

The Daily COVID-19 Literature Surveillance Summary

November 18, 2020



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COVID-19 Daily Literature Surveillance

COVID19LST



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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

EXECUTIVE SUMMARY

Epidemiology

- Pediatric cardiologists from the Association for European Pediatric and Congenital Cardiology's COVID-19 Rapid Response Team evaluated [286 children with symptoms of multisystem inflammatory syndrome in children \(MIS-C\)](#) and found 65% had laboratory evidence of current or past COVID-19 infection, 93% had cardiac involvement, and all had elevated inflammatory markers, suggesting pediatric patients with MIS-C should be monitored for cardiovascular complications and rising biomarkers.
- A literature review conducted by an international panel of pediatric dermatologists describes [documented skin manifestations of COVID-19 in children](#) including chilblain-like lesions, erythema multiforme, urticaria (10-20% of cutaneous manifestation reports), vesicular exanthema, and Kawasaki disease-like inflammatory syndrome (pediatric inflammatory multisystem syndrome with nonspecific skin symptoms and cardiovascular involvement).

Understanding the Pathology

- A retrospective cohort study by cardiac pathologists from the Mayo Clinic of post-mortem reviews of 15 patients with COVID-19, six patients with influenza, and six patients with no viral pathology found [patients with COVID-19 were significantly more likely to have fibrin microthrombi](#) (12/12 [100%] of COVID-19 vs 2/6 [33%] of influenza and control patients; p=0.006) and that these were found in a higher proportion of arterioles (p=0.003). One-third (33%) of COVID-19 patients had evidence of myocarditis and 26.7% evidence of amyloidosis.
- Physiology researchers use mechanism-based reasoning to propose an explanation as to why COVID-19 can have [varying clinical symptoms using three possible mechanisms](#): p38/MAPK pathway, JAK-STAT pathway, and the PGE2-EP receptors signaling pathway. From each of these pathways, the authors suggest the varying symptoms could be attributed to the level of prostaglandin E2 (PGE2) released, which causes a cytokine storm, and they further theorize that the amount of PGE2 could be directly correlated to disease severity.
- Investigators mainly from the Institute of Physiology in Berlin compared the respective [plasma disruption to the lung epithelium](#) between the plasma of 19 patients with severe COVID-19 (requiring intubation), 14 patients with moderate COVID-19 (requiring hospitalization but not intubation), and 15 healthy controls and found that addition of plasma from COVID-19 patients to healthy endothelial monolayers correlated with "significant endothelial gap formation and loss of junctional VE-cadherin". Additionally, when compared to the healthy control plasma, the plasma from COVID-19 patients not only resulted in increased severity of endothelial permeability but also rapid (within 1-2 hours) and long lasting (over 6 hours) effects, suggesting that endothelial-barrier-stabilizing adjunctive therapies administered to patients exhibiting signs of moderate to severe COVID-19 may delay progression to acute respiratory distress syndrome.

Management

- Neurosurgeons at the Laboratory of Experimental Neurosurgery and Cell Therapy in Milan, Italy compared blood samples from 47 healthy patients to samples from 111 SARS-CoV-2 positive patients and found [sphingosine-1-phosphate \(S1P\) and apolipoprotein M \(apoM; a carrier of S1P\) levels were significantly decreased in COVID-19 patients](#) compared to healthy patients (p<0.0001). COVID-19 patients requiring intensive care unit (ICU) admission had significantly lower levels of apoM, S1P, albumin, and HDL compared to those not requiring ICU care (p<0.0001), suggesting that the SARS-CoV-2 induced cytokine storm and acute phase response lowers levels of these specific biomarkers, and low levels of S1P (<0.6uM) and apoM may be clinical predictors of severe disease and decreased survival.

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CLIMATE

GLOBAL

THE COVID-19 STRESS MAY INFLUENCE ON THE SEX RATIO AT BIRTH

Abdoli A.. J Matern Fetal Neonatal Med. 2020 Nov 12:1-6. doi: 10.1080/14767058.2020.1846181. Online ahead of print.

Level of Evidence: Other - Opinion

BLUF

An Iranian parasitologist postulates the effect of COVID-19 induced stress, depression and anxiety in asymptomatic SARS-CoV-2 positive pregnant females on the sex ratio at birth (SRB; boys:girls). They review literature demonstrating that maternal stress increases inflammation (i.e. increased IL-6, IL-1b, CRP) and rate of complications such as prematurity, stillbirth, and fetal loss. Because the literature suggests male fetuses are more vulnerable to prenatal stress than female fetuses, the author suggests psychological stress related to the pandemic (Table 2) may decrease the SRB below its baseline as has occurred during other crises (Table 1).

ABSTRACT

The ratio of boys to girls (sex ratio) at birth (SRB) is about 1.01-1.05 in most populations and is influenced by various factors, such as maternal stress, maternal inflammation, and endocrine disruption. Male fetus is biologically weaker and more vulnerable to prenatal events than female fetuses. Hence, premature death (and consequently decline the SRB) is higher in boys than girls. The recent coronavirus disease 2019 (COVID-19) has been known to have a variety of stressful and psychological impacts. This stress may consequently enhance maternal inflammation, pregnancy complication, and fetal loss. Also, male fetuses have more adverse outcomes than female fetuses among asymptomatic pregnant women with SARS-CoV-2 infection. Inasmuch as the male fetus are more vulnerable to prenatal events and premature death, it is proposed that the SRB can decline in pregnant women following the COVID-19 stress. However, future studies are needed to define the impact of the COVID-19 on SRB rate.

FIGURES

Stressor	SRB alteration	Reference
Earthquake Bam earthquake, Iran (26th December 2003)	► A prominent decline in the SRB (~0.467) 11 months after the earthquake ($\chi^2 = 6.68$, $df = 1$, $p = .009$). ► Cumulative evidences have demonstrated a significant decline in the SRB after major earthquakes in Japan.	[10]
Earthquakes in Japan (a series of reports about the effects of earthquakes on SRB in Japan) Terrorist attacks The 11 September 2001 U.S. terrorist attacks.	► Cumulative evidences have shown that increased birth defects among males than females, increased male fetal loss, and decline in SRB following the 11 September 2001 U.S. terrorist attacks.	[11,12]
Terrorist attacks in Northern Ireland	► The SRB was significantly declined during the Troubles (1969–1998) than during the period before ($p = .0006$).	[13–15]
Terrorist attacks (Meta-Analysis of five studies).	► A significant decline (3%) in the odds ($p = .03$) of having a male live birth were detected 3–5 months after the attacks. 10% reduction in male live birth (OR 0.90, $p = .0001$) was found for lone wolf attacks.	[16]
Maternal psychological stress Maternal psychological stress (a cohort among 8719 Danish pregnant women from 1989 to 1992)	► The SRB was 47% and 52% for mothers with stress and unstressed group, respectively (OR 0.82, 95% CI 0.72–0.94).	[17]
Maternal prenatal stress (187 pregnant women were assessed in three subgroups, including psychologically stressed group (PSYG), physically stressed group (PHSG), and healthy control (HC))	► Both stressed groups had a lower percent of male births compared to the HG [56%, 40%, and 31% for HG, PSYG, and PHSG, respectively; ($\chi^2 = 6.87$, $p < .05$). The SRB ratio (105:100) was lower in the PSYG (2:3) and PHSG (4:9), and higher in the HG (23:18), showing diminished male births in maternal stress contexts.	[18]
		[19]

Table 1: "A snapshot on the effect of some stressful life events on the SRB".

Study objective and setting	Main findings	Reference
<p>► Systematic review and meta-analysis regarding psychological and mental impact of the COVID-19 on medical staff and general population.</p> <p>► Included articles were between 1 Nov 2019 to 25 May 2020.</p>	<p>► 62 studies with 162,639 participants from 17 countries were included.</p> <p>► The pooled prevalence of anxiety and depression was 33% (95% CI: 28–38%) and 28% (95% CI: 23–32%), respectively.</p> <p>► The most common risk factors were being women, being nurses, having high risks of contracting COVID-19, having lower socioeconomic status, and social isolation.</p> <p>► Protective factors included accurate and up-to-date information, having sufficient medical resources, and taking precautionary measures.</p>	[32]
<p>Psychological influence of the COVID-19 on pregnant women</p> <p>► To investigate the effects of the COVID-19 on depression and anxiety among Turkish pregnant women.</p> <p>► Online questionnaire survey.</p>	<p>► 35.4% of the case group ($N = 92$) obtained scores higher than 13 on the Edinburgh Postpartum Depression Scale (EPDS) which indicated a statistically significant effects of the COVID-19 on psychology, social isolation, and mean scores in the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI).</p>	[33]
<p>► To examined the effect of COVID-19 fear of on mental health, and preventive behaviors of Iranian pregnant women and their husbands.</p> <p>► Cross-sectional study of 290 pregnant women and their husbands ($N = 580$)</p> <p>► To investigate the symptoms of depression and anxiety and determination of associated factors with psychological distress among Canadian pregnant individuals during the current COVID-19 pandemic.</p> <p>► Cross-sectional study of among 1987 pregnant participants (April 2020).</p>	<p>► The findings demonstrated significant effect of fear of COVID-19 with depression, suicidal intention, mental quality of life, and COVID-19 preventive behaviors among the pregnant women and their husbands.</p> <p>► Prevalence of depression and anxiety were 37% and 57%; which substantially elevated these rates compared to similar pre-pandemic pregnancy cohorts</p>	[34]
		[59]

Table 2: "Psychological influence of the COVID-19".

EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

PEDIATRICS

ACUTE CARDIOVASCULAR MANIFESTATIONS IN 286 CHILDREN WITH MULTISYSTEM INFLAMMATORY SYNDROME ASSOCIATED WITH COVID-19 INFECTION IN EUROPE

Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, Kucinska B, Mannarino S, Tamariz-Martel A, Gutierrez-Larraya F, Soda G, Vandekerckhove K, Gonzalez Barlatey F, McMahon CJ, Marcora SA, Pace Napoleone C, Duong P, Tuo G, Deri A, Nepali G, Ilina M, Ciliberti P, Miller O; on behalf the AEPC COVID-19 rapid response team.. Circulation. 2020 Nov 9. doi: 10.1161/CIRCULATIONAHA.120.050065. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Pediatric cardiologists from the Association for European Pediatric and Congenital Cardiology's COVID-19 Rapid Response Team evaluated 286 children from 17 European countries with symptoms of multisystem inflammatory syndrome in children (MIS-C) (Table 1) between February and May 2020 (Figure 1). They found 65% had laboratory evidence of current or past COVID-19 infection, 93% had cardiac involvement, and all had elevated inflammatory markers. Authors suggest pediatric patients with MIS-C should be monitored for cardiovascular complications and rising biomarkers, which have been shown to correlate with need for intensive care.

ABSTRACT

Background: The aim of the study was to document cardiovascular clinical findings, cardiac imaging and laboratory markers in children presenting with the novel multisystem inflammatory syndrome (MIS-C) associated with COVID-19 infection.

Methods: A real-time internet-based survey endorsed by the Association for European Paediatric and Congenital Cardiologists (AEPC) Working Groups for Cardiac Imaging and Cardiovascular Intensive Care. Inclusion criteria was children 0-18 years admitted to hospital between February 1 and June 6, 2020 with diagnosis of an inflammatory syndrome and acute cardiovascular complications. **Results:** A total of 286 children from 55 centers in 17 European countries were included. The median age was 8.4 years (IQR 3.8-12.4 years) and 67% were males. The most common cardiovascular complications were shock, cardiac arrhythmias, pericardial effusion and coronary artery dilatation. Reduced left ventricular ejection fraction was present in over half of the patients and a vast majority of children had raised cardiac troponin (cTnT) when checked. The biochemical markers of inflammation were raised in majority of patients on admission: elevated CRP, serum ferritin, procalcitonin, NT-proBNP, IL-6 level and D-dimers. There was a statistically significant correlation between degree of elevation in cardiac and biochemical parameters and need for intensive care support ($p < 0.05$). Polymerase chain reaction (PCR) for SARS-CoV-2 was positive in 33.6% while IgM and IgG antibodies were positive in 15.7% and IgG 43.6 % cases, respectively when checked. One child died in the study cohort. **Conclusions:** Cardiac involvement is common in children with multisystem inflammatory syndrome associated with Covid-19 pandemic. A majority of children have significantly raised levels of NT pro-BNP, ferritin, D-dimers and cardiac troponin in addition to high CRP and procalcitonin levels. Compared to adults with Covid-19, mortality in children with MIS-C is uncommon despite multi-system involvement, very elevated inflammatory markers and need for intensive care support.

FIGURES

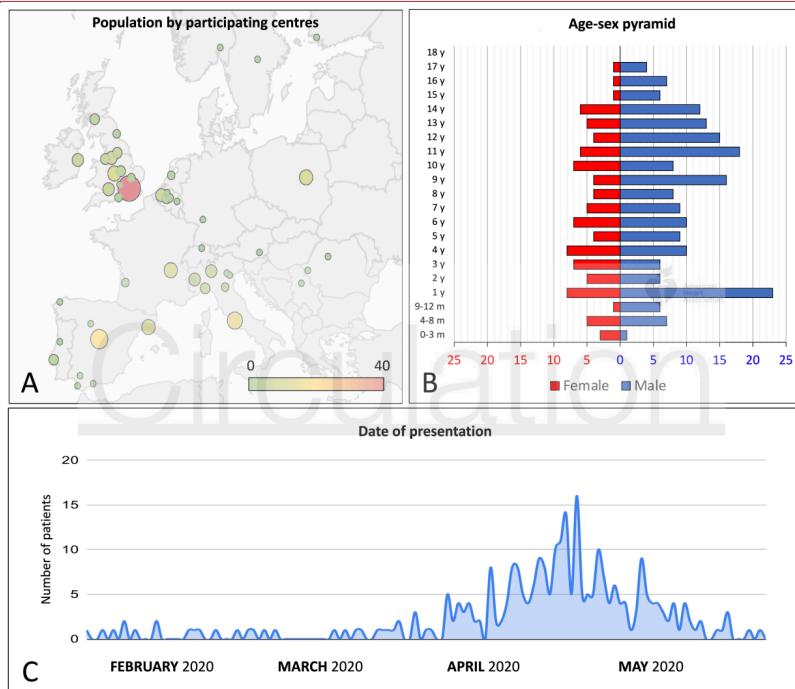


Figure 1: Study Demographics. A. Study population density across the 48 cities from 17 European countries. B. Age-sex pyramid distribution. C. Number of patients admitted to hospital during the European pandemic (February – May 2020).

Inflammatory syndrome	
1.	Persistent fever >38°C *
2.	Elevated laboratory markers of inflammation *
3.	Associated multiorgan dysfunction †
Acute cardiovascular complications	
1.	Acute coronary artery involvement
2.	Acute myocardial injury
3.	Arrhythmias
4.	Cardiogenic shock
5.	Pericardial effusion
6.	Thromboembolic complications

Children and adolescents (0-18 years) with Inflammatory syndrome: Persistent fever AND elevated laboratory markers of inflammation AND any of the acute cardiovascular complications.
Presence of associated multiorgan dysfunction is optional. *Mandatory. †Optional.

Table 1: Acute cardiovascular inflammatory syndrome inclusion criteria

SKIN MANIFESTATIONS OF COVID-19 IN CHILDREN: PART 2

Andina D, Belloni-Fortina A, Bodemer C, Bonifazi E, Chiriac A, Colmenero I, Diociaiuti A, El-Hachem M, Fertita L, van Gysel D, Hernández-Martín A, Hubiche T, Luca C, Martos-Cabrera L, Maruani A, Mazzotta F, Akkaya AD, Casals M, Ferrando J, Grimalt R, Grozdev I, Kinsler V, Morren MA, Munisami M, Nanda A, Novoa MP, Ott H, Pasman S, Salavastru C, Zawar V, Torrelo A; ESPD Group for the Skin Manifestations of COVID-19.. Clin Exp Dermatol. 2020 Nov 9. doi: 10.1111/ced.14482.

Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

A literature review conducted by an international panel of pediatric dermatologists describes documented skin manifestations of COVID-19 in children including chilblain-like lesions, erythema multiforme (Figure 1), urticaria (Figure 2; 10-20% of cutaneous manifestation reports), vesicular exanthema (Figure 3), and Kawasaki disease-like inflammatory syndrome (pediatric inflammatory multisystem syndrome with nonspecific skin symptoms and cardiovascular involvement). Authors hope their findings add to the growing knowledge of pediatric skin manifestations related to SARS-CoV-2 infection and inform clinicians to aid in accurate diagnoses.

ABSTRACT

The current COVID-19 pandemic is caused by the SARS-CoV-2 coronavirus. The initial recognized symptoms were respiratory, sometimes culminating in severe respiratory distress requiring ventilation, and causing death in a percentage of those infected. As time has passed, other symptoms have been recognized. The initial reports of cutaneous manifestations were from Italian dermatologists, probably because Italy was the first European country to be heavily affected by the pandemic. The overall clinical presentation, course and outcome of SARS-CoV-2 infection in children differ from those in adults, as do the cutaneous manifestations of childhood. In this review, we summarize the current knowledge on the cutaneous manifestations of COVID-19 in children after thorough and critical review of articles published in the literature and from the personal experience of a large panel of paediatric dermatologists in Europe. In Part 1, we discussed one of the first and most widespread cutaneous manifestations of COVID-19, chilblain-like lesions. In this part of the review, we describe other manifestations, including erythema multiforme, urticaria and Kawasaki disease-like inflammatory multisystemic syndrome. In Part 3, we discuss the histological findings of COVID-19 manifestations, and the testing and management of infected children for both COVID-19 and any other pre-existing conditions.

FIGURES



Figure 1 (a,b) Typical target and targetoid lesions in COVID-19-related erythema multiforme.



Figure 2 Urticaria in a child with COVID-19.



Figure 3 Vesicular exanthem of COVID-19.

UNDERSTANDING THE PATHOLOGY

COVID-19-ASSOCIATED NON-OCCLUSIVE FIBRIN MICROTHROMBI IN THE HEART

Bois MC, Boire NA, Layman AJ, Aubry MC, Alexander MP, Roden AC, Hagen CE, Quinton RA, Larsen C, Erben Y, Majumdar R, Jenkins SM, Kipp BR, Lin PT, Maleszewski JJ.. Circulation. 2020 Nov 16. doi: 10.1161/CIRCULATIONAHA.120.050754. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

In this retrospective cohort study conducted between April 2 and September 9, 2020, cardiac pathologists from the Mayo Clinic conducted post-mortem reviews on 15 patients with COVID-19, six patients with influenza, and six patients with no viral pathology (Table 1). They found patients with COVID-19 were significantly more likely to have fibrin microthrombi (12/12 [100%] of COVID-19 vs 2/6 [33%] of influenza and control patients; $p=0.006$)(Table 3) and that these were found in a higher proportion of arterioles ($p=0.003$)(Figure 3). One-third (33%) of COVID-19 patients had evidence of myocarditis and 26.7% evidence of amyloidosis. Based on these findings, the authors suggest COVID-19 infection is associated with development of fibrin microthrombi, though the observed degree of myocarditis does not sufficiently explain the reported degree of cardiac symptoms in patients with COVID-19.

FIGURES

Table 1. Cohort Demographics and Relevant Clinical Characteristics

	COVID-19* (n=15)	Influenza (n=6)	Controls (n=6)	p-value
Age, median (IQR)	78 (71, 86)	52 (46, 80)	74 (65, 81)	0.20 [‡]
Male sex, n (%)	12 (80.0%)	2 (33.3%)	2 (33.3%)	0.05 [†]
Comorbidities per patient*, median (IQR)	2 (1, 3)	2.5 (1, 3)	0.5 (0, 1)	0.18 [§]
Medications influencing coagulation, n (%) ^{††}				
Aspirin	5/9 (55.6%)	2/3 (66.7%)	2/4 (50.0%)	1.0 [¶]
Heparin/Lovenox	2/9 (22.2%)	0/3 (0.0%)	0/4 (0.0%)	1.0 [¶]
Clopidogrel	0/9 (0.0%)	0/3 (0.0%)	1/4 (25.0%)	0.44 [¶]
Apixaban	1/9 (11.1%)	0/3 (0.0%)	1/4 (25.0%)	1.0 [¶]
Warfarin	1/9 (11.1%)	0/3 (0.0%)	0/4 (0.0%)	1.0 [¶]
Coagulation Parameters, n, median (range)				
Plt count ($\times 10^9/\text{L}$)	12 215 (33-670)	4 144.5 (55-461)	5 222 (102-374)	0.82 [§]
D-dimer (ng/mL)	7 1145 (1.9-2475)	1 14065 (0-775)	3 336 (0-775)	0.8 [§]
Prothrombin time (PT), sec	9 15.9 (12.2-51.7)	4 18.7 (12.9-27.6)	6 15.5 (10.6-91.8)	0.70 [§]
Activated partial thromboplastin time (aPTT)	7 32 (27-83)	4 38.5 (35-63)	5 35 (24-39)	0.22 [‡]
INR	10 1.5 (1.1-4.6)	5 1.8 (1.2-2.5)	6 1.3 (1.0-8.2)	0.59 [‡]
Thrombin time (sec)	1 34.7	1 28.4	1 21.6	NA
Fibrinogen (mg/dL)	5 574 (236-774)	4 465 (345-576)	2 249 (71-427)	0.36 [§]
High-sensitivity troponin, (ng/L), n Median (range)	8 19.5 (0-461)	4 82 (28-223)	6 19 (0-90)	0.28 [§]
History of ACE inhibitor use, n (%)	6/9 (66.7%)	2/3 (66.7%)	0/4 (0%)	0.10 [¶]

NA = not applicable; n=number; Plt=platelet

*Defined as underlying chronic conditions, including systemic hypertension, hyperlipidemia, diabetes mellitus type 2 and chronic kidney disease

[†]Including both patients with active and cleared SARS-CoV-2 viral infection

^{††}Medications immediately preceding or during terminal illness and/or hospitalization; denominator denoted number of patients in each category with information present in the medical record

[‡] Kruskal-Wallis test

[†] Fisher's exact test

Table 3. Summary of Cardiac Pathology

	COVID-19* (n=15)	Active COVID-19† (n=12)	Influenza (n=6)	Controls (n=6)	p-value‡	Pairwise comparison for significant values
Gross characteristics						
Heart weight (g), median (range)	443.1 (286.3-545.0)	474.0 (286.3-545.0)	398.4 (269.0-592.0)	244.5 (197.0-560.3)	0.22§	
Percent of expected heart weight§ (%), median (range)	1.42 (0.97-1.94)	1.49 (0.97-1.94)	1.35 (1.04-2.13)	0.89 (0.78-2.11)	0.17§	
Histopathologic characteristics						
Microthrombosis, n (%)	12 (80.0%)	11 (91.7%)	2 (33.3%)	2 (33.3%)	0.006*	<i>COVID-19 vs influenza, p=0.02</i> <i>COVID-19 vs control, p=0.02</i>
Involved arterioles, median % of total (range)	6.3 (0.0-28.6)	7.3 (0.0-28.6)	0.0 (0.0-6.1)	0.0 (0.0-4.7)	0.003†	<i>COVID-19 vs influenza, p=0.01</i> <i>COVID-19 vs control, p=0.003</i>
Myocarditis, n (%)	5 (33.3%)	4 (33.3%)	1 (16.7%)	0 (0.0%)	0.38*	
Interstitial edema, n (%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	0 (0.0%)	0.11*	
Acute ischemic injury, n (%)	2 (13.3%)	2 (16.7%)	2 (33.3%)	0 (0.0%)	0.32*	

*Including both patients with active and cleared SARS-CoV-2 viral infection

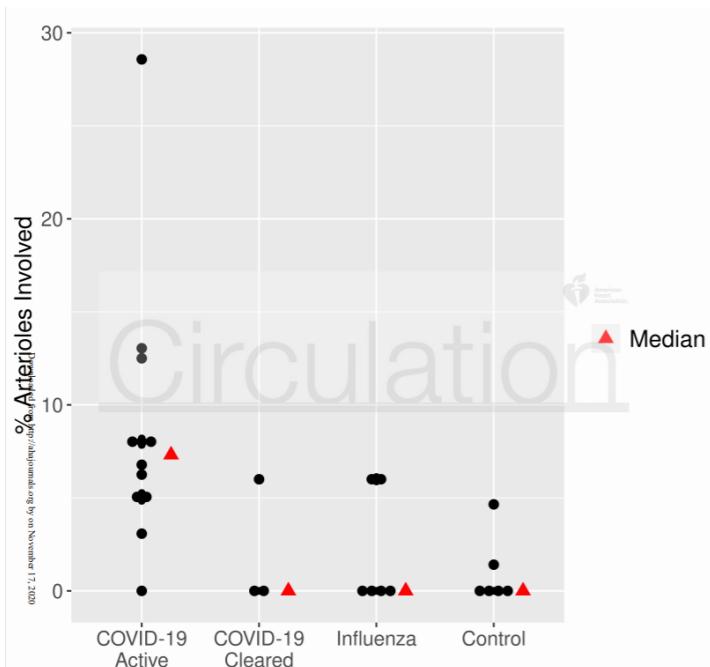
†COVID-19 cases with cleared infection excluded (n=3)

‡Denotes overall p-value including active COVID-19, influenza and control cases

§ As compared to age-, sex-, and weight-based controls (34)

¶ Kruskal-Wallis test

Fisher's exact test



'Figure 3. Frequency of fibrin microthrombi'

Active COVID-19 cases showed more frequent fibrin microthrombi than other postmortem control groups, including both virally mediated (Influenza) and non-virally mediated (Control) deaths.

PATOPHYSIOLOGICAL MECHANISMS OF LIVER INJURY IN COVID-19

Nardo AD, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M.. Liver Int. 2020 Nov 15. doi: 10.1111/liv.14730.
Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

Given reported prevalence of elevated liver enzymes of anywhere from 2.5%-76.3%, hepatologists from the Medical University of Vienna in Austria review literature relating to the pathophysiology of liver injury in COVID-19. They discuss possible mechanisms for hepatic injury: direct viral infection, systemic inflammatory response syndrome, hypoxemia, coagulopathy, endothelitis or cardiac congestion from right heart failure, drug-induced liver injury, and exacerbation of underlying liver disease (Figure 2). Because liver function contributes to both drug metabolism and acute phase reactions, these authors urge further research to better describe hepatic involvement in COVID-19.

ABSTRACT

The recent outbreak of coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has resulted in a world-wide pandemic. Disseminated lung injury with development of acute respiratory distress syndrome (ARDS) is the main cause of mortality in COVID-19. Although liver failure does not seem to occur in the absence of preexisting liver disease, hepatic involvement in COVID-19 may correlate with overall disease severity and serve as prognostic factor for development of ARDS. The spectrum of liver injury in COVID-19 may range from direct infection by SARS-CoV-2, indirect involvement by systemic inflammation, hypoxic changes, iatrogenic causes such as drugs and ventilation to exacerbation of underlying liver disease. This concise review discusses the potential pathophysiological mechanisms for SARS-CoV-2 hepatic tropism as well as acute and possibly long-term liver injury in COVID-19.

FIGURES

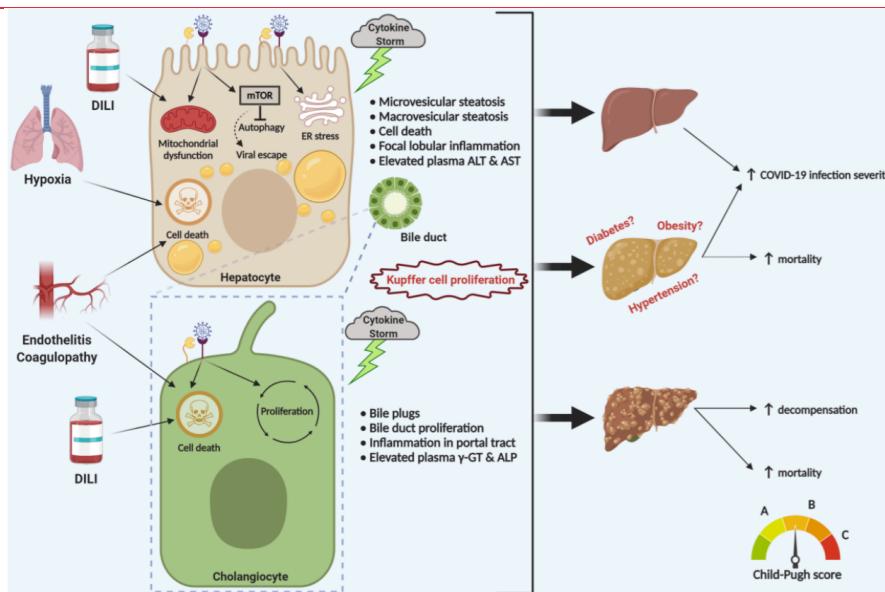


Figure 2: Proposed pathophysiology for liver injury upon SARS-CoV-2 infection. COVID-19-associated hepatocellular damage is mainly characterized by moderate steatosis, lobular and portal inflammation, apoptotic/necrotic foci and elevation of plasma ALT and AST (upper left panel). Preliminary observations suggest that the injury might be caused by hepatocellular infection with direct cytopathic effects of SARS-CoV-2, which could induce mitochondrial dysfunction and ER stress contributing to steatosis. Furthermore, SARS-CoV-2 infection might also activate mTOR, which eventually inhibits autophagy (as a mechanism of viral degradation) and facilitates viral escape from the immune system. In addition, cytokine storm, hypoxic conditions due to ARDS and drug-induced liver injury (DILI) may contribute. COVID-19-associated cholangiocellular injury has also been observed and is mainly characterized by bile duct proliferation, occasionally bile plug formation, and ALP (lower left panel). From a hepatological perspective, COVID-19-positive patients may be divided in three categories: patients without pre-existing chronic liver disease, patients with early stage chronic liver disease and patients with advanced chronic liver disease/liver cirrhosis. COVID-19-associated liver injury may have a more severe outcome in patients with pre-existing liver disease, such as non-alcoholic fatty liver disease (NAFLD) and associated metabolic comorbidity. Moreover, COVID-19 may induce hepatic decompensation with increased mortality in cirrhotic patients (right panel).

WHY DOES COVID-19 PATHOLOGY HAVE SEVERAL CLINICAL FORMS?

Aliabadi F, Ajami M, Pazoki-Toroudi H.. Bioessays. 2020 Nov 11:e2000198. doi: 10.1002/bies.202000198. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

Physiology researchers use mechanism-based reasoning to propose an explanation as to why COVID-19 can have varying clinical symptoms using three possible mechanisms: p38/MAPK pathway (Figure 3), JAK-STAT pathway (Figure 4), and the PGE2-EP receptors signaling pathway (Figure 5). From each of these pathways, the authors suggest the varying symptoms could be attributed to the level of prostaglandin E2 (PGE2) released, which causes a cytokine storm. They further theorize that the amount of PGE2 could be directly correlated to disease severity. The authors hope that their proposed mechanistic explanation will serve to guide future studies on PGE2 secretion and its impact on disease severity and organ involvement.

ABSTRACT

The outbreak of a new, potentially fatal virus, SARS-CoV-2, which started in December 2019 in Wuhan, China, and since developed into a pandemic has stimulated research for an effective treatment and vaccine. For this research to be successful, it is necessary to understand the pathology of the virus. So far, we know that this virus can harm different organs of the body. Although the exact mechanisms are still unknown, this phenomenon may result from the body's secretion of prostaglandin E2 (PGE2), which is involved in several inflammation and immunity pathways. Noticeably, the expression of this molecule can lead to a cytokine storm causing a variety of side effects. In this paper, we discuss those side effects in SARS-CoV-2 infection separately to determine whether PGE2 is, indeed, an important causative factor. Lastly, we propose a mechanism by which PGE2 production increases in response to COVID-19 disease and suggest the possible direct relation between PGE2 levels and the severity of this disease. Also see the video abstract here: <https://youtu.be/SnPFACjxxKw>.

FIGURES

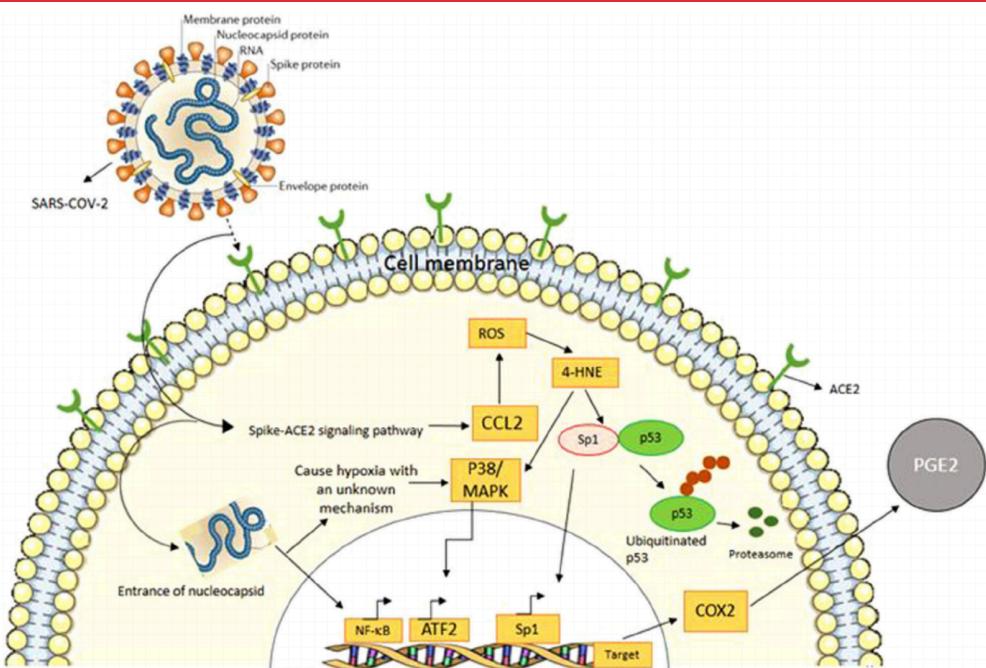


FIGURE 3 Three pathways by which COVID-19 increase PGE2. After infection of SARS-CoV2, its spike proteins interact with ACE2 which leads to activating a signaling pathway in addition to its nucleocapsid's entering into the cells. This signaling pathway may lead to upregulation of CCL2 which in turn upregulates reactive oxygen species (ROS). This activates 4-hydroxy-2-nonenal (4-HNE), a downstream product of ROS which can induce COX2 along with PGE2. Moreover, after entrance of SARS-CoV2, its nucleocapsids probably activate NF-κB signaling pathway and lead to upregulation of COX2 as well as PGE2. Furthermore, SARS-CoV2 can cause hypoxia through an unknown mechanism which results in activating p38/MAPK pathway. This pathway can activate cyclic AMP-dependent transcription factor (AFT2) which cause COX2 and PGE2 upregulation. The notable thing is that activation of each pathway is cell dependent

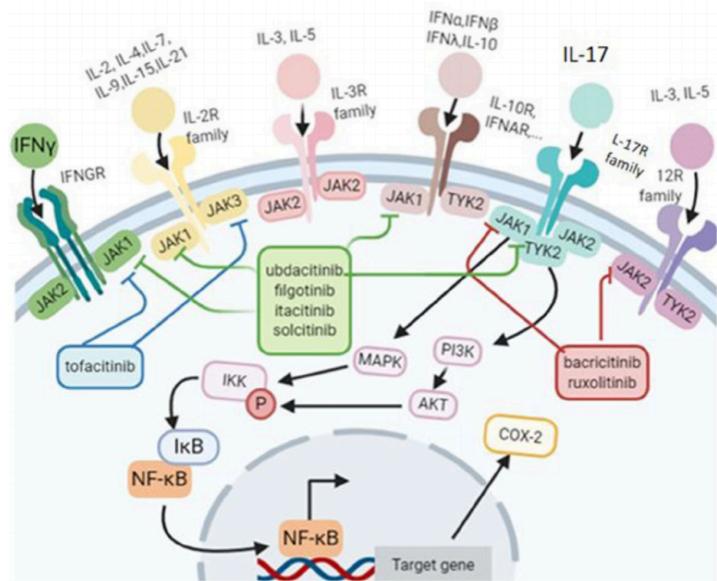


FIGURE 4 JAKinhibitors and mechanism of COX-2 production. JAK-STAT pathway can also affect the production of PGE2 through activating IL receptors. It leads to activating Phosphatidyl inositol 3-kinase (PI3K)/protein kinase B (AKT) and I κ B kinase (IKK)/Mitogen-Activated Protein Kinase (MAPK) pathways which induce NF- κ B signaling pathway

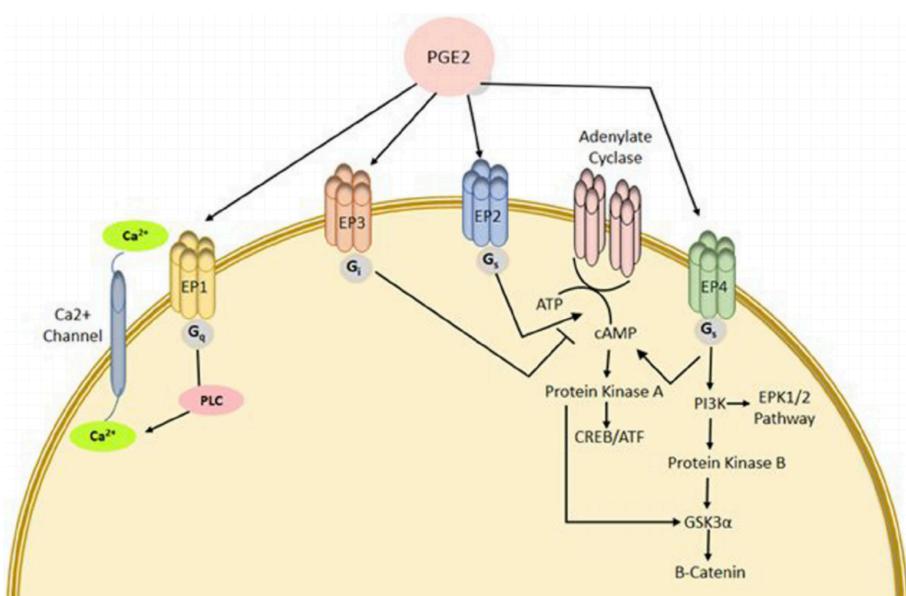


FIGURE 5 PGE2-EP receptors signaling pathway. After PGE2 binding, EP2 and EP4 Gs-coupled receptors activate adenylate cyclase-triggered cAMP/ PKA/CREB pathway. Additionally, they can both activate glycogen synthase kinase-3 (GSK3) β -catenin pathway.^[52] Furthermore, EP4 seems to be capable of signaling via the extracellular signal-regulated protein kinase (ERK1/2) pathway. Otherwise, EP1 and EP3 receptors activate Ca $^{2+}$ release and inhibit cAMP-functions, respectively

PLASMA MEDIATORS IN PATIENTS WITH SEVERE COVID-19 CAUSE LUNG ENDOTHELIAL BARRIER FAILURE

Michalick L, Weidenfeld S, Grimmer B, Fatykhova D, Solymosi PD, Behrens F, Dohmen M, Brack MC, Schulz S, Thomasch E, Simmons S, Müller-Redetzky H, Suttorp N, Kurth F, Neudecker J, Toennies M, Bauer TT, Eggeling S, Corman VM, Hocke AC, Witzenrath M, Hippensiel S, Kuebler WM.. Eur Respir J. 2020 Nov 5:2002384. doi: 10.1183/13993003.02384-2020. Online ahead of print.

Level of Evidence: 3 - Mechanism-based reasoning

BLUF

Investigators mainly from the institute of Physiology at Charité Universitätsmedizin Berlin compared the respective plasma disruption to the lung epithelium between the plasma of 19 patients with severe COVID-19 (requiring intubation), 14 patients with moderate COVID-19 (requiring hospitalization but not intubation), and 15 healthy controls (methods elucidated below). They found that addition of plasma from COVID-19 patients to healthy endothelial monolayers correlated with "significant endothelial gap formation and loss of junctional VE-cadherin". Additionally, when compared to the healthy control plasma, the plasma from COVID-19 patients not only resulted in increased severity of endothelial permeability but also rapid (within 1-2 hours) and long lasting (over 6 hours) effects. Based on these results, the authors theorize that endothelial-barrier-stabilizing adjunctive therapies administered to patients exhibiting signs of moderate to severe COVID-19 may delay progression to acute respiratory distress syndrome.

SUMMARY

The investigators compared "plasma mediator" disruption to lung epithelium among the COVID-19 patients of this study by:

- 1) electrical cell-substrate impedance sensing (Figure 1A)
- 2) measurement of trans-endothelial electrical resistance (Figure 1B)
- 3) immunofluorescence for vascular endothelial cadherin (VEcadherin) and F-actin (Figure 1C, 1D).

FIGURES

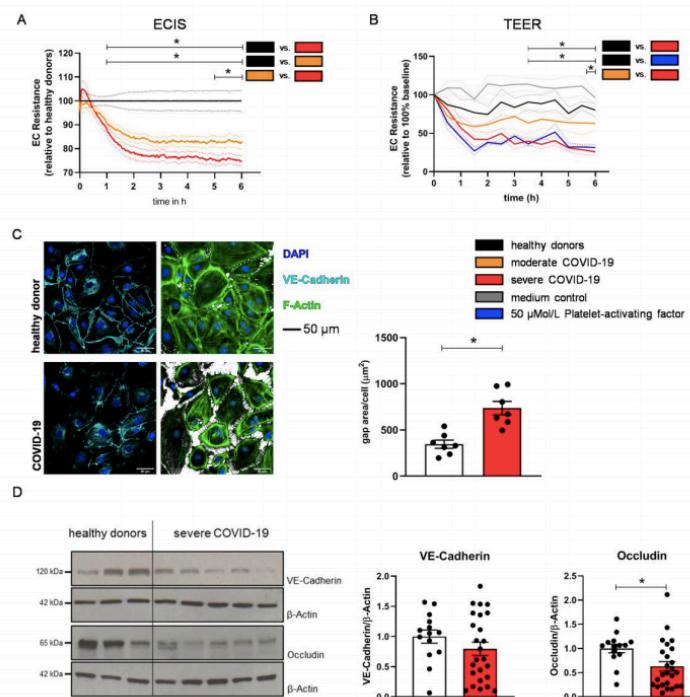


Figure 1. A. HPMEC monolayers when exposed to various plasmas analyzed using ECIS®. B. HPMEC monolayers when exposed to various plasmas analyzed using TEER. C. HPMEC monolayer disruption by immunofluorescence microscopy. D. Exposure of human lung tissue to severe COVID-19 plasma caused loss of the junctional molecule occludin while changes in VE-cadherin protein levels did not reach statistical significance.

IN ANIMAL MODELS

VIRULENCE AND PATHOGENESIS OF SARS-COV-2 INFECTION IN RHESUS MACAQUES: A NONHUMAN PRIMATE MODEL OF COVID-19 PROGRESSION

Zheng H, Li H, Guo L, Liang Y, Li J, Wang X, Hu Y, Wang L, Liao Y, Yang F, Li Y, Fan S, Li D, Cui P, Wang Q, Shi H, Chen Y, Yang Z, Yang J, Shen D, Cun W, Zhou X, Dong X, Wang Y, Chen Y, Dai Q, Jin W, He Z, Li Q, Liu L.. PLoS Pathog. 2020 Nov 12;16(11):e1008949. doi: 10.1371/journal.ppat.1008949. eCollection 2020 Nov.

Level of Evidence: Other - Modeling

BLUF

Infectious Disease researchers developed a rhesus macaque model to further understand dissemination and transmission of COVID-19 (Figure 1). They found that viral shedding can be detected in the nose and stool for up to 27 days after natural infection (Figure 2), and that the virus is largely found in the lower respiratory tract and lymph nodes (Figure 3), suggesting that future treatments and vaccine development should be made with the consideration of T cell and cytokine response in the lung tissue.

ABSTRACT

The COVID-19 has emerged as an epidemic, causing severe pneumonia with a high infection rate globally. To better understand the pathogenesis caused by SARS-CoV-2, we developed a rhesus macaque model to mimic natural infection via the nasal route, resulting in the SARS-CoV-2 virus shedding in the nose and stool up to 27 days. Importantly, we observed the pathological progression of marked interstitial pneumonia in the infected animals on 5-7 dpi, with virus dissemination widely occurring in the lower respiratory tract and lymph nodes, and viral RNA was consistently detected from 5 to 21 dpi. During the infection period, the kinetics response of T cells was revealed to contribute to COVID-19 progression. Our findings implied that the antiviral response of T cells was suppressed after 3 days post infection, which might be related to increases in the Treg cell population in PBMCs. Moreover, two waves of the enhanced production of cytokines (TGF-alpha, IL-4, IL-6, GM-CSF, IL-10, IL-15, IL-1beta), chemokines (MCP-1/CCL2, IL-8/CXCL8, and MIP-1beta/CCL4) were detected in lung tissue. Our data collected from this model suggested that T cell response and cytokine/chemokine changes in lung should be considered as evaluation parameters for COVID-19 treatment and vaccine development, besides of observation of virus shedding and pathological analysis.

FIGURES

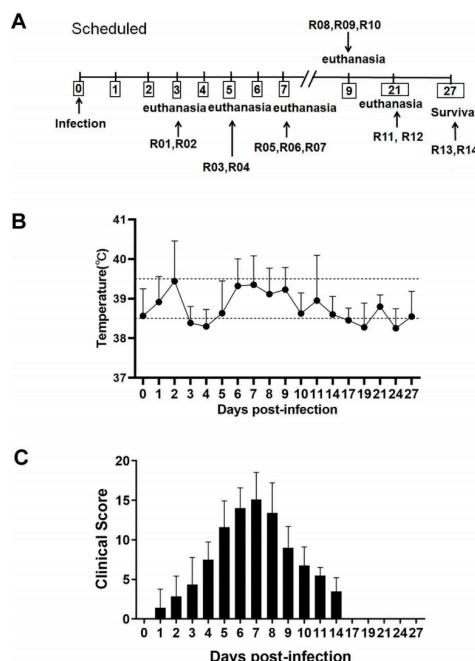


Fig 1. Experimental schedule and clinical signs in rhesus macaques inoculated with SARS-CoV-2. (A) Schedule of viral inoculation and necropsies. (B) Monitoring of the body temperature of infected animals for 27 days. (C) Animals were scored for 27 days, and their mean clinical score \pm SD was calculated.

A POSSIBLE CASE OF VERTICAL TRANSMISSION OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) IN A NEWBORN WITH POSITIVE PLACENTAL IN SITU HYBRIDIZATION OF SARS-COV-2 RNA

Alamar I, Abu-Arja MH, Heyman T, Roberts DJ, Desai N, Narula P, Dugulska B.. J Pediatric Infect Dis Soc. 2020 Nov 10;9(5):636-639. doi: 10.1093/jpids/piaa109.

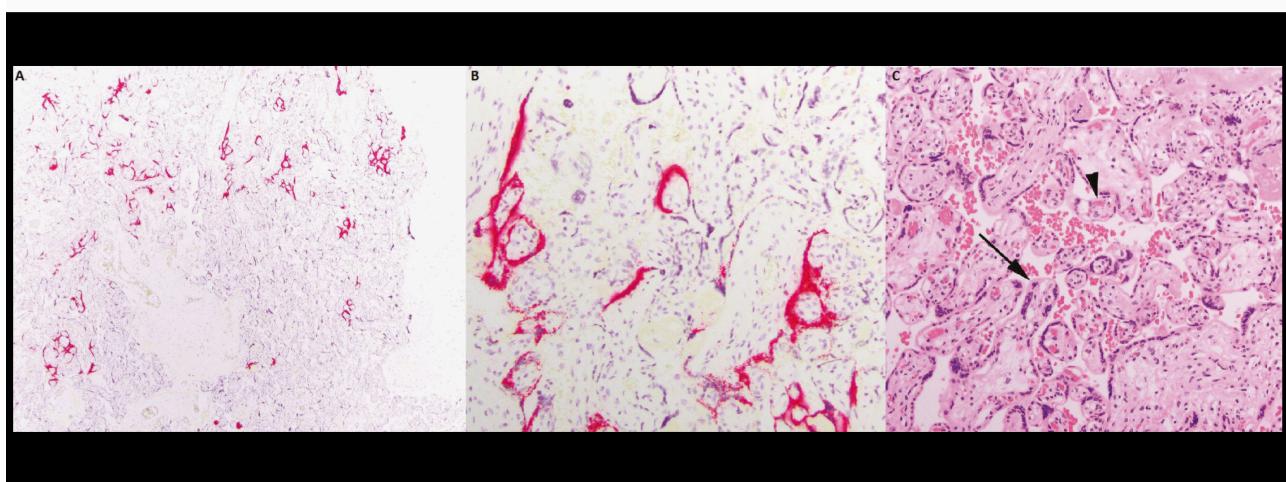
Level of Evidence: Other - Case Report

BLUF

A case report by pediatricians from New York Presbyterian Brooklyn Methodist Hospital described a 32 year-old female who presented at 35+6 gestational age with vaginal bleeding, contractions, fever, chills, fatigue, dyspepsia and anosmia, then subsequently gave birth via cesarian section. She tested positive for SARS-CoV-2 via qRT-PCR on postpartum day 1 and the infant also tested positive (via qRT-PCR) at 24 hours, 48 hours and 7 days of life. Additionally, placental in situ hybridization showed presence of SARS-CoV-2 RNA (Figure 2). Based on this, the authors suggest vertical transmission of SARS-CoV-2 may be possible, though they do not exclude the possibility of horizontal transmission during breastfeeding following birth.

FIGURES

Figure 2.



Noninfarcted chorionic villi from the placenta to illustrate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in syncytiotrophoblast. A, In situ hybridization for SARS-CoV-2 RNA at 4 \times original showing clusters of positive red staining of villi. B, In situ hybridization for SARS-CoV-2 RNA at 20 \times original demonstrating a strong signal in syncytiotrophoblast in some but not all villi. C, Hematoxylin and eosin stained section of chorionic villi to identify syncytiotrophoblast (arrow) and vasculosyncytial membranes (arrowhead) 20 \times original.

DIAGNOSTIC RADIOLOGY

VARIATIONS IN CT UTILIZATION, PROTOCOLS, AND RADIATION DOSES IN COVID-19 PNEUMONIA: RESULTS FROM 28 COUNTRIES IN THE IAEA STUDY

Homayounieh F, Holmberg O, Al Umairi R, Aly S, Basevičius A, Costa PR, Darweesh A, Gershman V, Ilves P, Kostova-Lefterova D, Renha SK, Mohseni I, Rampado O, Rotaru N, Shirazu I, Sinitsyn V, Turk T, Van Ngoc Ty C, Kalra MK, Vassileva J.. Radiology. 2020 Nov 10:203453. doi: 10.1148/radiol.2020203453. Online ahead of print.

Level of Evidence: 4 - Local non-random sample

BLUF

Radiologists conduct an international, multicenter, retrospective study of 782 patients from 54 healthcare sites in 28 countries between May 2020 to July 2020 to assess variations in CT protocol, utilization, and radiation doses. They found that 75% of the healthcare sites used CT scans to assess pneumonia severity in COVID-19 positive patients, while less than half of these countries used CT to make a diagnosis of pneumonia. The authors suggest a need for specific international guidelines on scanning protocols due to the cumulative radiation exposure and variability of how COVID-19 pneumonia is diagnosed and monitored.

ABSTRACT

Background There is lack of guidance on specific CT protocols for imaging patients with coronavirus disease 2019 (COVID-19) pneumonia. Purpose To assess international variations in CT utilization, protocols, and radiation doses in patients with COVID-19 pneumonia. Materials and Methods In this retrospective data collection study, the International Atomic Energy Agency (IAEA) coordinated a survey between May and July 2020 regarding CT utilization, protocols, and radiation doses from 62 healthcare sites in 34 countries across five continents for CT exams performed in COVID-19 pneumonia. The questionnaire obtained information on local prevalence, method of diagnosis, most frequent imaging, indications for CT, and specific policies on use of CT in COVID-19 pneumonia. Collected data included general information (patient age, weight, clinical indication), CT equipment (CT make and model, year of installation, number of detector rows), scan protocols (body region, scan phases, tube current and potential), and radiation dose descriptors (CT dose index (CTDIvol) and dose length product (DLP)). Descriptive statistics and generalized estimating equations were performed. Results Data from 782 patients (median age (interquartile range) of 59(15) years) from 54 healthcare sites in 28 countries were evaluated. Less than one-half of the healthcare sites used CT for initial diagnosis of COVID-19 pneumonia and three-fourth used CT for assessing disease severity. CTDIvol varied based on CT vendors (7-11mGy, p<0.001), number of detector-rows (8-9mGy, p<0.001), year of CT installation (7-10mGy, p=0.006), and reconstruction techniques (7-10mGy, p=0.03). Multiphase chest CT exams performed in 20% of sites (11 of 54) were associated with higher DLP compared with single-phase chest CT exams performed in 80% (43 of 54 sites) (p=0.008). Conclusion CT use, scan protocols, and radiation doses in patients with COVID-19 pneumonia showed wide variation across healthcare sites within the same and different countries. Many patients were scanned multiple times and/or with multiphase CT scan protocols. See also the editorial by Lee.

DECREASED SERUM LEVEL OF SPHINGOSINE-1-PHOSPHATE: A NOVEL PREDICTOR OF CLINICAL SEVERITY IN COVID-19

Marfia G, Navone S, Guarnaccia L, Campanella R, Mondoni M, Locatelli M, Barassi A, Fontana L, Palumbo F, Garzia E, Ciniglio Appiani G, Chiumello D, Miozzo M, Centanni S, Riboni L.. EMBO Mol Med. 2020 Nov 14:e13424. doi: 10.15252/emmm.202013424. Online ahead of print.

Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

Neurosurgeons at the Laboratory of Experimental Neurosurgery and Cell Therapy in Milan, Italy compared blood samples from 47 healthy patients to samples from 111 SARS-CoV-2 positive patients and found sphingosine-1-phosphate (S1P) and apolipoprotein M (apoM; a carrier of S1P) levels were significantly decreased in COVID-19 patients compared to healthy patients ($p<0.0001$, Figure 1). COVID-19 patients requiring intensive care unit (ICU) admission had significantly lower levels of apoM, S1P, albumin, and HDL compared to those not requiring ICU care ($p<0.0001$, Figure 3). Authors suggest the SARS-CoV-2 induced cytokine storm and acute phase response lowers levels of these specific biomarkers, and low levels of S1P ($<0.6\mu\text{M}$) and apoM may be clinical predictors of severe disease and decreased survival (Figure 6).

ABSTRACT

The severity of coronavirus disease 2019 (COVID-19) is a crucial problem in patient treatment and outcome. The aim of this study is to evaluate circulating level of sphingosine-1-phosphate (S1P) along with severity markers, in COVID-19 patients. One hundred-eleven COVID-19 patients, and forty-seven healthy subject were included. The severity of COVID-19 was found significantly associated to anemia, lymphocytopenia, and significant increase of neutrophil-to-lymphocyte ratio, ferritin, fibrinogen, aminotransferases, lactate dehydrogenase (LDH), C-reactive protein (CRP), and D-dimer. Serum S1P level was inversely associated with COVID-19 severity, being significantly correlated with CRP, LDH, ferritin, and D-dimer. The decrease in S1P was strongly associated with the number of erythrocytes, the major source of plasma S1P, and both apolipoprotein M and albumin, the major transporters of blood S1P. Not last, S1P was found to be a relevant predictor of admission to an intensive care unit, and patient's outcome. Circulating S1P emerged as negative biomarker of severity/mortality of COVID-19 patients. Restoring abnormal S1P levels to a normal range, may have the potential to be a therapeutic target in patients with COVID-19.

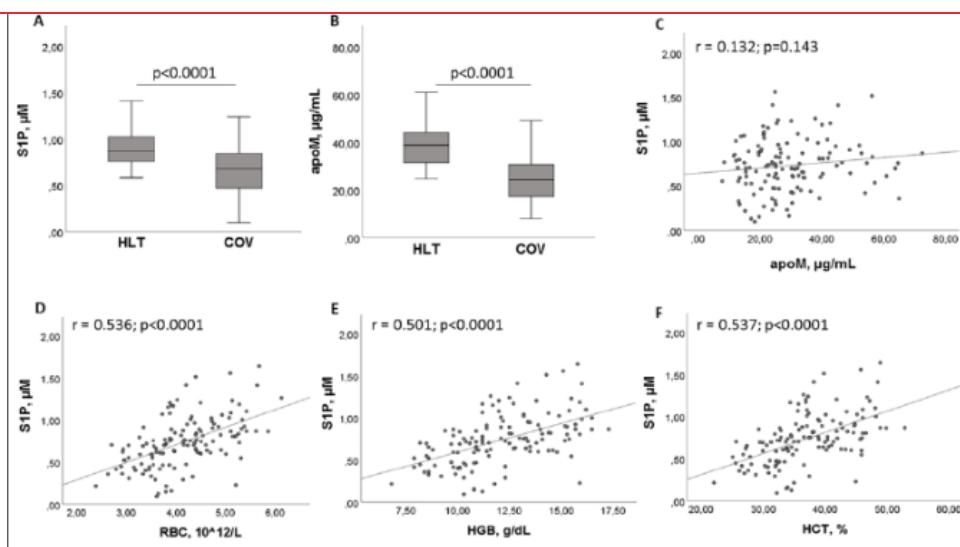
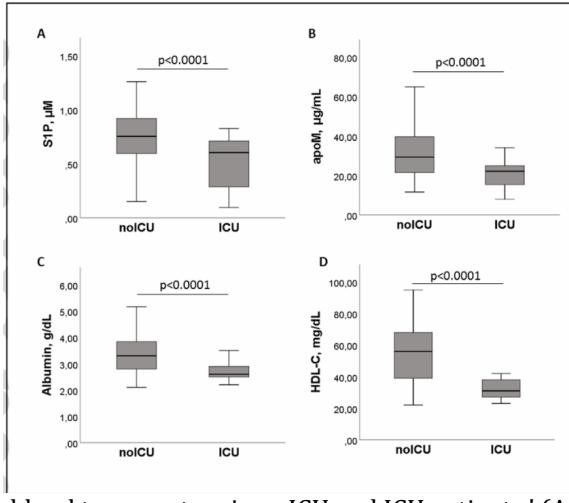
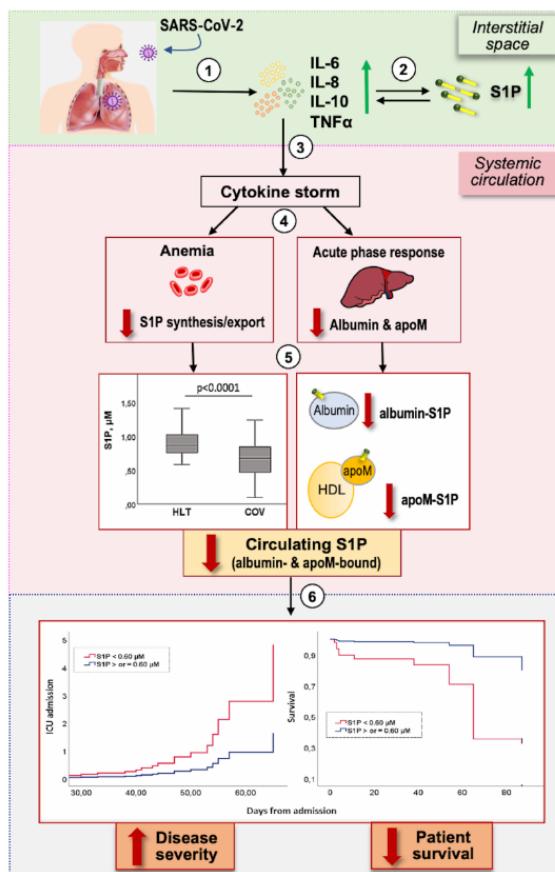
FIGURES

Figure 1: Serum levels of S1P and apoM in HLT and COV patients.¹ A, B: serum levels of S1P (A) and apoM (B) in HLT (n=47) and COV (n=111) patients. The box-plots represent the interquartile range with median value (central line); the whiskers represent the measured range of HLT and COV. Each measurement was run in triplicate, and performed at least twice. Two-tailed Student's t-test was used for statistical analysis. ***p < 0.0001. C-F: Pearson correlation between S1P and apoM (C), RBC number (D), HGB concentration (E), HCT value (F). Scatter plots, together with the fitted regression line, are shown. Pearson correlation was performed for statistical analysis. Exact p values or ***p < 0.0001 are reported



'Figure 3: Serum levels of S1P and its blood transporters in noICU and ICU patients.' (A-D) The serum concentrations of S1P (A), apoM (B), albumin (C) and HDL-C (D) in noICU (n=89) and ICU (n= 22) patients are shown. The box-plots represent the interquartile range with median (central line); the whiskers represent the measured range of noICU and ICU patients. Each S1P and apoM measurement was run in triplicate, and performed at least twice in independent assays. Two-tailed Student's t-test was used for statistical analysis. ***p < 0.0001



'Figure 6: Overview of the proposed mechanisms underlying S1P involvement in COVID-19 pathophysiology and severity.' After SARS-CoV-2 infection, a local inflammation occurs, with increased pro-inflammatory cytokines (1). This promotes an interstitial increase of S1P, which in turn potentiates cytokine secretion by different cells (2). The exuberant local cytokine levels result in a systemic cytokine storm (3). This gives on to different alterations (4), including anemia (with impaired S1P synthesis/export) and acute phase response in the liver (with decrease in the negative acute phase proteins albumin and apoM, which act as S1P transporters). These alterations lead to a progressive drop of circulating S1P, with decrease in both apoM/S1P and albumin/S1P (5). The reduction of S1P in the systemic circulation correlate with COVID-19 severity (6) and patient outcome

R&D: DIAGNOSIS & TREATMENTS

DEVELOPMENTS IN DIAGNOSTICS

EFFECTIVE SCREENING OF SARS-COV-2 NEUTRALIZING ANTIBODIES IN PATIENT SERUM USING LENTIVIRUS PARTICLES PSEUDOTYPED WITH SARS-COV-2 SPIKE GLYCOPROTEIN

Tandon R, Mitra D, Sharma P, McCandless MG, Stray SJ, Bates JT, Marshall GD.. Sci Rep. 2020 Nov 5;10(1):19076. doi: 10.1038/s41598-020-76135-w.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Investigators at the University of Mississippi Medical Center pseudotyped SARS-CoV-2 spike glycoprotein (SPG) on vectors and tested the transduction efficiency in mammalian cell lines expressing hACE2 receptor and found that the third generation lentiviral (pLV) vector pseudotyped glycoproteins most efficiently (Figure 2, 3). Further, the pLV particles were able to be neutralized from newly recovered COVID-19 patients (Figure 4), suggesting that pLV pseudotyped virus could potentially be used as a screening test for neutralizing anti-SARS-CoV-2 antibodies in patient's serum.

ABSTRACT

Pseudotyped particles have significant importance and use in virology as tools for studying the biology of highly pathogenic viruses in a lower biosafety environment. The biological, chemical, and serological studies of the recently emerged SARS-CoV-2 will be greatly aided by the development and optimization of a suitable pseudotyping system. Here, we pseudotyped the SARS-CoV-2 Spike glycoprotein (SPG) on a traditional retroviral (MMLV) as well as a third generation lentiviral (pLV) vector and tested the transduction efficiency in several mammalian cell lines expressing SARS-CoV-2 receptor hACE2. While MMLV pseudotyped the vesicular stomatitis virus G glycoprotein (VSV-G) efficiently, it could not pseudotype the full-length SPG. In contrast, pLV pseudotyped both glycoproteins efficiently; however, much higher titers of pLV-G particles were produced. Among all the tested mammalian cells, 293Ts expressing hACE2 were most efficiently transduced using the pLV-S system. The pLV-S particles were efficiently neutralized by diluted serum ($>:640$) from recently recovered COVID-19 patients who showed high SARS-CoV-2 specific IgM and IgG levels. In summary, pLV-S pseudotyped virus provides a valid screening tool for the presence of anti SARS-CoV-2 specific neutralizing antibodies in convalescent patient serum.

FIGURES

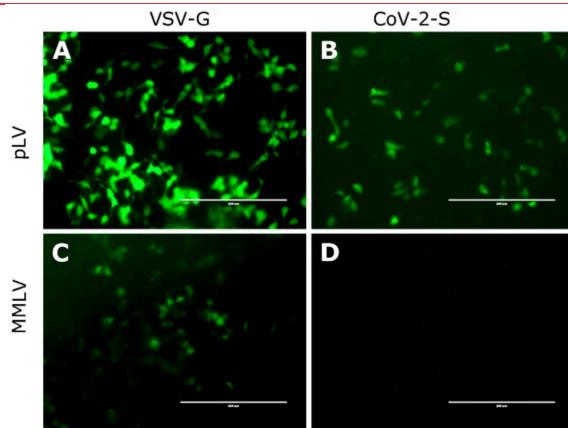


Figure 2. Transduction of HEK293T cells with lentiviral vector (pLV) pseudotyped with VSV-G (A) or CoV-2-S protein (B), and retroviral vector (MMLV) pseudotyped with VSV-G (C) or CoV-2-S (D). Both lentiviral and retroviral backbones incorporate enhanced green fluorescent protein (eGFP) that is expressed upon integration into target cells. The fluorescence was recorded at 48 h post transduction. Magnification 20X. Scale bar: 200 μ m.

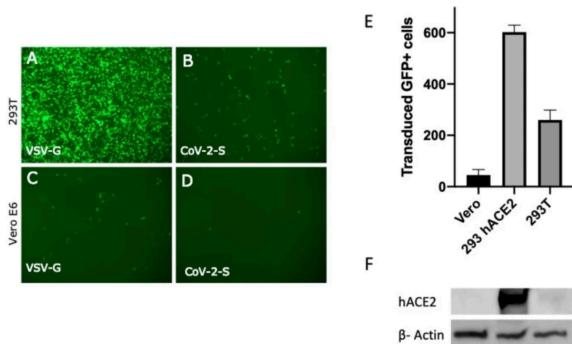


Figure 3. (A) Transduction of pLV pseudotyped with VSV-G (A,C) or CoV-2 Spike glycoprotein (B,D) in HEK293T (A,B) or Vero E6 (C,D) cells. The lentiviral backbone incorporates enhanced green fluorescent protein (eGFP) that is expressed upon integration into target cells. The fluorescence was recorded at 48 h post transduction. Magnification 4X. (E) Transduction efficiency of pLV pseudotyped with CoV-2 Spike glycoprotein in Vero E6, hACE2-HEK293T and 293T cells. The fluorescence was recorded at 48 h post transduction. The experiments were done in triplicates and standard error of mean was plotted as error bars. (F) Whole cell lysates from Vero E6, hACE2-293T and 293T cells were run on SDS-PAGE and probed with anti ACE2 antibody. Beta-actin was used as a loading control.

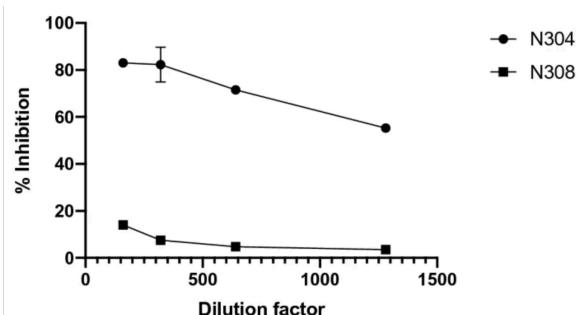


Figure 4. Neutralization of SARS-CoV-2 S glycoprotein pseudotyped pLV (pLV-S) using diluted patient serum. The serum was obtained from a convalescent patient (N304) or a mildly symptomatic individual (N308) at 30 days after onset of symptoms.

Patient N304 tested positive for SARS-CoV-2 in a RT-PCR diagnostic test and N308 tested negative. Relative inhibition of pseudovirions at serial dilutions of patient serum compared to mock-serum control is shown. The fluorescence was recorded at 48 h post transduction. The titers were performed in triplicates and standard error of mean was plotted as error bars. Some error bars are within the symbols.

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CONTRIBUTORS

Danika Scott
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Eva Shelton
Jonathan Baker
Julia Ghering
Krithika Kumarasan
Tyler Gallagher
Veronica Graham

EDITORS

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