The Daily COVID-19 Literature Surveillance Summary

July 10, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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

EXECUTIVE SUMMARY

CLIMATE:

- Using data from the IQVIA Total Patient Tracker, researchers found that between February 2020 and March 2020 the number of dispensed hydroxychloroquine prescriptions nearly doubled and that the number receiving this medication in combination with azithromycin increased by 1044%. Authors warn that evidence behind the efficacy and safety of hydroxychloroquine is limited in regards to COVID-19 treatment and that this surge will limit the amount available to patients that rely on this drug for other disease processes.
- American health policy experts found that the case rate among prisoners was 5.5 times higher than the general US population (3251 vs 587/100,000) with an adjusted death rate three times higher than expected, corroborating suspicions that prison conditions heighten SARS-CoV-2 transmission risk.
- Hospital survey data from five low-income countries identified shortages in PPE, sanitation, respiratory supplies, diagnostic tests, and inadequate storage and delivery of vaccines in these countries. The authors attribute these shortages to decreased global resources, unequal sale of supplies favoring wealthier countries, and limited bargaining power of low-income countries; thus, they advocate for increased international action for equal global distribution of vital pandemic control resources.

EPIIDEMIIOLOGY:

- A retrospective cohort study of 515 COVID-19 patients in Rome, Italy found that liver test abnormalities were present in 161 (31.3%) patients, but this was not associated with increased mortality (OR=0.84 [95%CI 0.49-1.41], p=0.51). However, peak values of ALP (alk phos) were predictive of a worse prognosis (odds ratio [OR]=1.007 [95%CI 1.002-1.01], p=0.005), suggesting liver involvement in COVID-19 patients without severe underlying liver disease is mild, not associated with increased mortality, and tends to resolve over time.

UNDERSTANDING THE PATHOLOGY:

- To update SARS-CoV-2's phylogenetic classification and origins, virology and microbiology researchers from India conducted in silico comparisons of key residues from receptor binding domains (RBDs) of the S-protein and O-linked glycans in bat (RaTG13) and Pangolin-CoV genomes with that of SARS-CoV-2. Their analysis showed that 11 SARS-CoV-2 isolates were closely related to RaTG13 (97.41%) and Pangolin-CoV (92.22%), supporting existing theory that represents the formation of a new clade within the beta-CoV division of Coronavirinae.

MANAGEMENT:

- A retrospective cohort study of 79 critically-ill COVID-19 patients found that patients with serum IgM ≥ 50 AU/ml at day 25 of infection had higher in-hospital mortality (p=0.026); and was also correlated with risk of ARDS, septic shock, mechanical ventilation, and corticosteroid usage. Antibody remeasurement in 42 patients found a correlation between decreased IgM titers and reduced mortality (p=0.031), suggesting that prolonged seroconversion from IgM to IgG (>25 days) may be a useful prognostic indicator of inadequate immune response and more severe disease.

ADJUSTING PRACTICE DURING COVID-19:

- A review by Belgian anesthesiologists identifies risk factors in patients undergoing nonoperating room anesthesia (NORA) as the need for this intervention has increased during the COVID-19 pandemic. They found the highest risk factors for poor outcomes were respiratory infections (OR 23.55-17.46), respiratory commodities (OR 8.18), upper GI endoscopy (OR 5.66), and morbid obesity (OR 4.25), emphasizing the importance of preoperative screening for COVID-19 to minimize exposure risk for staff and decrease perioperative morbidity and mortality.

CLIMATE

US HYDROXYCHLOROQUINE, CHLOROQUINE, AND AZITHROMYCIN OUTPATIENT PRESCRIPTION TRENDS, OCTOBER 2019 THROUGH MARCH 2020

Shehab N, Lovegrove M, Budnitz DS.. JAMA Intern Med. 2020 Jul 6. doi: 10.1001/jamainternmed.2020.2594. Online ahead of print.

Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

Using data from the IQVIA Total Patient Tracker, researchers found that between February 2020 and March 2020 the number of dispensed hydroxychloroquine prescriptions nearly doubled and that the number receiving this medication in combination with azithromycin increased by 1044% (Figure 1). The authors warn that the evidence behind the efficacy and safety of hydroxychloroquine is limited in regards to COVID-19 treatment and that this surge in hydroxychloroquine distribution will limit the amount available to patients that rely on this drug for other disease processes.

FIGURES

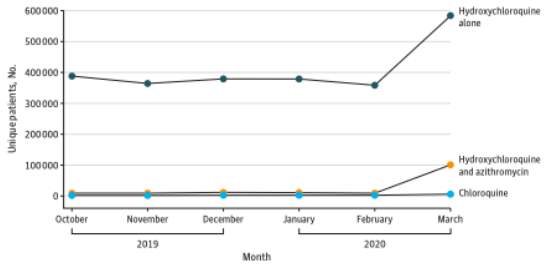


Figure 1. Hydroxychloroquine, Chloroquine, and Combined Hydroxychloroquine and Azithromycin Dispensing From Retail Pharmacies, United States, October 2019 Through March 2020.

DISPARITIES

COVID-19 CASES AND DEATHS IN FEDERAL AND STATE PRISONS

Saloner B, Parish K, Ward JA, DiLaura G, Dolovich S.. JAMA. 2020 Jul 8. doi: 10.1001/jama.2020.12528. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

American health policy experts analyzed publicly reported national data from the US Department of Corrections from March 31-June 6, 2020 and found that the case rate among prisoners was 5.5 times higher than the general US population (3251 vs 587/100,000) (Figure) with an adjusted death rate three times higher than expected (Table), corroborating suspicions that prison conditions heighten SARS-CoV-2 transmission risk.

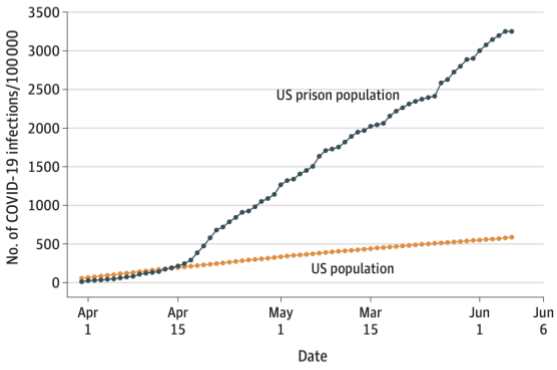
FIGURES

Table. Mortality Attributable to Coronavirus Disease 2019 (COVID-19) Among Prison and US Populations

Population by age group, y	Prison population in 1000s[a]	US population			
		In 1000s[b]	COVID-19 deaths[c]	Age-specific COVID-19 mortality rate/100 000	Expected prison deaths/100 000[d]
Men					
≤24	115	52 333	87	0.17	0.19
25-34	377	22 727	433	1.91	7.19
35-44	331	20 257	1184	5.84	19.32
45-54	222	19 923	3236	16.24	36.12
55-64	117	19 865	7558	38.05	44.36
≥65	37	23 923	38 899	162.60	60.59
Women					
≤24	8	50 545	50	0.10	0.01
25-34	36	22 482	207	0.92	0.33
35-44	28	20 770	465	2.24	0.63
45-54	16	20 776	1352	6.51	1.06
55-64	6	21 890	3881	17.73	1.10
≥65	1	28 865	38 254	132.53	1.90
Total[e]	1295	324 356	95 608	29.47	172.80[f]

[a] Derived from 2018 published estimates from US Bureau of Justice statistics (https://www.bjs.gov/content/pub/pdf/p18.pdf).
[b] Estimated from 2019 US Census Bureau data (https://www.census.gov/data/tables/2019/demo/age-and-sex/2019-age-sex-composition.html).
[c] Estimated from the US Centers for Disease Control and Prevention as of June 6, 2020 (https://data.cdc.gov/NCHS/Provisional-COVID-19-Death-Counts-by-Sex-Age-and-S/9bhg-hcku).
[d] Calculated as the age-specific mortality rate in the US population × the prison population.
[e] The age- and sex-standardized mortality ratio is 510/172.8 = 2.95 and was calculated as the observed prison deaths as of June 6, 2020/expected US deaths as of June 6, 2020.
[f] Because prison deaths attributable to COVID-19 are not reported by age and sex strata, an indirect standardization method was used.

Figure. Trends in Cumulative Coronavirus Disease 2019 (COVID-19) Confirmed Case Rate per 100 000 People for Prison and US Populations



Data are from the UCLA Law COVID-19 Behind Bars Data Project and the US Centers for Disease Control and Prevention.[3,4] The US population is 327 167 439 and the US prison population is 1 295 285.

GLOBAL RESOURCE SHORTAGES DURING COVID-19: BAD NEWS FOR LOW-INCOME COUNTRIES

McMahon DE, Peters GA, Ivers LC, Freeman EE.. PLoS Negl Trop Dis. 2020 Jul 6;14(7):e0008412. doi: 10.1371/journal.pntd.0008412. eCollection 2020 Jul.

Level of Evidence: 3 - Local non-random sample

BLUF

Authors from Boston, Massachusetts conducted a COVID-19 service provision assessment using hospital survey data from five low-income countries (Figure 1) and found shortages in PPE, sanitation, respiratory supplies, diagnostic tests, and inadequate storage and delivery of vaccines. The authors attribute these shortages to decreased global resources, unequal sale of supplies

favoring wealthier countries, and limited bargaining power; thus, they advocate for increased international action for equal global distribution of vital pandemic control resources.

SUMMARY

In order to assess COVID-19 preparedness and PPE supplies in low income countries, authors analyzed data from service provision assessments using nationally representative surveys of hospitals between 2014 and 2019 in Afghanistan, Democratic Republic of the Congo, Haiti, Nepal, and Tanzania. The author's analysis of PPE, sanitation supplies, and respiratory devices (Figure 1) found that 24-51% of hospitals have face masks, 22-92% medical gowns, 3-22% eye protection, 52-87% soap and running water, 12-48% pulse oximeters, 10-82% oxygen tanks, and 28-45% bag-masks. In addition to the limited PPE, sanitation supplies, and respiratory support resources, the authors highlight the limited diagnostic testing and vaccine administration capabilities as issues low-income countries face in accessing and securing resources necessary to control and limit the COVID-19 pandemic.

FIGURES

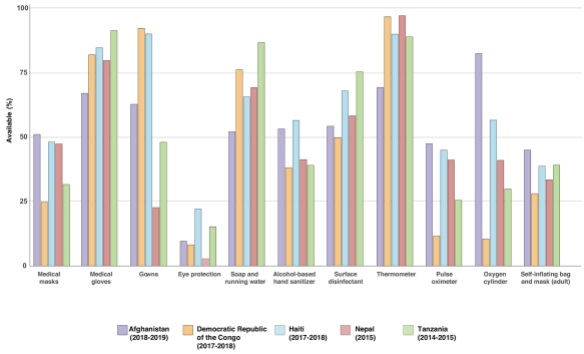


Figure 1: Availability of hospital clinic PPE, sanitation, and functional diagnostics and therapeutics across nationally representative samples of hospitals in 5 low-income countries.

EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

LIVER INVOLVEMENT IS NOT ASSOCIATED WITH MORTALITY: RESULTS FROM A LARGE COHORT OF SARS-COV-2 POSITIVE PATIENTS

Romana Ponziani F, Del Zompo F, Nesci A, Santopaolo F, Ianiro G, Pompili M, Gasbarrini A; "Gemelli against COVID-19" group.. Aliment Pharmacol Ther. 2020 Jul 6. doi: 10.1111/apt.15996. Online ahead of print.

Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A retrospective cohort study of 515 SARS-CoV-2 positive adults (age >18 years; confirmed via real-time polymerase chain reaction [PCR]) at the Fondazione Policlinico Universitario Agostino Gemelli Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) in Rome from 6 March to 16 April 2020 examined liver involvement and its impact on patient morbidity and mortality. Authors found liver test abnormalities in 161 (31.3%) patients and report a non-association with increased mortality (OR=0.84 [95%CI 0.49-1.41], p=0.51). Increases in AST, ALT, and GGT were 20.4%, 19%, and 13.6%, respectively; only 5% of changes increased beyond three times the upper limit of normal (ULN). Conversely, ALP peak values were predictive of a worse prognosis (odds ratio [OR]=1.007 [95%CI 1.002-1.01], p=0.005). Authors suggest liver involvement in SARS-CoV-2 positive patients without severe underlying liver disease is mild, not associated with increased mortality, and tends to resolve over time (Figure 2).

ABSTRACT

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is frequently associated with liver tests abnormalities. AIMS: To describe the evolution of liver involvement during SARS-CoV-2 infection and its effect on clinical course and mortality. METHODS: Data of 515 SARS-CoV-2 positive patients were collected at baseline and during follow-up, last evaluation or death. Stratification based on need for hospitalization, severe disease and admission to intensive care unit (ICU) was performed. The association between liver tests abnormalities (baseline and peak values) and ICU admission or death was also explored. RESULTS: Liver tests abnormalities were found in 161 (31.3%) patients. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) were increased in 20.4%, 19% and 13.6% of patients, respectively. Baseline liver tests abnormalities were associated with increased risk of ICU admission (OR 2.19 [95%CI 1.24-3.89], p=0.007) but not with mortality (OR 0.84 [95%CI 0.49-1.41], p=0.51). Conversely, ALP peak values were correlated with the risk of death (OR 1.007 [95%CI 1.002-1.01], p=0.005) along with age, multiple comorbidities, acute respiratory distress syndrome (ARDS), ICU admission, and C-reactive protein. Alterations of liver tests worsened within 15 days after hospitalization; however, in patients with the longest median follow-up, the prevalence of liver tests alterations decreased over time, returning similar to that of baseline. CONCLUSIONS: In SARS-CoV-2 positive patients without pre-existing severe chronic liver disease, baseline liver tests abnormalities are associated with the risk of ICU admission and tend to normalize over time. ALP peak value seems to be predictive of a worse prognosis.

FIGURES

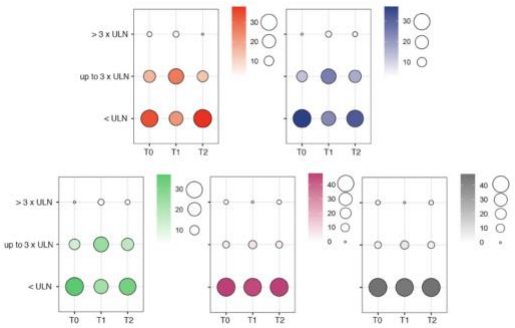


Figure 2: Bubble plot showing the evolution of liver tests in 53 hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and long follow-up. Color intensity and size of the circles are proportional to the number of patients with or without liver tests alterations (aspartate aminotransferase [AST], red; alanine aminotransferase [ALT], blue; gamma glutamyl transferase [GGT], green; alkaline phosphatase [ALP], purple; total bilirubin, grey) at baseline (T0), within 15 days after the admission (T1) and at the last evaluation or death (T2).

UNDERSTANDING THE PATHOLOGY

THE MECHANISM AND TREATMENT OF GASTROINTESTINAL SYMPTOMS IN PATIENTS WITH COVID-19

Ye Q, Wang B, Zhang T, Xu J, Shang S.. Am J Physiol Gastrointest Liver Physiol. 2020 Jul 8. doi: 10.1152/ajpgi.00148.2020. Online ahead of print.

Level of Evidence: 5 - Review / Literature Review

BLUF

In their review of COVID-19's gastrointestinal (GI) manifestations, medical researchers from Hangzou, China found that SARS-CoV-2 binds ACE2 receptors in the intestinal tract and may be transmitted through feces, with diarrhea being the most common GI symptom and colitis a possible eventual sequela (Figure 1). Furthermore, in reviewed studies, COVID-19 patients with GI symptoms showed higher levels of inflammatory markers, electrolyte and hepatic dysfunction, and rate of acute respiratory distress syndrome (ARDS). The authors suggest that there might be therapeutic benefit to probiotics and drugs capable of ACE2-inhibition including azathioprine. Enteral nutrition may be used where needed.

ABSTRACT

In addition to the typical respiratory response, new coronavirus pneumonia (COVID-19) is also associated with very common gastrointestinal symptoms. Cases with gastrointestinal symptoms are more likely to be complicated by liver injury and acute respiratory distress syndrome (ARDS), and diarrhea can also lead to electrolyte disturbances, causing nausea and vomiting, headache, fatigue, etc. If not treated in time, coma and circulatory failure may ensue. As SARS-CoV-2 infects the human body through the combination of ACE2 in the gastrointestinal tract, the mechanism underlying the gastrointestinal symptoms may involve damage to the intestinal mucosal barrier and promotion of the production of inflammatory factors, causing cytokine storms. Indeed, after cells in the lungs become infected by SARS-CoV-2, effector CD4+ T cells reach the small intestine through the gut-lung axis, causing intestinal immune damage and diarrhea; early extensive use of antibacterial and antiviral drugs can also lead to diarrhea in patients. Thus, treatment options for COVID-19 patients should be promptly adjusted when they have gastrointestinal symptoms. Additionally, when drug-induced diarrhea occurs, drugs should be withdrawn or reduced, and microecological regulators should be applied to maintain the intestinal microecological balance and prevent secondary bacterial infections. To guarantee effective treatment, attention should be paid to the patient's enteral nutrition and digestive tract function. As SARS-CoV-2 has been detected in the feces of COVID-19 patients, future prevention and control efforts must consider the possibility of fecal-oral transmission of the virus.

FIGURES

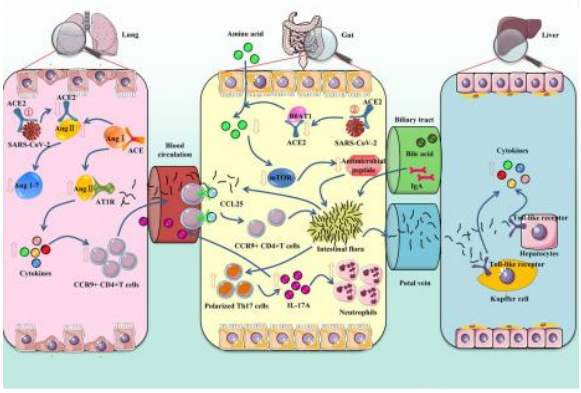


Figure 1. The mechanism of gastrointestinal symptoms in patients with COVID-19.
1) Gut-lung axis: SARS-CoV-2 binds with ACE2 to enter the lung, , resulting in the accumulation of AngII and the decrease of Ang1-7. AngII combined with AT1R promotes cytokine release and increases CCR9+CD4+T cells. CCL25 promotes the recruitment of CCR9+CD4+T cells into the small intestine. The changed flora then promotes the polarization of Th17 cells, and finally IL-17A causes the recruitment of neutrophils. Cytokines and bacteria also enter the lung through the bloodstream, further affecting the lung inflammation.

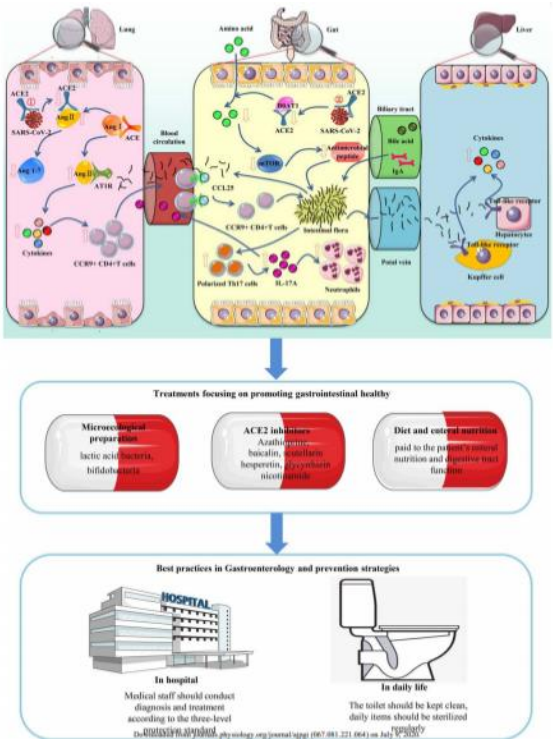


Figure 1. The mechanism of gastrointestinal symptoms in patients with COVID-19.
2) Gut-liver axis: SARS-CoV-2 binds with ACE2 to enter the intestine, inhibits the absorption of the B0AT1/ACE2 transport pathway, and then affects the activation of mTOR to reduce the expression of antimicrobial peptides. The intestinal flora is transferred to the liver through the portal vein, where it binds to toll-like receptors,causing hepatitis. The liver also can transports metabolites to the intestine through the biliary tract.

ANCESTRAL ORIGIN, ANTIGENIC RESEMBLANCE AND EPIDEMIOLOGICAL INSIGHTS OF NOVEL CORONAVIRUS (SARS-COV-2): GLOBAL BURDEN AND BANGLADESH PERSPECTIVE

Uddin MB, Hasan M, Harun-Al-Rashid A, Ahsan MI, Imran MAS, Ahmed SSU.. Infect Genet Evol. 2020 Jul 1:104440. doi: 10.1016/j.meegid.2020.104440. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

In Bangladesh, authors conducted a phylogenic study using the viral proteins spike, membrane, envelope and nucleoprotein of SARS-CoV-2, HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HKU1, MERS-CoV, HKU4, HKU5 and BufCoV-HKU26, which showed evolutionary relationships with SARS-CoV (Figures 1-3). These findings have implications for treatments targeting these viral proteins.
Most notable phylogenic analysis results are as follows:
- SARS-CoV-2 aligned in the same clade with SARS-CoV
- With the respective homologous proteins of SARS-CoV spike, membrane, envelope, and nucleoproteins of SARS-CoV-2 were 87.0%, 96.4%, 96.1% and 94.3% identical, respectively.

ABSTRACT

SARS-CoV-2, a new coronavirus strain responsible for COVID-19 has emerged in Wuhan City, China and still continuing its worldwide pandemic nature. Considering the severity of the disease, a number of studies are underway, and full genomic sequences have already been released in the last few weeks to enable the understanding of the evolutionary origin and molecular characteristics of this virus. Bioinformatics analysis, satellite derived imaging data and epidemiological attributes were employed to investigate origin, immunogenic resemblance and global threat of newly pandemic SARS-CoV-2 including Bangladesh perspective. Based on currently available genomic information, a phylogeny study was employed focusing four types of representative viral proteins (spike, membrane, envelope and nucleoprotein) of SARS-CoV-2, HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HKU1, MERS-CoV, HKU4, HKU5 and BufCoV-HKU26. The findings clearly demonstrated that SARS-CoV-2 exhibited evolutionary convergent relation with previously reported SARS-CoV. It was also found that SARS-CoV-2 proteins were highly similar and identical to SARS-CoV proteins, though proteins from other coronaviruses showed lower level of similarity and identical patterns. The cross-checked conservancy analysis of SARS-CoV-2 antigenic epitopes showed significant conservancy with antigenic epitopes derived from SARS-CoV. The study also prioritized the temperature comparison through satellite imaging alongside compiling and analyzing the epidemiological outbreak information on the 2019 novel coronavirus based on several open datasets on COVID-19 (SARS-CoV-2) and discussed possible threats to Bangladesh.

FIGURES

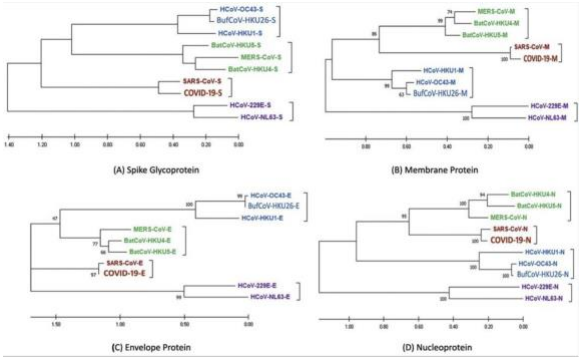


Figure 1: Phylogeny study of SARS-CoV-2 with the other member of coronavirus family. A phylogentic tree was constructed with(A) Spike (S) glycopreotein, (B) Membrane (M) protein, (C) Envelope (E) protein and (D) Nucleoprotein (N) of COVID-19 with HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HKU1, MERS-CoV, HKU4, HKU5 and BufCoV-HKU26 coronaviruses by using Maximum Likelihood Method of MEGA X.

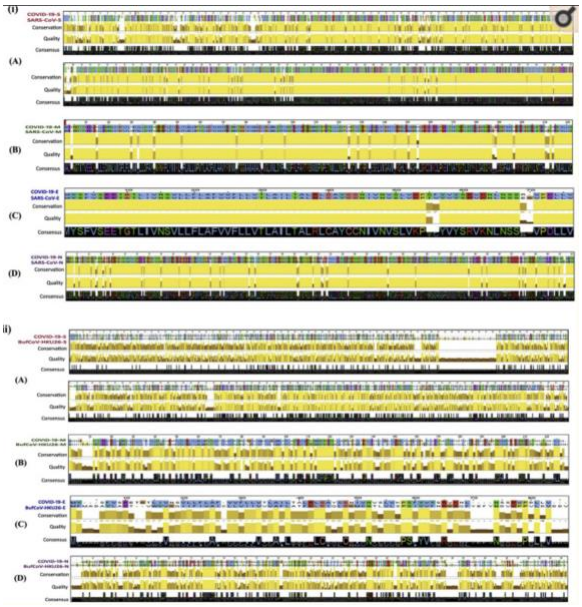
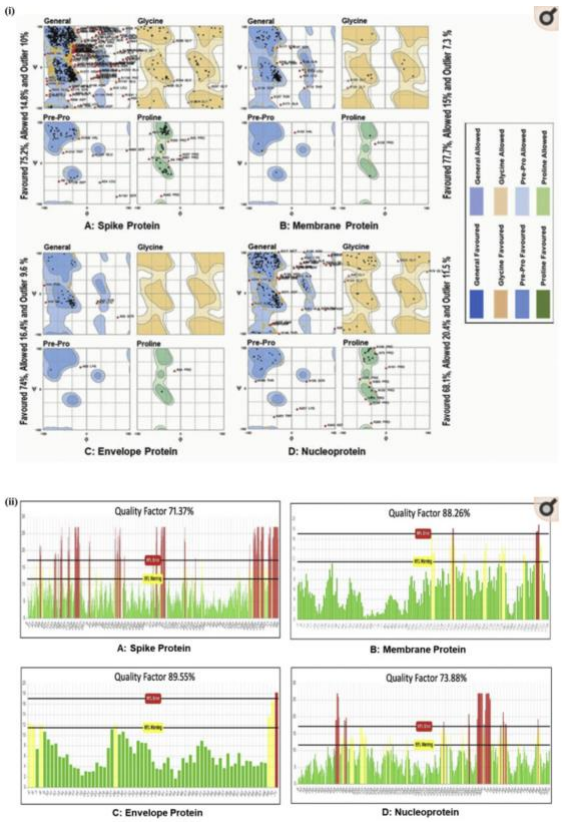


Figure 2. (i): Multiple sequence alignment of SARS-CoV-2 proteins with SARS-CoV. Multiple sequence alignment of (A) COVID-19-S and SARS-CoV-S, (B) COVID-19-M and SARS-CoV-M, (C) COVID-19-E and SARS-CoV-E and (D) COVID-19-N and SARS-CoV-N was visualized. Conservation showed based on 11 base scales where yellow color bar indicates the full conservation. Alignment quality was based on BLOSUM 62 substitution matrix score where yellow color indicates good quality. All the colors changes according to the conservation and alignment quality. Black bars showed the consensus sequence. This alignment was visualized by Jalview 2.8 and color scheme used is Clustalx. (ii): Multiple sequence alignment of SARS-CoV-2 proteins with BufCoV-HKU26. Multiple sequence alignment of (A) COVID-19-S and BufCoV-HKU26-S, (B) COVID-19-M and BufCoV-HKU26-M, (C) COVID-19-E and BufCoV-HKU26-E and (D) COVID-19-N and BufCoV-HKU26-N was visualized. Conservation showed based on 11 base scales where yellow color bar indicates the full conservation. Alignment quality was based on BLOSUM 62 substitution matrix score where yellow color indicates good quality. All the colors changes according to the conservation and alignment quality. Black bars showed the consensus sequence. This alignment was visualized by Jalview 2.8 and color scheme used is Clustalx. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



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IN SILICO

AN UPDATE ON ORIGIN OF SARS-COV-2: DESPITE CLOSEST IDENTITY, BAT (RATG13) AND PANGOLIN DERIVED CORONAVIRUSES VARIED IN THE CRITICAL BINDING SITE AND O-LINKED GLYCAN RESIDUES

Malaiyan J, Arumugam S, Mohan K, Radhakrishnan GG.. J Med Virol. 2020 Jul 7. doi: 10.1002/jmv.26261. Online ahead of print.

Level of Evidence: Other - Modeling

BLUF

To update SARS-CoV-2's phylogenetic classification and origins, virology and microbiology researchers from Tamil Nadu, India conducted in silico comparisons of key residues from receptor binding domains (RBDs) of the S-protein and O-linked glycans in bat (RaTG13) and Pangolin-CoV genomes with that of SARS-CoV-2. Their analysis showed that 11 SARS-CoV-2 isolates were closely related to RaTG13 (97.41% identity) and Pangolin-CoV (92.22% identity).They suggest that while more detailed research is needed, these findings support the formation of a new clade within the beta-CoV division of Coronavirinae.

ABSTRACT

The initial cases of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) occurred in Wuhan, China, in December 2019 and swept the world by 23 June 2020 with 8,993,659 active cases, 469,587 deaths across 216 countries, areas or territories. This strongly implies global transmission occurred before the lockdown of China. However, the initial source's transmission routes of SARS-CoV-2 remain obscure and controversial. Research data suggest bat (RaTG13) and pangolin carried CoV were the proximal source of SARS-CoV-2. In this study, we used systematic phylogenetic analysis of Coronavirinae subfamily along with wild type human SARS-CoV, MERS-CoV, and SARS-CoV-2 strains. The key residues of the receptor-binding domain (RBD) and O-linked glycan were compared. SARS-CoV-2 strains were clustered with RaTG13 (97.41% identity), Pangolin-CoV (92.22% identity) and Bat-SL-CoV (80.36% identity), forms a new clade-2 in lineage B of beta-CoV. The alignments of RBD contact residues to ACE2 justified? Those SARS-CoV-2 strains sequences were 100% identical by each other, significantly varied in RaTG13 and pangolin-CoV. SARS-CoV-2 has a polybasic cleavage site with an inserted sequence of PRRA compared to RaTG13 and only PRR to pangolin. Only serine (Ser) in pangolin and both threonine (Thr) and serine (Ser) O-linked glycans were seen in RaTG13, suggesting that a detailed study needed in Pangolin (Manis javanica) and bat (Rhinolophus affinis) related CoV.

IN VITRO

THROMBOTIC MICROANGIOPATHY, DIC-SYNDROME AND COVID-19: LINK WITH PREGNANCY PROTHROMBOTIC STATE

Makatsariya AD, Slukhanchuk EV, Bitsadze VO, Khizroeva JKH, Tretyakova MV, Tsibizova VI, Elalamy I, Gris JC, Grandone E, Makatsariya NA, Mashkova T.. J Matern Fetal Neonatal Med. 2020 Jul 6:1-9. doi: 10.1080/14767058.2020.1786811. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

In this review, authors from Russia offer a detailed description of the pathophysiology of the prothrombotic state. They note that the novel SARS-CoV-2 can cause thrombotic microangiopathy (TMA) development in patients, and suggest that pregnant patients, already in a hypercoagulable state (Table 4), are at increased risk for developing this complication. The authors share the International Society of Thrombosis and Hemostasis advice that all hospitalized COVID-19 patients should be prophylactically treated with low-molecular weight heparin, and note several other therapeutic options for other COVID-19 complications (Table 5).

ABSTRACT

For last months, humanity has faced a formidable unknown enemy, which is presented as a new coronavirus infection. Despite the fact that the causative agents of new diseases appear at a certain frequency and that the virus SARS-CoV-2 has certain common properties with its predecessors, at the moment we are dealing with a new unknown pathogenesis of the development of severe complications in patients with risk factors. A final understanding of pathological process mechanisms is the goal of the scientific community. Summarizing research data from different countries, it became obvious that in severe cases of viral infection, we are dealing with a combination of the systemic inflammatory response syndrome, disseminated intravascular coagulation and thrombotic microangiopathy (TMA). Thrombotic microangiopathy is represented by a group of different conditions in which thrombocytopenia, hemolytic anemia, and multiple organ failure occur. The article reflects the main types of TMA, pathogenesis and principles of therapy. The main participants in the process are described in detail, including the von Willebrand factor and ADAMTS-13. Based on the knowledge available, as well as new data obtained from patients with COVID-19, we proposed possible models for the implementation of conditions such as sepsis, TMA, and DIC in patients with severe new coronavirus infection. Through a deeper understanding of pathogenesis, it will be possible to develop more effective diagnosis and therapy.

FIGURES

Table 4. The changes in hemostasis system during the pregnancy – physiological hypercoagulation. (Table view)

Parameters	Changes
Cogulation factors:	
I, V, VII, VIII, IX, X	Increase
XI	Decrease
Anticoagulants:	
Thrombomodulin, APC-resistance	Increase
Protein S	Decrease
Antithrombin, Protein C	No changes
Fibrinolysis factors:	
PAI-I, PAI-II, TAFI, antiplasmin	Increase
Adhesion factors – vWF	Increase
Microparticles:	
endothelial and platelets microparticles	Increase
ADAMTS-13	Decrease in the II-III trimesters
Placental factors:	
Tissue factor	Increase
TFPI	Decrease

Table 5. Potential suggested therapy to reduce excessive thrombinemia and cytokine storm. (Table view)

Potential COVID treatment strategies	Therapeutic candidates
Anticoagulant therapy	Low-molecular-weight heparins
Phosphodiesterase inhibitors	Pentoxifylline, dipyridamole
Anticytokine drugs	Anakinra, Canakinumab, Tocilizumab
Anticomplement therapy	Eculizumab, heparin and others
Immunosupression	Glucocorticoids (methylprednisolone, dexamethasone), Human intravenous immunoglobulin

MANAGEMENT

ACUTE CARE

SERUM IGM AGAINST SARS-COV-2 CORRELATES WITH IN-HOSPITAL MORTALITY IN SEVERE/CRITICAL PATIENTS WITH COVID-19 IN WUHAN, CHINA

Liu X, Zheng X, Liu B, Wu M, Zhang Z, Zhang G, Su X.. Aging (Albany NY). 2020 Jul 6;12. doi: 10.18632/aging.103417. Online ahead of print.

Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

The authors conducted a retrospective cohort study (Wuhan Asia General Hospital, 1/22/2020 - 3/6/2020) of 79 severe/critical COVID-19 patients (Table 1) and found that patients with serum IgM ≥ 50 AU/ml at day 25 of infection had higher in-hospital mortality (p=0.026); there were also correlations between IgM levels and risk of ARDS, septic shock, mechanical ventilation, and corticosteroid usage (Table 3). Antibody remeasurement in 42 patients found a correlation between decreased IgM titers and reduced mortality (p=0.031). These findings suggest that measuring IgM titers over the infection course may be useful in monitoring COVID-19 disease progression in the hospital setting.

ABSTRACT

Severe/critical patients with coronavirus disease 2019 (COVID-19) have become the central issue in the current global pandemic due to their high mortality rate. However, the relationship between antibody response and clinical outcomes has not been well described in this group. We conducted a single-center, retrospective, cohort study to investigate the relationship between serum immunoglobulin G (IgG) and IgM and clinical outcomes in severe/critical patients with COVID-19. Seventy-nine severe/critical patients with COVID-19 admitted in Wuhan Asia General Hospital in Wuhan, China during January 22, 2020 to March 6, 2020 were included. Serum antibodies were measured at day 25 (SD, 7) post illness onset. The median IgG titer was 113 (IQR 81-167) AU/ml, and IgM titer was 50 (IQR, 23-105) AU/ml. Patients whose IgM titer >= 50 AU/ml had higher in-hospital mortality (p=0.026). IgM titer >= 50 AU/ml was also correlated with higher incidences of Acute Respiratory Distress Syndrome (ARDS) and sepsis shock. Antibody remeasurements were performed in 42 patients, where IgM titer declined significantly in survivors (p=0.031). Serum IgM titer changes according to the COVID-19 progression. The severe/critical patients with COVID-19 have a higher risk of clinical adverse events when IgM titer >= 50 AU/ml. Further decreasing of IgM could imply a better outcome in severe/critical cases.

FIGURES

Table 1. Clinical characteristics of patients with different IgM titers.

	IgM < 50 AU/ml (n=39)	IgM ≥ 50 AU/ml (n=40)	P
Age, years	64±11	61±14	0.315
Men	25(64)	25(63)	0.883
Current smoker	5(13)	2(5)	0.221
Comorbidity			
Chronic obstructive lung disease	3(8)	2(5)	0.623
Hypertension	17(44)	14(35)	0.434
Diabetes	7(18)	6(15)	0.724
Coronary heart disease	4(10)	2(5)	0.378
Chronic kidney disease	0(0)	2(5)	0.494
Symptoms			
Fever	30(77)	34(85)	0.360
Cough	28(72)	29(73)	0.944
Sputum	15(38)	11(28)	0.300
Myalgia	1(3)	5(13)	0.201
Fatigue	22(56)	22(55)	0.900
Diarrhoea	6(15)	6(15)	0.962
Dyspnea	25(64)	24(60)	0.707
Time from illness onset to hospital admission, days	10(7-14)	12(10-14)	0.172
Time from illness onset to first antibody detection, days	26(21-31)	23(19-29)	0.183
Time from hospital admission to first antibody detection, days	13(9-21)	11(7-15)	0.153
Vital signs on admission			
Temperature, °C	36.9±0.6	36.9±0.9	0.774
Systolic pressure, mmHg	129±18	128±18	0.857
Diastolic pressure, mmHg	78±12	76±9	0.461
Heart rate, beats/min	91±18	87±14	0.275
Disease severity state			0.003
Severe	36(92)	26(65)	
Critical	3(8)	14(35)	

Data are mean ± SD, median (IQR) or n (%). IgM = Immunoglobulin M.

Table 2. Laboratory measurements of patients with different IgM titers.

	IgM < 50 AU/ml (n=39)	IgM ≥ 50 AU/ml (n=40)	P
Arterial blood gas analysis			
PH	7.38±0.06	7.40±0.05	0.136
PaCO2, mmHg	44±7	42±8	0.277
PaO2, mmHg	59±6	56±7	0.044
SaO2, %	91±4	89±4	0.039
White blood cell count, $\times 10^9$/L	6.9±3.0	7.1±2.8	0.777
Neutrophil count, $\times 10^9$/L	5.5±2.9	5.8±2.9	0.608
Lymphocyte count, $\times 10^9$/L	0.9±0.4	0.9±1.0	0.800
Haemoglobin, g/L	126±15	126±19	0.812
Platelet count, $\times 10^9$/L	249±118	228±87	0.369
ALT, U/L	24(18-44)	39(16-63)	0.161
Albumin, g/L	34±4	32±5	0.010
Creatinine, μmol/L	86±26	83±38	0.730
Prothrombin time, s	12.0±0.8	12.4±1.2	0.085
Fibrinogen, g/L	5.0±1.9	5.2±1.7	0.623
D-dimer, mg/L	0.95(0.44-2.59)	1.81(0.77-9.06)	0.020
Cardiac troponin T, pg/ml	10(6-18)	12(8-20)	0.666
NT-proBNP, pg/ml	80(59-252)	264(73-590)	0.031
C-reactive protein, mg/L	40(12-107)	69(27-126)	0.119
IL-6, pg/mL	17(6-70)	42(12-119)	0.141
TNF-α, pg/mL	11(8-17)	9(5-12)	0.111

Data are mean ± SD or median (IQR). IgM = Immunoglobulin M. PH = Pondus Hydrogenii. PaCO2 = partial pressure of carbon dioxide. PaO2 = partial pressure of oxygen. SaO2 = arterial oxygen saturation. ALT = alanine aminotransferase. NT-proBNP = N-terminal pro-brain nattiuretic peptide. IL-6=Interleukin-6. TNF-α = tumor necrosis factor-α.

Table 3. Treatments and outcomes of patients with different IgM titers

	IgM < 50 AU/ml(n=39)	IgM ≥ 50 AU/ml(n=40)	P
Drugs			
Antiviral treatment	36(92)	38(95)	0.675
Antibiotics	36(92)	39(98)	0.359
Corticosteroids	16(41)	32(80)	<0.001
Chinese traditional medicine	39(100)	39(98)	1.000
Oxygen inhalation	38(97)	38(95)	0.571
Mechanical ventilation	3(8)	14(35)	0.003
Non-invasive	3(8)	13(33)	0.006
Invasive	0(0)	9(23)	0.002
Other advanced supportive therapy	1(3)	4(10)	0.175
IABP	0(0)	1(3)	0.320
CRRT	1(3)	4(10)	0.175
ECMO	0(0)	2(5)	0.157
Outcomes			
ARDS	2(5)	14(35)	0.001
Septic shock	2(5)	9(23)	0.026
In-hospital mortality	2(5)	9(23)	0.026
Hospital length of stay, days	29(21-30)	29(19-31)	0.941

Data are median (IQR) or n (%). IgM = Immunoglobulin M. IABP = Intra-aortic balloon pump. CRRT = continuous renal replacement therapy. ECMO = extracorporeal membrane oxygenation. ARDS = Acute Respiratory Distress Syndrome.

Mansouri N, Marjani M, Tabarsi P, von Garnier C, Mansouri D.. Immunol Invest. 2020 Jul 7:1-7. doi: 10.1080/08820139.2020.1789655. Online ahead of print.

Level of Evidence: Other - Case Report

BLUF

This case report describes a 42 year old male with no prior medical history who developed cytokine release syndrome (CRS) associated with COVID-19 and subsequently recovered following treatment with oral colchicine (see Summary). Authors suggest colchicine as a safe and inexpensive potential treatment option for mild to moderate CRS in COVID-19 patients, or in adjunction with routine antiviral agents to prevent CRS in COVID-19 patients with early lung involvement.

SUMMARY

Details of case report as follows:
After initial COVID-19 diagnosis via nasopharyngeal swab PCR, chest computed tomography (CT) revealed bilateral basilar ground glass opacities (Figure 1) and the patient was treated with oseltamivir and hydroxychloroquine twice daily for 5 days, followed by improvement of respiratory symptoms. On day 10, a diagnosis of CRS with a monoarticular gout flare was made based on the patient's presentation with high fever (40 C), shaking chills, myalgia, severe weakness and acute kidney injury associated with significantly elevated inflammatory markers (fibrinogen, LDH, D-dimer, ferritin and IL-6), while repeat CT showed marked improvement in alveolar infiltrates (Figure 2).The patient was started on oral colchicine 1 mg twice daily and notable improvement was observed after 48 hours. He continued colchicine therapy for 14 days and subsequently his nasopharyngeal swab was negative (on two consecutive occasions), laboratory values all returned to normal range (WBC, platelet count, LDH, ferritin, fibrinogen, D-dimer, IL-6 and uric acid), ESR declined, CRP was undetectable, and he was asymptomatic.

The authors advocate for consideration of colchicine therapy to treat mild to moderate CRS in COVID-19 patients, even in an outpatient setting. They additionally suggest colchicine as a candidate to prevent CRS (in adjunction with routine antiviral agents) in COVID-19 patients with early lung involvement. Authors acknowledge the need for randomized controlled studies to adequately assess the benefits of this therapy.

ABSTRACT

We describe the case of a 42 year old, healthy patient with Covid-19 who despite improvement in his respiratory symptoms developed a mild to moderate cytokine release syndrome (CRS) and an associated monoarticular gout flare. Since the patient refused admission to the hospital and had stable vital signs, we chose to treat him with a safe anti-inflammatory and non-immunosuppressive therapy. To hit two birds with one stone, we considered colchicine, as it has systemic anti-inflammatory effects and is also effective in gout flare. Unexpectedly, 48 hours after treatment, not only did his ongoing fever and toe pain disappear, he also had significant improvements in his general state of health and all his inflammatory markers including fibrinogen, ferritin, D-dimer, and IL-6 levels normalized. To our knowledge, the use of colchicine in Covid-19 and CRS has not been reported. This observation merits the consideration of colchicine as a safe, inexpensive and oral medication for the treatment of mild to moderate CRS in Covid-19 patients. More importantly, in Covid-19 patients with early lung involvement colchicine may be an appropriate candidate to prevent CRS in adjunction with routine antiviral agents. Indeed, multicenter, randomized controlled studies are required to evaluate the benefits of this therapy.

FIGURES

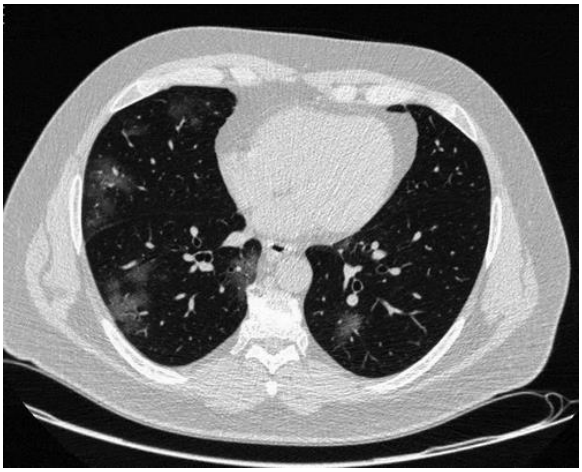

Figure 1: Axial CT image at presentation shows bilateral pleural-based ground glass opacities.

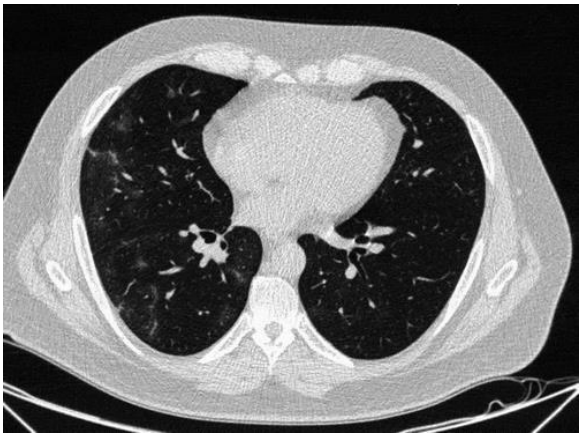

Figure 2: Axial CT image 10 days later shows improvement in previously noted lung infiltrates.

ADJUSTING PRACTICE DURING COVID-19

ANAESTHESIA

RISK STRATIFICATION IN PATIENTS UNDERGOING NONOPERATING ROOM ANESTHESIA

Bockstael B, Najafi N, Poelaert J.. Curr Opin Anaesthesiol. 2020 Aug;33(4):571-576. doi: 10.1097/ACO.0000000000000888.

Level of Evidence: Other - Review / Literature Review

BLUF

A review authored by anesthesiologists in Brussels, Belgium identifies risk factors in patients undergoing nonoperating room anesthesia (NORA) as need increases. The highest risk factors for poor outcomes were respiratory infections (with and without comorbidities) (OR 23.55-17.46), respiratory commodities alone (OR 8.18), Upper GI endoscopy (OR 5.66), and morbid obesity (OR 4.25). The authors also emphasized the importance of preoperative screening for COVID-19 to minimize exposure risk for staff. They recommend these evaluations for risk to promote patient and staff safety as demand for NORA continues to increase.

ABSTRACT

PURPOSE OF REVIEW: A growing numerical and complexity of patients requiring nonoperating room anesthesia (NORA) necessitates a multidisciplinary approach of a highly experienced team in a highly technological setting of the cathlab or radiology suite. These requirements are even more magnified in the context of the coronavirus disease 2019 (COVID-19) pandemic. RECENT FINDINGS: This review describes the aspects of risk stratification both in adults and children with respect to patient morphology, airway management, cardiorespiratory function and finally future developments, which could beneficially interfere with imminent management in NORA. Moreover, some particular features related to COVID-19 are also discussed. SUMMARY: Apart from a thorough preoperative assessment, preventive strategies and well-chosen monitoring should be implemented to preclude inadvertent events in sometimes high-risk patients. Timely preventive measures and early recognition of complications could only be achieved by a multidisciplinary cooperating team. In addition, the implementation of safety measurements due to the infectious transmission to both the patients and care givers is crucial.

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