies

Type of shock	Etiologies	Extremities	Cardiac output	Mixed venous O_2	LV systolic function	RV size/function
Distributive	Sepsis Cytokine storm* Medication-related vasoplegia Anaphylaxis Neurogenic	Warm (sometimes cold)	Normal or high	Normal or high	Normal or high	Normal
Cardiogenic	Pre-existing heart disease Acute myocardial ischemia Cardiomyopathy Acute myocarditis	Cold	Low	Low	Low	Normal or dilated/reduced function
	Acute valvular disease	Cold	Low	Low	Normal or hyperdynamic	Variable
	Right ventricle failure*	Cold	Low	Low	Normal or hyperdynamic	Dilated/reduced function
Obstructive	Pulmonary embolism*	Cold	Low	Low	Normal or hyperdynamic	Dilated/reduced function
	Dynamic hyperinflation (auto-PEEP) Pericardial tamponade Abdominal compartment syndrome Pneumothorax*	Cold	Low	Low	Normal or hyperdynamic	Normal
Hypovolemic	Volume depletion Hemorrhage	Cold	Low	Low	Normal or hyperdynamic	Normal

LV = left ventricle; RV = right ventricle

NEUROLOGY

COVID-19-RELATED ENCEPHALOPATHY RESPONSIVE TO HIGH DOSES GLUCOCORTICOIDS

Pugin D, Vargas MI, Thieffry C, Schibler M, Grosgurin O, Pugin J, Lalive PH.. Neurology. 2020 Jul 17:10.1212/WNL.0000000000010354. doi: 10.1212/WNL.0000000000010354. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

This case series from Switzerland describes encephalopathy in five patients intubated for COVID-19 acute respiratory distress syndrome (ARDS). Patients' Glasgow Coma Scores (GCSs) ranged from 4-9, and researchers noted the presence of type IV oligoclonal bands in the patients' cerebrospinal fluid (CSF) and abnormal contrast enhancement in the intracerebral vascular walls on MRI without evidence of arterial stenosis, inflammatory plaques, or leptomeningeal enhancement (Figure 1). The patients were started on a course of IV methylprednisolone (Figure 2), which resulted in positive clinical outcomes, with improved GCSs in all patients and extubation of three of the five patients. These findings point to the potential utility of corticosteroid treatment for COVID-19 associated encephalopathy.

FIGURES

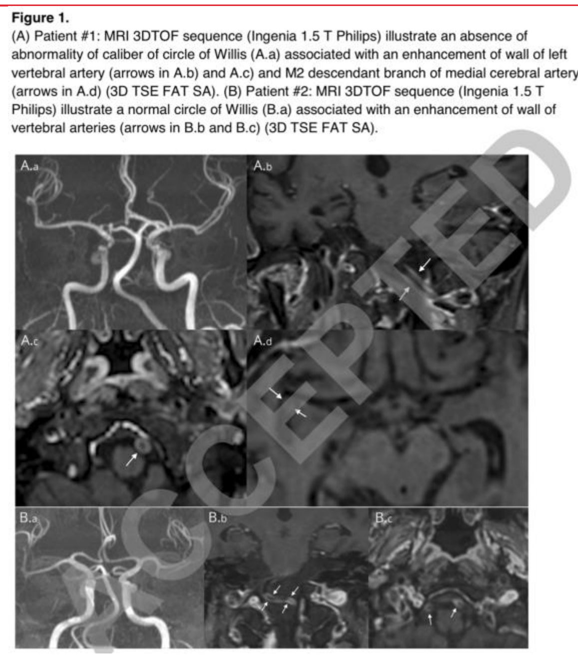


Figure 1. (A) Patient #1: MRI 3DTOF sequence (Ingenia 1.5 T Philips) illustrate an absence of abnormality of caliber of circle of Willis (A.a) associated with an enhancement of wall of left vertebral artery (arrows in A.b) and A.c) and M2 descendant branch of medial cerebral artery (arrows in A.d) (3D TSE FAT SA). (B) Patient #2: MRI 3DTOF sequence (Ingenia 1.5 T Philips) illustrate a normal circle of Willis (B.a) associated with an enhancement of wall of vertebral arteries (arrows in B.b and B.c) (3D TSE FAT SA).

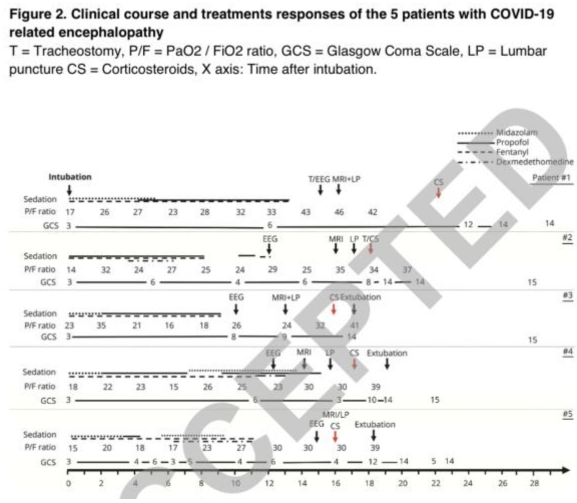


Figure 2. Clinical course and treatments responses of the 5 patients with COVID-19 related encephalopathy. T = Tracheostomy, P/F = PaO2 / FiO2 ratio, GCS = Glasgow Coma Scale, LP = Lumbar puncture CS = Corticosteroids, X axis: Time after intubation.

INTERVENTIONAL RADIOLOGY

POLICIES AND GUIDELINES FOR COVID-19 PREPAREDNESS: EXPERIENCES FROM THE UNIVERSITY OF WASHINGTON

Mossa-Basha M, Medverd J, Linnau KF, Lynch JB, Wener MH, Kicska G, Staiger T, Sahani DV.. Radiology. 2020 Aug;296(2):E26-E31. doi: 10.1148/radiol.2019201326.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

Guidelines from the Department of Radiology at the University of Washington have implemented the following guidelines:
- Rescheduling elective examinations.
- Testing all admitted inpatients for COVID-19.
- Using portable imaging on suspected COVID-19 patients, when possible (Figure 1).
- Performing radiographs through glass, when possible (Figure 2).
- Using proper airborne and/or contact precautions.
- Thoroughly disinfecting rooms after each patient encounter.
- Only scheduling critical and time-sensitive invasive procedures (Table).
- Directing COVID-19 positive patients needing radiology to outpatient imaging centers.
- Increasing the ability for radiologists and staff to work remotely.

The authors encourage all departments to have policies and guidelines similar to these in place in preparation for possible COVID-19 surges in their area.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic initially manifested in the United States in the greater Seattle area and has rapidly progressed across the nation in the past 2 months, with the United States having the highest number of cases in the world. Radiology departments play a critical role in policy and guideline development both for the department and for the institutions, specifically in planning diagnostic screening, triage, and management of patients. In addition, radiology workflows, volumes, and access must be optimized in preparation for the expected surges in the number of patients with COVID-19. In this article, the authors discuss the processes that have been implemented at the University of Washington in managing the COVID-19 pandemic as well in preparing for patient surges, which may provide important guidance for other radiology departments who are in the early stages of preparation and management.

FIGURES

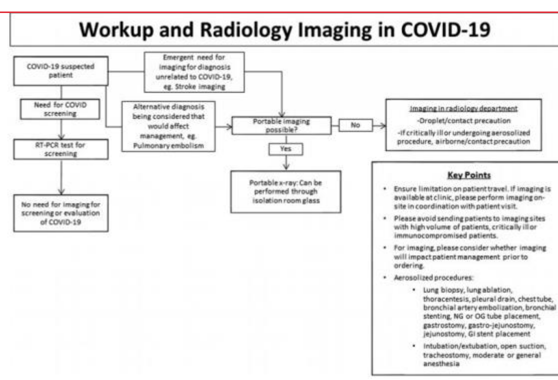


Figure 1. Flowchart shows work-up and radiologic imaging in patients suspected of having coronavirus disease 2019 (COVID-19). GI = gastrointestinal, NG = nasogastric, OG = orogastric, RT-PCR = reverse-transcription polymerase chain reaction.

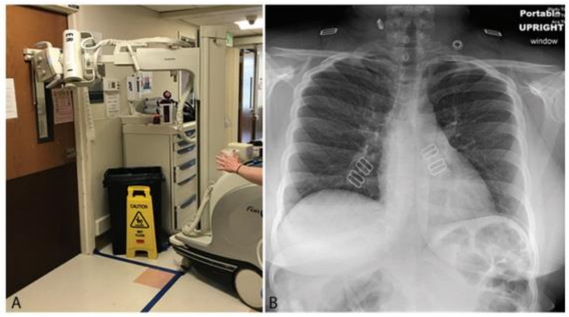


Figure 2. Chest radiography through glass. A, Technologists position the portable radiography unit outside the patient room, with the tube facing the wire-reinforced isolation room window. B, Anteroposterior chest radiograph obtained through glass is of diagnostic quality.

Approach for Scheduling Procedures

Procedure Category	Designation	Description
1	Elective and/or nonurgent	If delayed, will not harm patients in the next 2–6 months; these procedures can be delayed until after postponement period
2	Time sensitive	Short delay is acceptable, within a certain time frame
3	Critical	Cannot be delayed; these procedures should be scheduled immediately

Note.—Procedure requests are reviewed by radiologists in consensus with the ordering clinician.

Figure 2. Chest radiography through glass. A, Technologists position the portable radiography unit outside the patient room, with the tube facing the wire-reinforced isolation room window. B, Anteroposterior chest radiograph obtained through glass is of diagnostic quality.

OPHTHALMOLOGY

LETTER TO EDITOR ON COVID-19 AND OPHTHALMOLOGY: AN UNDERAPPRECIATED OCCUPATIONAL HAZARD

Khatri A, Kharel M, Chaurasiya BD, K C A, Khatri BK.. Infect Control Hosp Epidemiol. 2020 Jul 20:1-6. doi: 10.1017/ice.2020.344. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Authors surveyed 24 opthalmologists who had returned from furlough regarding the adjustment to new personal protective equipment (PPE) policies and identified these main concerns (Table 1):
- fogging of glasses and difficulty focusing through face shields is severely limiting for precision procedures
- 'Do it yourself' (DIY) PPE is widely used without quantifiable protection value

FIGURES

Problems	Frequency(%)	Problem Scale (Mode values)
Thermal discomfort / Sweating	18(75%)	3
Muffled voice (unable to understand)	22(91.6%)	3
Fogging*	19(79.1%)	5
Difficulty in using Slit lamps	10(41.6%)	4
Difficulty in focusing using face shields	17(70.8%)	5
Unsure of DIY protectives/shields	15(62.5%)	4
Total Participants : 24		
*14 of the 24 were spectacle users, all complained of fogging		

Table 1: Problems related with discomfort and difficulty in performing regular examination for ophthalmologists with use of personal protective equipment

AGING AND THERAPY-RELATED HYPOGAMMAGLOBULINEMIA CAUSING PNEUMONIA: AN OVERLOOKED CURABLE ENTITY IN THE CHAOTIC COVID-19 PANDEMIC

Zaidi SZA, Zaidi FZ, AlShehry N, Zaidi ARZ, Zaidi SZ, Abdullah SM.. J Med Virol. 2020 Jul 18. doi: 10.1002/jmv.26318. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A letter to the editor constructed in Riyadh, Saudi Arabia discussed how focusing on ruling out COVID-19 in elderly patients presenting with respiratory illness may lead to missing easily treatable underlying causes such as hypogammaglobulinemia. This letter suggests that healthcare workers must remain vigilant and not limit the differential diagnosis of respiratory etiologies solely to COVID-19.

SUMMARY

Additional topics discussed:
-Hypogammaglobulinemia is prevalent in both the very young and very old and can cause a decline in IgM and IgG.
-A 71 year old male patient with hypogammaglobulinemia had his condition worsen while waiting for COVID-19 to be ruled out. He was successfully treated with IVIg.
-Hypogammaglobulinemia puts individuals at risk for Streptococcus pneumoniae and Haemophilus influenzae infections.
-A retrospective cohort study found that 72.2% of patients with hematological malignancy presenting with a pneumococcal infection had underlying hypogammaglobulinemia.

DEVELOPMENTS IN DIAGNOSTICS

SHOULD POINT-OF-CARE ULTRASOUND BECOME PART OF HEALTHCARE WORKER TESTING FOR COVID?

Smallwood N, Walden A, Parulekar P, Dachsel M.. Clin Med (Lond). 2020 Jul 17:clinmed.2020-0442. doi: 10.7861/clinmed.2020-0442. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

The English authors suggest a combination of swab RT-PCR testing with the point of care lung ultrasound (LUS) to improve the accuracy of COVID-19 detection amongst healthcare workers due to the high false-negative rate of RT-PCR testing. Currently, however, data supporting the use of LUS as a screening tool and further research is warranted.

ABSTRACT

The NHS in England has rapidly expanded staff testing for COVID-19 in order to allow healthcare workers who would otherwise be isolating with symptoms suspicious of COVID-19 to be cleared to work. However, the high false negative rate associated with current RT-PCR tests could put other staff, family members and patients at risk. We believe combining swab testing with real-time lung ultrasound (LUS) would improve the ability to rule-in COVID-19 infection in those requiring screening.

DEVELOPMENTS IN TREATMENTS

CLINICAL OUTCOMES AND ADVERSE EVENTS IN PATIENTS HOSPITALISED WITH COVID -19, TREATED WITH OFF- LABEL HYDROXYCHLOROQUINE AND AZITHROMYCIN

Kelly M, O'Connor R, Townsend L, Coghlan M, Relihan E, Moriarty M, Carr B, Melanophy G, Doyle C, Bannan C, O'Riordan R, Merry C, Clarke S, Bergin C.. Br J Clin Pharmacol. 2020 Jul 20. doi: 10.1111/bcp.14482. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

Authors from St. James Hospital and Trinity College in Dublin, Ireland conducted a retrospective study of 134 patients diagnosed with SARS-CoV-2 by polymerase chain reaction (PCR) to compare overall clinical improvement, mortality, ICU stay, and adverse effects between patients administered hydroxychloroquine plus azithromycin and a control group that did not receive treatment. The study showed no statistically significant different clinical improvement by day seven of treatment between the two groups (Table 1), but a higher incidence of QT prolongation (p=0.028), mortality (p=0.03), and ICU transfer (p=0.16) was found in the treatment group compared to the control group (Figure 1). Authors note that the study highlights the need for further investigation into potential adverse effects of drugs being rapidly repurposed during this pandemic.

ABSTRACT

AIM: To assess clinical outcomes and adverse drug events in patients hospitalised with COVID -19 treated with off- label hydroxychloroquine and azithromycin. METHODS: We performed a retrospective analysis of hospitalised patients that had a positive polymerase chain reaction (PCR) test for SARS-CoV-2 and received hydroxychloroquine plus azithromycin (HCQ/Az) or no targeted therapy. The primary end point was clinical improvement on day 7 defined as either hospital discharge or an improvement of two points on a six-category ordinal scale. Secondary outcomes included mortality at day 28, intensive care (ICU) admission, requirement for mechanical ventilation and incidence of adverse events (AEs). RESULTS: Data from a total of 134 patients was evaluated, 82 patients received HCQ/Az and 52 patients received no targeted therapy. Clinical improvement was seen in 26.8% of patients who received HCQ/Az but this was not significant. The rates of ICU transfer and mechanical ventilation were higher in the treatment group, these differences were not significant. Mortality at day 28 was significantly higher in the treatment group (p 0.03). Hypoglycaemia elevated liver function tests (LFTs) and QT prolongation were monitored in both groups. The risk of QT prolongation was significantly higher in the treatment group. Treatment was stopped early in 6 (7.3%) patients due AEs. CONCLUSION: Although patients who received HCQ/Az were more severely ill the administration of these repurposed drugs did not result in clinical improvement, and was associated with a significant increase in toxicity. This descriptive study highlights the importance of monitoring all repurposed agents for adverse events.

FIGURES

Parameter	Treatment Group (n 82)	Non-Treatment Group (n 52)	Significance
Female, n (%)	27 (33%)	24 (46%)	ns
Median Age (IQR) (years)	64.8 (29-93)	68 (21-91)	ns
Co-morbidities (mean)	2.5	3	ns
WCC (*10^9/L) median Day 0	6.2(1-32)	7.3 (2.7-17)	ns
WCC (*10^9/L) median Day 5	7.3 (1-20)	6.1 (2.7-17.2)	p 0.03
CRP median Day 0	81.5 (1-311)	28 (1-374)	p <0.0001
CRP median Day 5	40 (1-346)	29 (1-350)	p 0.03
FiO2 requirements median Day 0	24% (21-100)	21% (21-100)	p <0.0001
FiO2 requirements median Day 5	21% (21-100)	21% (21-100)	p <0.0001
LFTs >ULN Day 0	43 (52)	29 (55)	ns
LFTs >ULN Day 5	51 (62)	36 (69)	ns
CIS Day 0	3 (2-5)	2 (2-5)	P <0.0001
CIS Day 7	3 (1-6)	2 (1-5)	ns

Table 1: Demographics and Cohort Characteristics at Day 0 and Day 5. IQR = interquartile range; WCC = white cell count; CRP = C-reactive protein; fraction of inspired oxygen FiO2; LFTs = liver function tests ULN = upper limit normal CIS = clinical improvement scale ns = non-significant (p>0.05).

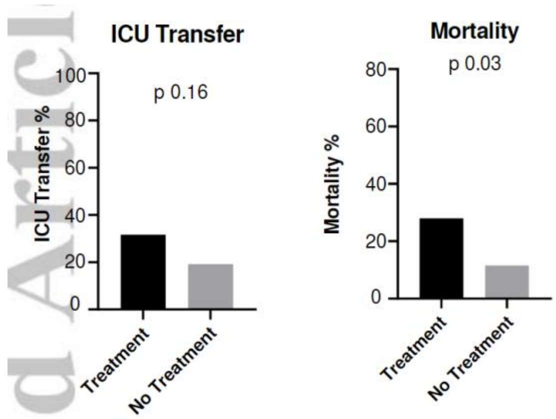


Figure 1. ICU transfer and Mortality rates between groups.

PSYCHOLOGICAL IMPACT OF QUARANTINE ON CAREGIVERS AT A CHILDREN'S HOSPITAL FOR CONTACT WITH CASE OF COVID-19

Kim H, Park KJ, Shin YW, Lee JS, Chung S, Lee T, Kim MJ, Jung J, Lee J, Yum MS, Lee BH, Koh KN, Ko TS, Lim E, Lee JS, Lee JY, Choi JY, Han HM, Shin WA, Lee NJ, Kim SH, Kim HW.. J Korean Med Sci. 2020 Jul 20;35(28):e255. doi: 10.3346/jkms.2020.35.e255.

Level of Evidence: 3 - Local non-random sample

BLUF

Authors at Asan Medical Center in Seoul, Korea investigated the psychological impacts of mandatory quarantine of 72 caregivers due to contact with a COVID-19 patient in a children's hospital. The highest reported were worrying (94.4%) and nervousness (90.3%), there were some reports of suicidal (4.2%) and homicidal (1.4%) ideations, and fear of infection of the patient (91.7%) and fear of infection of oneself (86.1%) were the most frequently reported stressors (Table 1). Authors emphasize the need to balance carefully the benefits of mandatory quarantine against its psychological costs to patients and caregivers when making decisions.

ABSTRACT

Quarantine often provokes negative psychological consequences. Thus, we aimed to identify the psychological and behavioral responses and stressors of caregivers quarantined with young patients after a close contact to a coronavirus disease 2019 case at a children's hospital. More than 90% of the caregivers reported feelings of worry and nervousness, while some of them reported suicidal ideations (4.2%), and/or homicidal ideations (1.4%). Fear of infection of the patient (91.7%) and/or oneself (86.1%) were most frequently reported stressors. A multidisciplinary team including infection control team, pediatrician, psychiatrist, nursing staff and legal department provided supplies and services to reduce caregiver's psychological distress. Psychotropic medication was needed in five (6.9%), one of whom was admitted to the psychiatry department due to suicidality. Quarantine at a children's hospital makes notable psychological impacts on the caregivers and a multidisciplinary approach is required.

FIGURES

Table 1. Psychological and behavioral responses and stressors of the caregivers during quarantine

Responses or stressors	Caregivers (n = 72)
Responses	
Worrying	68 (94.4)
Nervousness	65 (90.3)
Anger	23 (31.9)
Sleep disturbance	22 (30.6)
Weeping	22 (30.6)
Feeling loss of control for external events	17 (23.6)
Acting out	7 (9.7)
Avoidance	6 (8.3)
Depression	6 (8.3)
Suicidal ideation	3 (4.2)
Hopelessness	2 (2.8)
Panic attack	2 (2.8)
Homicidal ideation	1 (1.4)
Refusal to test for SARS-CoV-2	1 (1.4)
Stressors	
Fear of infection of the patient	66 (91.7)
Fear of infection of oneself	62 (86.1)
Frustration and boredom	25 (34.7)
Fear for the aggravation of the underlying disease of the patient	18 (25.0)
Inadequate information	14 (19.4)
Inadequate supplies	11 (15.3)
Difficulty in childcare	9 (12.5)
Worry about other family members	7 (9.7)
Being stigmatized	5 (6.9)
Financial loss	1 (1.4)

Data are presented as number (%).
SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

ACKNOWLEDGEMENTS

CONTRIBUTORS

Akshara Malla
Alisa Malyavko
Carter Butuk
Ellen Reidy
Eva Shelton
Jesse Abelson
Julia Ghering
Krithika Kumarasan
Maryam Naushab
Priscilla Natcher
Renate Meckl
Ryan Wertz
Simran Mand

EDITORS

Allen Doan
Cameron Richards
Julie Tran
Maggie Donovan
Michelle Arnold
Thamanna Nishath

SENIOR EDITORS

Allison Hansen
Avery Forrow
Charlotte Archuleta
Kyle Ellingsen

EXECUTIVE SENIOR EDITOR

Stephen Ferraro

CHIEF EDITOR

Jasmine Rah

ADVISOR

Will Smith