The Daily COVID-19 Literature Surveillance Summary

January 8, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

- The authors present a case report of a 29-year-old SARS-CoV-2 positive woman with minimal, mild symptoms who underwent an uncomplicated and successful vaginal delivery to a healthy baby boy at the University of Missouri Women and Children's Hospital in April 2020. After birth, the patient's placenta was subsequently analyzed using hematoxylin-and-eosin (H&E) staining, which revealed evidence of general placental vascular malperfusion possibly due to hypertrophic arteriolopathy along with immunohistochemistry (IHC) staining which revealed the presence of SARS-CoV-2 in chorionic villi endothelial cells. Current literature on COVID-19 in pregnant patients is somewhat conflicting regarding morbidity, miscarriage rates, susceptibility, and the possibility of vertical transmission; the authors posit that this case is the first report of placental SARS-CoV-2 in the setting of mild COVID-19 disease, where the patient had only symptoms of mild myalgias.

R&D: Diagnosis & Treatments

- A prospective study conducted at a Malaysian COVID-19 quarantine center of 217 asymptomatic adult males, where 160 tested positive, found a far greater SARS-CoV-2 detection rate using morning salivary samples (93.1%) when compared to nasopharyngeal swabs (52.5%) ($p<0.001$, 45.6% concordance, 47.5% discordance). These results suggest that the higher accuracy of salivary analysis could play a role in improved diagnostics, decreasing direct healthcare worker-patient interaction and risk of transmission, improving transport preservation, reducing test wait time, and allowing for self-collection.

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SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

COVID-19 COAGULOPATHY: AN IN-DEPTH ANALYSIS OF THE COAGULATION SYSTEM

Martín-Rojas RM, Pérez-Rus G, Delgado-Pinos VE, Domingo-González A, Regalado-Artamendi I, Alba-Urdiales N, Demelo-Rodríguez P, Monsalvo S, Rodríguez-Macías G, Ballesteros M, Osorio-Prendes S, Díez-Martín JL, Pascual C.. Eur J Haematol. 2020 Aug 4. doi: 10.1111/ejh.13501. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cohort study of patients with COVID-19 pneumonia (n=206; Table 1) conducted at Gregorio Marañon Hospital in Madrid, Spain between 3 April and 3 May 2020 found non-survivors had significantly higher D-dimer than survivors (median 1472.5 versus 385 ng/ml; p=0.004), and higher D-dimer was correlated with thrombosis via bivariate analysis (incidence of 11.1%; hazard ratio [HR] 1.99; 95% CI 1.3-3.1; p=0.002). Authors suggest COVID-19 infection is associated with coagulopathy and poor prognosis despite lack of significant coagulation factor consumption (Figure 1).

ABSTRACT

BACKGROUND: Abnormal coagulation parameters have been reported in COVID-19 patients. Although the underlying mechanism of COVID-19 coagulopathy remains unknown, it has been suggested to be a form of disseminated intravascular coagulation (DIC). OBJECTIVES: The aim of our study was to analyze the coagulation parameters of patients with COVID-19, determine if coagulation factors consumption occurs and identify potential prognostic biomarkers of the disease. PATIENTS/METHODS: Blood samples from hospitalized patients with COVID-19 pneumonia were collected. We performed basic coagulation tests and quantification of coagulation factors and physiological inhibitor proteins. Laboratory data were compared with clinical data and outcomes. RESULTS: The study involved 206 patients (63.6% male). D-dimer was particularly elevated (median 450 ng/ml; IQR 222.5-957.3). Free protein S levels were below the normal range (median 56.6%; IQR: 43.6-68.9) and factor VIII showed an increasing trend (median 173.4%; IQR: 144.1-214.9). However, all coagulation factors were within normal limits. We found no correlation between abnormal coagulation parameters and thrombosis, except for higher D-dimer (HR 1.99; 95% CI 1.3-3.1; p=0.002). CONCLUSIONS: COVID-19 is associated with coagulopathy that correlates with poor prognosis. However, we did not demonstrate a consumption of coagulation factors, as seen in DIC.

Parameters	Normal values	Results (n=206)	Survivors (n= 188)	Non-survivors (n= 18)	p value
Demographics and clinical parameters					
Age (years)	-	63.6 ± 13.4	62.4 ± 12.9	76.0 ± 12.3	< 0.001*
Sex (male/female)	-	131/75	120/68	11/7	0.81
Comorbidities (yes/no)	-	161/45	143/45	18/0	0.015*
DIC (yes/no)	-	11/195	7/181	4/14	0.001*
Routine laboratory tests					
Hemoglobin (g/dL)	12-16	13 (11.5-14.2)	13.1 (12.1-14.3)	11.5 (10.2-13.7)	0.021*
Platelets (x10³/μL)	140-400	279.69 (186.5-365)	262 (190-370)	203 (104-365.7)	0.013*
Leucocytes (x10³/μL)	4-10	7.2 (5.4-9.9)	6.9 (5.3-9.5)	9.9 (7.8-13.6)	0.001*
Neutrophils (x10³/μL)	1.8-7.5	5.5 (3.3-8.1)	5.3 (3.2-7.9)	8.6 (6.4-12.8)	< 0.001*
Lymphocytes (x10³/μL)	1.3-3.5	1 (0.4-0.8)	1 (0.7-1.4)	0.6 (0.4-0.8)	0.007*
C-reactive protein (mg/dL)	0-0.5	2.9 (0.8-8.6)	2.8 (1.1-8.7)	8.4 (4.02-26.02)	0.043*
Procalcitonin (μg/L)	0-0.5	0.07 (0.03-0.14)	0.06 (0.03-0.13)	0.11 (0.05-0.38)	0.011*
Ferritin (μg/L)	5-204	710 (404-1389)	731 (405-1425)	763 (598.2-1354.5)	0.331
Interleukin 6 (pg/mL)	0-4.3	34.4 (7.6-90.4)	32.5 (6.6-60.6)	139.2 (80.3-195.5)	< 0.001*
Coagulation parameters tests					
PT (sec)	10.5-13.5	12.8 (12.1-13.6)	12.7 (12-13.4)	14 (12.7-15.6)	< 0.001*
INR	0.8-1.2	1.15 (1.09-1.23)	1.13 (1-1.2)	1.25 (1.2-1.4)	< 0.001*
APTT(sec)	27-38	29.7 (26.8-32.6)	29.5 (27.3-32.5)	29.9 (26.4-30.8)	0.181
Fibrinogen (mg/dL)	200-400	571.2 ± 187.7	575 ± 183.7	526.9 ± 226.5	0.389
D-dimer (ng/ml)	0-250	450 (222.5-957.3)	385 (214-916.8)	1472.5 (390.8-3238.5)	0.004*
Free Protein S (%)	70-140	56.6 (43.6-68.9)	56.1 (43.7-67.8)	50.7 (38.9-59.9)	0.477
Protein C (%)	70-140	123 (105-155)	128 (107-159.3)	107 (76.5-119.8)	0.001*
Antithrombin (%)	70-140	105 (92-117.3)	107 (93-118)	86 (69-101.3)	0.008*
Factor II (%)	60-140	99.7 (87.7-110.9)	102.3 (89.4-110.9)	82.7 (75-94)	< 0.001*
Factor V (%)	60-140	111.6 (94.4-135.8)	111.6 (92.2-135.8)	115.9 (103.8-138.6)	0.460
Factor VII (%)	60-140	81.7 (68.3-100.7)	81.9 (69.5-102.4)	66.2 (51.7-76.2)	0.02*
Factor VIII (%)	50-200	173.4 (144.1-214.9)	173.4 (140.2-215.4)	167.7 (143.2-181.8)	0.105
Factor IX (%)	60-140	142.8 (122.6-170.6)	142.8 (124.2-169.9)	147.1 (123.5-178.1)	0.522
Factor X (%)	60-140	109.1 (92.9-126.8)	111.1 (98.1-128)	86.3 (79.4-112.9)	0.007*
Factor XI (%)	60-140	125.8 (104.2-147.6)	128.7 (107.1-148.6)	147.1 (123.5-178.1)	0.522
Factor XII (%)	60-140	115.1 (87.1-149.1)	119 (92.5-153.9)	110 (91.8-137.3)	0.21

Table 1. Demographics, clinical, laboratory and coagulation parameters of COVID-19 patients.

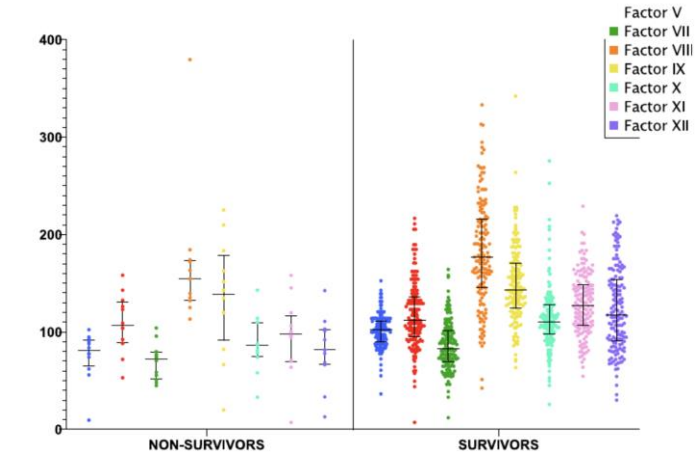

Figure 1. Comparison of coagulation factors and physiological inhibitory proteins between survivors and non-survivors.

PREGNANT PERSONS

PLACENTAL SARS-COV-2 IN A PREGNANT WOMAN WITH MILD COVID-19 DISEASE

Hsu AL, Guan M, Johannesen E, Stephens AJ, Khaleel N, Kagan N, Tuhlei BC, Wan XF.. J Med Virol. 2020 Aug 4. doi: 10.1002/jmv.26386. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

The authors present a case report of a 29-year-old SARS-CoV-2 positive woman with minimal, mild symptoms who underwent an uncomplicated and successful vaginal delivery to a healthy baby boy at the University of Missouri Women and Children's Hospital in April 2020. After birth, the patient's placenta was subsequently analyzed using:
1. Hematoxylin-and-eosin (H&E) staining, which revealed evidence of general placental vascular malperfusion possibly due to hypertrophic arteriolopathy; notably, there were no signs of fetal malperfusion or micro-thrombi (Figure 1) and
2. Immunohistochemistry (IHC) staining for specific antibodies to SARS-CoV-2 which reveled the presence of SARS-CoV-2 in chorionic villi endothelial cells (Figure 2).
Current literature on COVID-19 in pregnant patients is somewhat conflicting regarding morbidity, miscarriage rates, susceptibility, and the possibility of vertical transmission; the authors posit that this case is the first report of placental SARS-CoV-2 in the setting of mild COVID-19 disease, where the patient had only symptoms of mild myalgias.

ABSTRACT

BACKGROUND: The full impact of COVID-19 on pregnancy remains uncharacterized. Current literature suggests minimal maternal, fetal, and neonatal morbidity and mortality.1 COVID-19 manifestations appear similar between pregnant and non-pregnant women.2 OBJECTIVES/STUDY DESIGN: We present a case of placental SARS-CoV-2 virus in a woman with mild COVID-19 disease, then review the literature. RT-PCR was performed to detect SARS-CoV-2. Immunohistochemistry staining was performed with specific monoclonal antibodies to detect SARS-CoV-2 antigen or to identify trophoblasts. RESULTS: A 29 year-old multigravida presented at 40-4/7 weeks for labor induction. With myalgias two days prior, she tested positive for SARS-CoV-2. We demonstrate maternal vascular malperfusion, with no fetal vascular malperfusion, as well as SARS-CoV-2 virus in chorionic villi endothelial cells, and also rarely in trophoblasts. CONCLUSIONS: To our knowledge, this is the first report of placental SARS-CoV-2 despite mild COVID-19 disease (no symptoms of COVID-19 aside from myalgias); patient had no fever, cough, or shortness of breath, but only myalgias and sick contacts. Despite her mild COVID-19 disease in pregnancy, we demonstrate placental vasculopathy and presence of SARS-CoV-2 virus across the placenta. Evidence of placental COVID-19 raises concern for placental vasculopathy (potentially leading to fetal growth restriction and other pregnancy complications) and possible vertical transmission - especially for pregnant women who may be exposed to COVID-19 in early pregnancy. This raises important questions of whether future pregnancy guidance should include stricter pandemic precautions, such as screening for a wider array of COVID-19 symptoms, increased antenatal surveillance, and possibly routine COVID-19 testing throughout pregnancy.

FIGURES

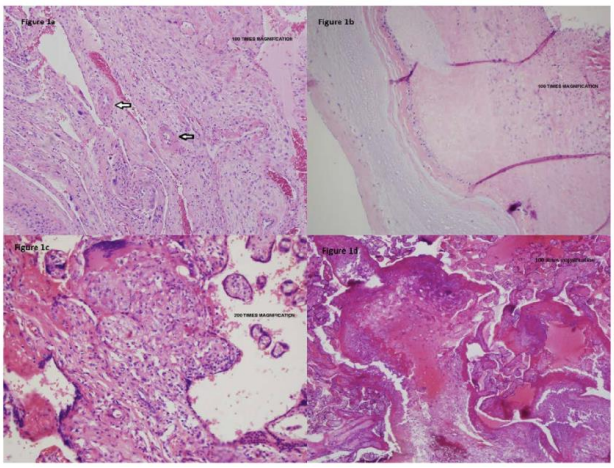

Figure 1. Placental vasculopathy in a pregnant woman with mild COVID-19 disease. Placental membranes showed decidua with scattered arterioles with thickened smooth muscle, consistent with hypertrophic arteriolopathy (vasculopathy) (Figure 1a – umbilical cord and placental membranes) and subchorionic laminar necrosis (Figure 1b – placental parenchyma under the umbilical cord). Placental disc showed focal areas of lympho-histiocytic inflammation consistent with chronic villitis (Figure 1c – central placental parenchyma) and scattered islands of extravillous trophoblasts (Figure 1d – peripheral placental parenchyma).

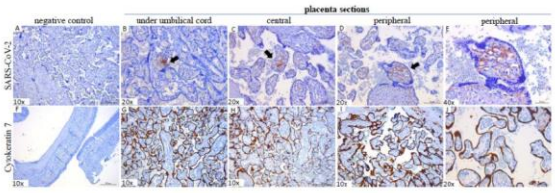

Figure 2. Presence of SARS-CoV-2 virus across the placenta in a patient with mild COVID-19 disease. Immunohistochemistry (IHC) staining of SARS-CoV-2 virus in a COVID-19 negative patient, delivery prior to the COVID-19 outbreak (Figure 2a). IHC of SARS-CoV-2 from three placental sections (2b: under umbilical cord, 2c: central placental disc, 2d-e: peripheral placental disc at 20x and 40x). IHC of cytokeratin-7 (CK-7) marker in control ferret nasal turbinate tissue (Figure 2f). IHC of CK-7 from three placental sections (2g: under umbilical cord, 2h: central placental disc, 2i-j: peripheral placental disc at 10x and 20x). Arrows or brown staining indicate immunoreactive antigens. Bars = 20/50/100 µm shown at the right bottom corner of each panel. IHC was performed with SARS-CoV-2 nucleocapsid-specific rabbit monoclonal antibody (Sino Biological, Wayne, PA) and goat anti-rabbit IgG (Vector lab, Burlingame, CA). To identify trophoblasts, IHC was performed using rabbit recombinant anti-Cytokeratin 7 (CK7) monoclonal antibody (Abcam, Cambridge, MA) and goat anti-rabbit IgG (Vector lab, Burlingame, CA).

PEDIATRICS

HEMATOLOGICAL PARAMETERS AND PERIPHERAL BLOOD MORPHOLOGIC ABNORMALITIES IN CHILDREN WITH COVID-19

Yarali N, Akcabelen YM, Unal Y, Parlakay AN.. Pediatr Blood Cancer. 2020 Aug 6:e28596. doi: 10.1002/pbc.28596. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

In this letter, the authors compared hematological features in COVID-19 positive (n=30) and negative (n=40) children presenting to the emergency department in City Hospital Ankara, Turkey from April 1 to April 15, 2020 with symptoms of fever, cough, rhinorrhea, and sore throat. COVID-19 positive patients demonstrated neutrophils with lobulation abnormalities, vacuolated monocytes and lowered neutrophil and leukocyte counts (p=0.02) (Figure 1). Authors suggest the lack of thrombocytopenia in children with COVID-19 may be responsible for the improved outcomes observed in children.

FIGURES

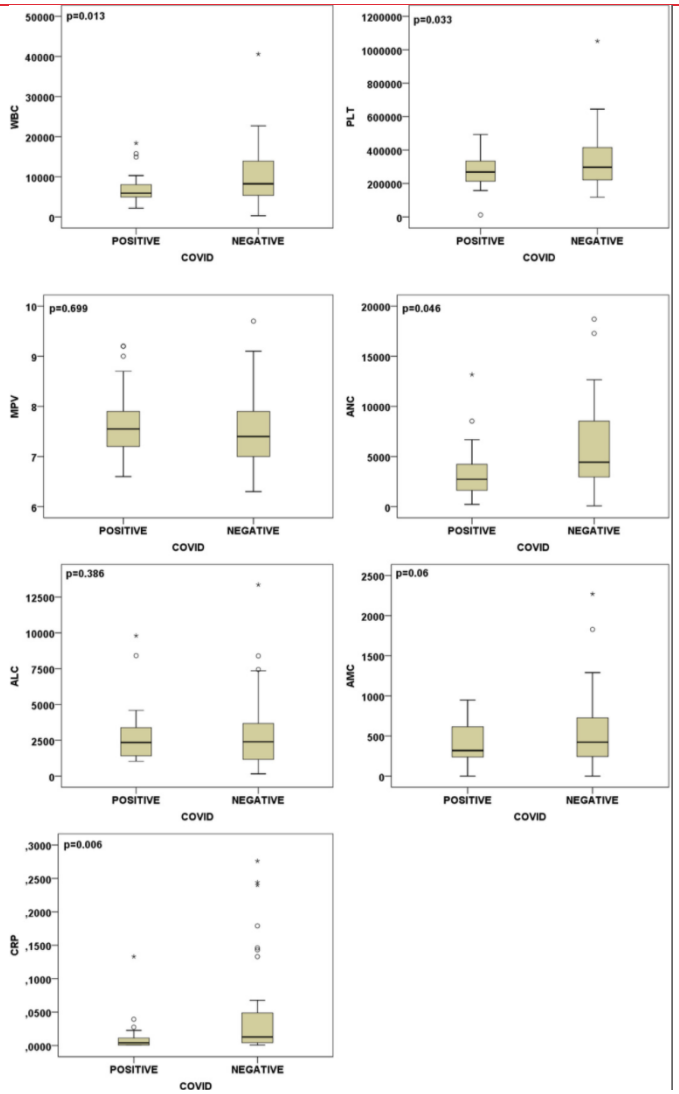

Figure 1: Scatter box plot of blood count parameters and CRP levels of the patients with SARS-CoV-2 test-positive and -negative groups. (ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; ARL, absolute reactive lymphocyte; CRP, C-reactive protein; MPV, mean platelet volume; WBC, white blood cell)

LONGITUDINAL DYNAMICS OF THE NEUTRALIZING ANTIBODY RESPONSE TO SARS-COV-2 INFECTION

Wang K, Long QX, Deng HJ, Hu J, Gao QZ, Zhang GJ, He CL, Huang LY, Hu JL, Chen J, Tang N, Huang AL.. Clin Infect Dis. 2020 Aug 3:ciaa1143. doi: 10.1093/cid/ciaa1143. Online ahead of print.
Level of Evidence: 3 - Mechanism-based reasoning

BLUF

The authors utilized real time RT-qPCR to analyze SARS-CoV-2 specific IgG and virus specific neutralizing antibodies (NAb) levels from 30 COVID-19 patients from April to June 2020 at Yongchuan Hospital in Chongqing, China and found that NAb levels positively correlated at week 3 of infection with IgG antibody levels, with NAb peak levels at day 33 of disease course and a gradual decrease over the next 3 months (Figure 1). NAb levels also positively correlated with levels of plasma proinflammatory cytokines. Although the humoral response is short-lived, the authors conclude that NAb may play a vital role in viral clearance, convalescent serum extraction, drug screening, and vaccine development.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) is a global pandemic with no licensed vaccine or specific antiviral agents for therapy. Little is known about the longitudinal dynamics of SARS-CoV-2-specific neutralizing antibodies (NAbs) in COVID-19 patients. METHODS: Blood samples (n=173) were collected from 30 COVID-19 patients over a 3-month period after symptom onset and analyzed for SARS-CoV-2-specific NAbs, using the lentiviral pseudotype assay, coincident with the levels of IgG and proinflammatory cytokines. RESULTS: SARS-CoV-2-specific NAb titers were low for the first 7-10 d after symptom onset and increased after 2-3 weeks. The median peak time for NAbs was 33 d (IQR 24-59 d) after symptom onset. NAb titers in 93 3% (28/30) of the patients declined gradually over the 3-month study period, with a median decrease of 34 8% (IQR 19 6-42 4%). NAb titers increased over time in parallel with the rise in IgG antibody levels, correlating well at week 3 (r = 0 41, p & 0 05). The NAb titers also demonstrated a significant positive correlation with levels of plasma proinflammatory cytokines, including SCF, TRAIL, and M-CSF. CONCLUSIONS: These data provide useful information regarding dynamic changes in NAbs in COVID-19 patients during the acute and convalescent phases.

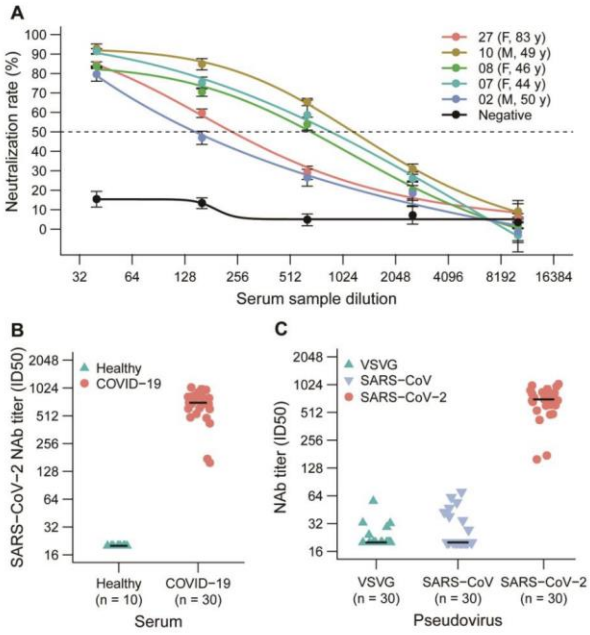

Figure 1: Analysis of the plasma response to SARS-CoV-2 infection. (A) Sera from five convalescent COVID-19 patients neutralized the SARS-CoV-2 pseudovirus. A serum sample from a healthy individual served as the negative control. The assay was performed in triplicate, and the median percentage of neutralization is shown. (B) SARS-CoV-2 neutralizing antibody (NAb) titers of 20 plasma samples from COVID-19 convalescent patients and ten plasma samples from healthy donors. (C) Neutralizing antibody titers against VSV, SARS-CoV, and SARS-CoV-2 pseudovirus in the sera from 30 convalescent COVID-19 patients.

ATTENUATED INTERFERON AND PROINFLAMMATORY RESPONSE IN SARS-COV-2-INFECTED HUMAN DENDRITIC CELLS IS ASSOCIATED WITH VIRAL ANTAGONISM OF STAT1 PHOSPHORYLATION

Yang D, Chu H, Hou Y, Chai Y, Shuai H, Lee AC, Zhang X, Wang Y, Hu B, Huang X, Yuen TT, Cai JP, Zhou J, Yuan S, Zhang AJ, Chan JF, Yuen KY.. J Infect Dis. 2020 Aug 4;222(5):734-745. doi: 10.1093/infdis/jiaa356.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

An in-vitro study by authors affiliated with the University of Hong Kong and Hainan Medical University investigated the viral protein expression, replication kinetics, and host response in monocyte-derived dendritic cells (moDCs) and monocyte-derived macrophages (MDMs) upon infection by SARS-CoV-2. Based on the findings (illustrated below), the authors suggest that SARS-CoV-2-infected moDCs and MDMs in the lungs of COVID-19 patients may be a source of pro-inflammatory cytokine production, exacerbating the COVID-19 manifestation.

SUMMARY

Several findings of this study are summarized below:
•moDCs and MDMs were permissive to SARS-CoV-2 infection and efficient nucleocapsid (N) protein expression but not SARS-CoV-2 viral replication (Figure 2).
•Any Inteferon (IFN) gene upregulation, including IFN-type-I, type-II, or type-III, was not activated in either infected moDCs or MDMs.
•Pro-inflammatory cytokines and chemokines gene expressions were activated in infected MDMs but not in infected moDCs with the exception of IP10 (Figure 5).
•The attenuated IFN response in infected moDCs was found to be associated with viral antagonism of STAT1 phosphorylation (Figure 6).

ABSTRACT

Clinical manifestations of COVID-19 vary from asymptomatic virus shedding, non-specific pharyngitis, to pneumonia with silent hypoxia and respiratory failure. Dendritic cells and macrophages are sentinel cells for innate and adaptive immunity that affect the pathogenesis of SARS and MERS. However, the interplay between SARS-CoV-2 and these cell types remains unknown. Herein, we investigated the infection and host response of monocyte-derived dendritic cells (moDCs) and macrophages (MDMs) infected by SARS-CoV-2. We demonstrated that moDCs and MDMs were permissive to SARS-CoV-2 infection and protein expression but did not support productive virus replication. Importantly, SARS-CoV-2 launched an attenuated interferon response in both cell types. Additionally, SARS-CoV-2 triggered significant pro-inflammatory cytokine/chemokine expression in MDMs but not in moDCs. Further investigations suggested that this attenuated immune response to SARS-CoV-2 in moDCs was associated with viral antagonism of STAT1 phosphorylation. These findings on pathogenesis may explain the mild and insidious course of COVID-19 till late deterioration.

Figure 2

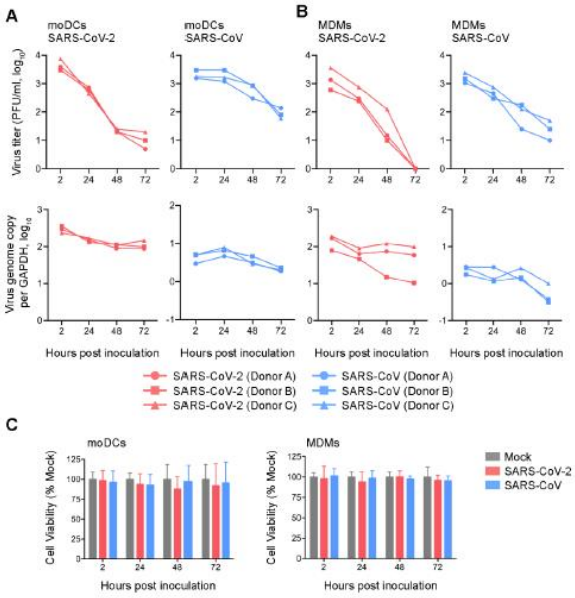

Figure 2. Infection of SARS-CoV-2 in moDCs and MDMs were not productive.

(A) MoDCs and (B) MDMs were infected with SARS-CoV-2 or SARS-CoV at an MOI of 1. The live infectious virus particles in the supernatants and the viral genome copy in the cell lysates were determined by plaque assays and qRT-PCR, respectively. (C) The cell viability of moDCs and MDMs upon SARS-CoV-2 or SARS-CoV infection at an MOI of 1 was quantified at the indicated hours post infection using CellTiterGlo assays. The mean cell viability of SARS-CoV-2- or SARS-CoV-infected cells was compared with that of mock-infected cells at each time point. The results represented mean and standard deviations from three individual donors in three independent experiments. Statistical significance between the groups was determined with one-way ANOVA and was consider significant when $p < 0.05$.

Figure 2. Infection of SARS-CoV-2 in moDCs and MDMs was not productive. MoDCs (A) and MDMs (B) were infected with SARS-CoV-2 or SARS-CoV at an MOI of 1. The live infectious virus particles in the supernatants and the viral genome copy in the cell lysates were determined by plaque assays and qRT-PCR, respectively. C, The cell viability of moDCs and MDMs upon SARS-CoV-2 or SARS-CoV infection at an MOI of 1 was quantified at the indicated hours post infection using CellTiterGlo assays. The mean cell viability of SARS-CoV-2– or SARS-CoV–infected cells was compared with that of mock-infected cells at each time point. The results represent mean and standard deviations from 3 individual donors in 3 independent experiments. Statistical significance between the groups was determined with 1-way ANOVA and was consider significant when P less than .05. Abbreviations: MOI, multiplicity of infection; PFU, plaque-forming unit; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; moDCs, monocyte-derived dendritic cells; MDMs, monocyte-derived macrophages; qRT-PCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 5

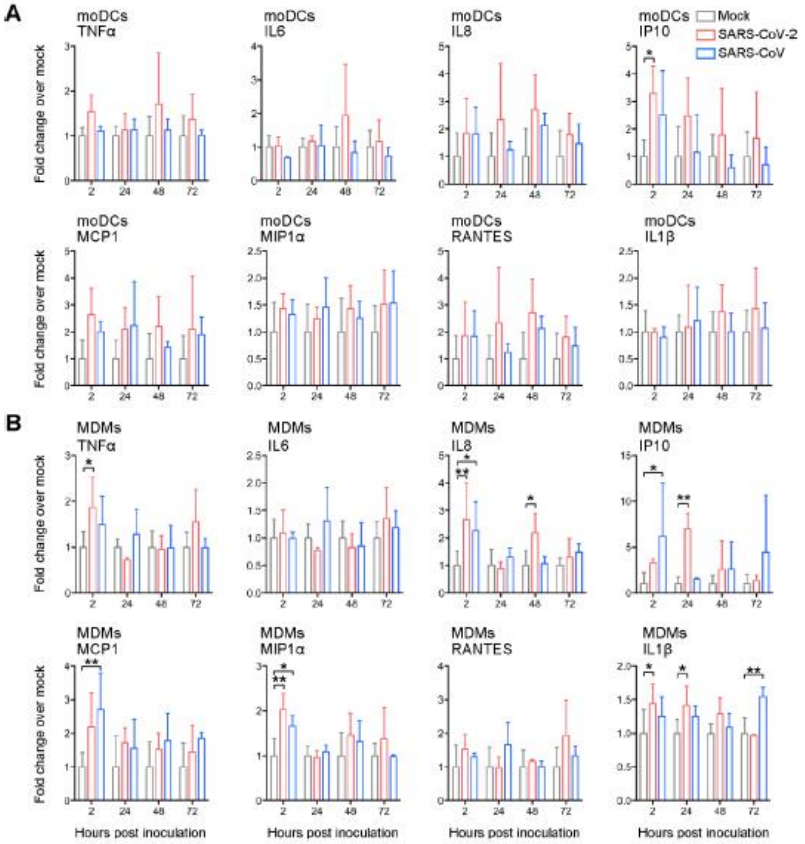

Figure 5. SARS-CoV-2 induced significant pro-inflammatory response in MDMs but not moDCs.

(A) MoDCs and (B) MDMs were inoculated with SARS-CoV-2 or SARS-CoV at an MOI of 1. The cell lysates were harvested for qRT-PCR analysis of representative pro-inflammatory cytokines and chemokines. The results represented mean and standard deviations from three to six individual donors in three independent experiments. Statistical significance between the groups was determined with two-way ANOVA and was consider significant when $p < 0.05$. * Indicated $p < 0.05$ and ** represented $p < 0.01$.

Figure 5. SARS-CoV-2 induced significant proinflammatory response in MDMs but not moDCs. MoDCs (A) and MDMs (B) were inoculated with SARS-CoV-2 or SARS-CoV at an MOI of 1. The cell lysates were harvested for qRT-PCR analysis of representative proinflammatory cytokines and chemokines. The results represent mean and standard deviations from 3 to 6 individual donors in 3 independent experiments. Statistical significance between the groups was determined with 2-way ANOVA and was consider significant when P less than .05. * P less than .05, ** P less than .01. Abbreviations: MOI, multiplicity of infection; TNF-α, tumor necrosis factor-α; IP-10, IFN-γ inducible protein-10; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage-inflammatory protein-1α; RANTES, regulated upon activation normal T-cell expressed and secreted; moDCs, monocyte-derived dendritic cells; MDMs, monocyte derived macrophages; qRT-PCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 6

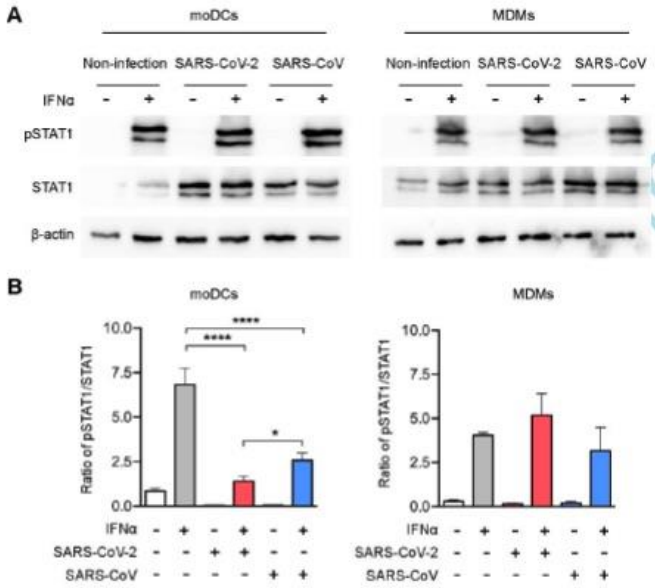

Figure 6. SARS-CoV-2 antagonized STAT1 phosphorylation in moDCs.

MoDCs and MDMs were mock-infected or infected with SARS-CoV-2 or SARS-CoV at an MOI of 10. After 24 hours post infection, the cells were untreated or treated with 1000 U/mL of recombinant human IFNα for 40 minutes. The cell lysates were collected for the detection of STAT1, pSTAT1, and β-actin by Western blots. (A) Representative blots were shown from three individual donors in three independent experiments. (B) Quantitation was calculated as the ratio of pSTAT1 over STAT1 protein. Statistical analysis were performed with one way-ANOVA and the differences were considered significant when $p < 0.05$. *$p < 0.05$ and ****$p < 0.0001$.

Figure 6. SARS-CoV-2 antagonized STAT1 phosphorylation in moDCs. MoDCs and MDMs were mock-infected or infected with SARS-CoV-2 or SARS-CoV at an MOI of 10.
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COMMENT ON: FREQUENCY OF FACE TOUCHING WITH AND WITHOUT A MASK IN PEDIATRIC HEMATOLOGY/ONCOLOGY HEALTH CARE PROFESSIONALS: FOR APPLICATION TO THE COVID-19 PANDEMIC

Church LE, Nagi G.. Pediatr Blood Cancer. 2020 Aug 3:e28634. doi: 10.1002/pbc.28634. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Authors affiliated with King's College London respond to a study which found a significant decrease in face touching among health care professionals wearing a mask compared to those not wearing a mask. The authors express concerns that a lack of training in mask donning and doffing among the general public could lead to greater infection risk when wearing masks and that factors such as wearing glasses with a mask could increase discomfort and lead to an increase in face touching for readjustment. A new United Kingdom mandate requiring masks on public transportation and in stores may allow for further investigation into face touching while wearing a mask among the general population.

NEUROLOGY

LARGE VESSEL STROKE IN SIX PATIENTS FOLLOWING SARS-COV-2 INFECTION: A RETROSPECTIVE CASE STUDY SERIES OF ACUTE THROMBOTIC COMPLICATIONS ON STABLE UNDERLYING ATHEROSCLEROTIC DISEASE

Lapergue B, Lyoubi A, Meseguer E, Avram I, Denier C, Venditti L, Consoli A, Guedon A, Houdart E, Weisenburger-Lile D, Piotin M, Maier B, Obadia M, De Broucker T.. Eur J Neurol. 2020 Aug 6. doi: 10.1111/ene.14466. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

This retrospective case series conducted in France from March 19 to April 19, 2020 describes 6 patients with preexisting vascular risk factors admitted to 6 different stroke centers with confirmed SARS-CoV-2 infection who developed large vessel ischemic stroke (mean onset of 11.5 days following first respiratory symptoms). On imaging, all but one of the six cases showed a large thrombus on an underlying mild atheroma, leading the authors to propose that SARS-CoV-2 infection may complicate underlying mild atherosclerotic disease and that healthcare providers should be aware of the high-risk of these patients.

ABSTRACT

BACKGROUND AND PURPOSE: Ischemic stroke has been described in association with COVID-19. Several pathophysiological mechanisms have been suggested i.e prothrombotic state, cardiac injury etc. We sought to assess the potential association between ischemic stroke associated with SARS-CoV-2 infection and underlying atherosclerotic lesions. METHODS: We conducted a retrospective analysis of stroke related to large vessel occlusion among patients with SARS-CoV-2 infection and underlying mild atherosclerotic disease. between 03/19 and 04/19, 2020 in six different stroke centers in the Ile-d- France area, France. RESULTS: The median age was 52 years, median BMI was 29.5. All patients displayed previous vascular risk factors such as high blood pressure, diabetes, dyslipidemia or BMI >25. The delay between the first respiratory symptoms of COVID-19 and stroke was 11.5 days. At baseline, all had tandem occlusions, i.e intra and extracerebral thrombus assessed with CT or MR imaging. Cases displayed a large thrombus in the cervical carotid artery with underlying mild non stenosing atheroma, after an etiological workup based on angio-CT or MR imaging and/or cervical echography. CONCLUSION: Our study should alert clinicians to scrutinize any new onset of ischemic stroke during COVID-19 infection, mainly in patients with vascular risk factors or underlying atherosclerotic lesions.

COVID-19 AND MISSED ROUTINE IMMUNIZATIONS: DESIGNING FOR EFFECTIVE CATCH-UP IN CANADA

MacDonald NE, Comeau JL, Dubé È, Bucci LM.. Can J Public Health. 2020 Aug 6. doi: 10.17269/s41997-020-00385-4. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

An opinion piece written by members of the Department of Pediatrics at Dalhousie University and IWK Health Centre in Halifax, Nova Scotia claim that the COVID-19 pandemic has caused a significant setback in vaccination rates around the globe, paving the way for outbreaks of vaccine-preventable diseases (VPD). To prevent this from happening, the authors suggest we need to identify who has missed routine immunizations, effectively and safely catch this population up, and communicate/readjust immunization programs accordingly. This would not only allow catch up on VPDs, but also prepare immunization programs across the globe for when a COVID-19 vaccine becomes available.

ABSTRACT

COVID-19 has led to disruption in routine immunization programs around the globe and here in Canada. The National Advisory Committee on Immunization (NACI) in Canada has indicated that this sets the stage for serious outbreaks of vaccine-preventable diseases. The World Health Organization has evidence-based guidance on how to address missed opportunities for vaccination, albeit predominately applicable for low- and middle-income countries. In Canada, immunization applies beyond infant and childhood immunization, with immunization across the life course being recommended by NACI. Three components stand out and must be integrated and used concurrently for best effect on catch-up in Canada: (1) Identify who has been missed across the life course; (2) detect delivery gaps, adapt and adjust, and develop multipronged tailored strategies for catch-up; and (3) communicate, document, evaluate and readjust the immunization programs. All must be adapted to the reality of the evolving COVID-19 pandemic. We cannot go back to a pre-COVID-19 world. However, ensuring that routine immunization and catch-up programs are done well during this pandemic strengthens the immunization foundation in Canada for when COVID-19 vaccines become available.

VIRAL LOAD DYNAMICS IN SPUTUM AND NASOPHARYNGEAL SWAB IN PATIENTS WITH COVID-19

Liu R, Yi S, Zhang J, Lv Z, Zhu C, Zhang Y.. J Dent Res. 2020 Aug 3:22034520946251. doi: 10.1177/0022034520946251. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

A retrospective cohort study conducted at Renmin Hospital of Wuhan University by researchers in Wuhan, China found SARS-CoV-2 viral loads remained positive longer in sputum samples versus nasopharyngeal (NP) samples in COVID-19 inpatients (n=31; Figure 2) and viral loads were higher in sputum compared to NP samples (statistically non-significant; Figure 1), while those with underlying disease (hypertension and diabetes) showed a slower viral load decrease in sputum samples overall (Figure 3). Authors suggest sputum samples could be useful in COVID-19 detection and preventing transmission, even with negative nasopharyngeal samples.

ABSTRACT

Coronavirus disease 2019 (COVID-19) has caused a global pandemic associated with substantial morbidity and mortality. Nasopharyngeal swabs and sputum samples are generally collected for serial viral load screening of respiratory contagions, but temporal profiles of these samples are not completely clear in patients with COVID-19. We performed an observational cohort study at Renmin Hospital of Wuhan University, which involved 31 patients with confirmed COVID-19 with or without underlying diseases. We obtained samples from each patient, and serial viral load was measured by real-time quantitative polymerase chain reaction. We found that the viral load in the sputum was inclined to be higher than samples obtained from the nasopharyngeal swab at disease presentation. Moreover, the viral load in the sputum decreased more slowly over time than in the nasopharyngeal group as the disease progressed. Interestingly, even when samples in the nasopharyngeal swab turned negative, it was commonly observed that patients with underlying diseases, especially hypertension and diabetes, remained positive for COVID-19 and required a longer period for the sputum samples to turn negative. These combined findings emphasize the importance of tracking sputum samples even in patients with negative tests from nasopharyngeal swabs, especially for those with underlying conditions. In conclusion, this work reinforces the importance of sputum samples for SARS-CoV-2 detection to minimize transmission of COVID-19 within the community.

FIGURES

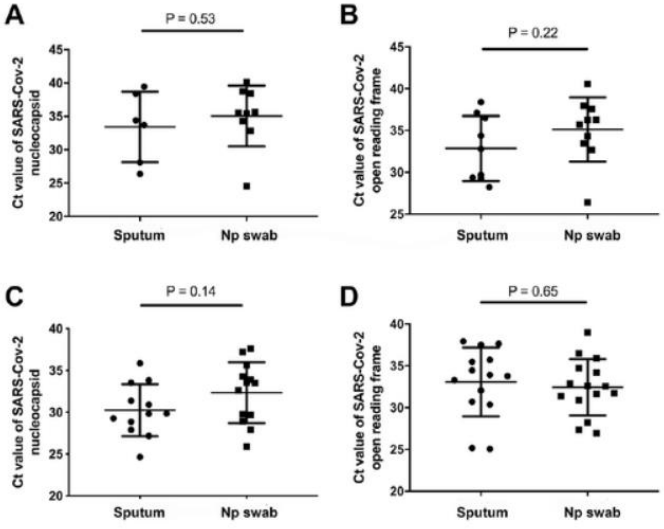

Figure 1. Detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with and without underlying diseases in different sample types. Comparison of SARS-CoV-2 Ct values in sputum and nasopharyngeal swab samples without underlying diseases: (A) NP and (B) ORF. Comparison of SARS-CoV-2 NP Ct values in sputum and nasopharyngeal swab samples with underlying diseases: (C) NP and (D) ORF. Values are presented as mean ± SD. Ct, cycle threshold; NP, nucleocapsid protein; ORF, open reading frame 1ab.

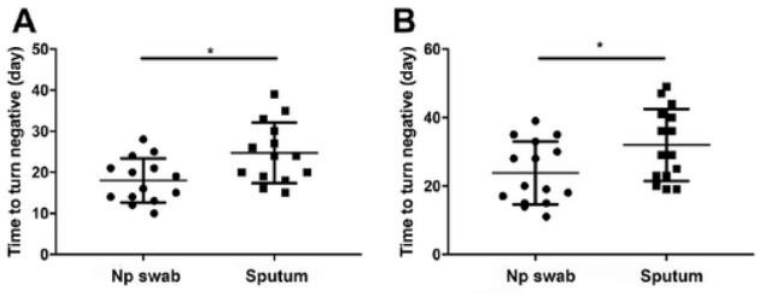

Figure 2. Comparison of the time required for samples to turn negative in the sputum and nasopharyngeal swab sample groups: (A) patients without underlying diseases and (B) patients with underlying diseases. Values are presented as mean ± SD. *P < 0.05.

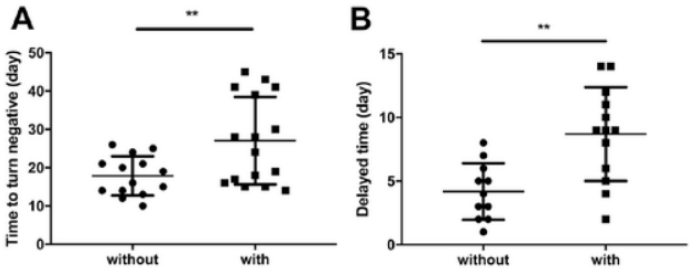

Figure 3. Association between underlying diseases and duration of severe acute respiratory syndrome coronavirus-2 infection. (A) The duration of nasopharyngeal swab samples turning negative in patients with and without underlying diseases. (B) The delayed time required for samples to turn negative in the sputum samples in patients with and without underlying diseases. Values are presented as mean ± SD. **P < 0.005.

COMPARING NASOPHARYNGEAL SWAB AND EARLY MORNING SALIVA FOR THE IDENTIFICATION OF SARS-COV-2

Rao M, Rashid FA, Sabri FSAH, Jamil NN, Zain R, Hashim R, Amran F, Kok HT, Samad MAA, Ahmad N.. Clin Infect Dis. 2020 Aug 6:ciaa1156. doi: 10.1093/cid/ciaa1156. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

A prospective study conducted at a Malaysian COVID-19 quarantine center of 217 asymptomatic adult males, where 160 tested positive, found a far greater SARS-CoV-2 detection rate using morning salivary samples (93.1%) when compared to nasopharyngeal swabs (52.5%) ($p<0.001$, 45.6% concordance, 47.5% discordance). These results suggest that the higher accuracy of salivary analysis could play a role in improved diagnostics, decreasing direct healthcare worker-patient interaction and risk of transmission, improving transport preservation, reducing test wait time, and allowing for self-collection.

ABSTRACT

BACKGROUND: The ideal SARs-CoV-2 testing method would be accurate and also be patient-performed to reduce exposure to healthcare workers. The aim of this study was to compare patient-performed testing based on a morning saliva sample with the current standard testing method, healthcare worker-collected sampling via a nasopharyngeal swab (NPS). METHODS: This was a prospective single center study which recruited 217 asymptomatic adult male participants in a COVID-19 quarantine center who had tested positive for SARS-CoV-2 8-10 days prior isolation. Paired NPS and saliva specimens were collected and processed within 5 hours of sample collection. Real time reverse transcriptase polymerase chain reaction (RT-PCR) targeting Envelope (E) and RNA-dependent RNA polymerase (RdRp) genes was performed and the results were compared. RESULTS: Overall, 160 of the 217 (74%) participants tested positive for Covid-19 based on saliva, NPS, or both testing methods. The detection rate for SARS-CoV-2 was higher in saliva compared to NPS testing (93.1%, 149/160 vs 52.5%, 84/160, $p<0.001$). The concordance between the two tests was 45.6% (virus was detected in both saliva and NPS in 73/160), while 47.5% were discordant (87/160 tested positive for one while negative for the other). The Ct values for E and RdRp genes were significantly lower in saliva specimens compared to NP swab specimens. CONCLUSIONS: Our findings demonstrate that saliva is a better alternative specimen for detection of SARS-CoV-2. Taking into consideration, the simplicity of specimen collection, shortage of PPE and the transmissibility of the virus, saliva could enable self-collection for an accurate SARS-CoV-2 surveillance testing.

PROTEOMICS AND INFORMATICS FOR UNDERSTANDING PHASES AND IDENTIFYING BIOMARKERS IN COVID-19 DISEASE

Whetton AD, Preston GW, Abubeker S, Geifman N.. J Proteome Res. 2020 Jul 24. doi: 10.1021/acs.jproteome.0c00326. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

This literature review illustrates the utility of proteomic plasma biomarkers (e.g. C-reactive protein, D-dimers and lactate dehydrogenase) in predicting the course, outcome, and resulting tissue damage from COVID-19. Biomarkers at various stages of disease are being used to make clinical decisions, emphasizing the need for both clinical sensitivity and specificity during their detection. The authors advocate for the use of artificial intelligence for data analysis while sifting through multimodal clinical information from patients such as respiratory function, age, sex, imaging results and presence of co-morbidities. The authors predict that health informatics and genomic data will be important in informing clinical decisions.

ABSTRACT

The emergence of novel coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 coronavirus, has necessitated the urgent development of new diagnostic and therapeutic strategies. Rapid research and development, on an international scale, has already generated assays for detecting SARS-CoV-2 RNA and host immunoglobulins. However, the complexities of COVID-19 are such that a fuller definition of patient status, trajectory, sequelae and responses to therapy is now required. There is accumulating evidence - from studies of both COVID-19 and the related disease SARS - that protein biomarkers could help to provide this definition. Proteins associated with blood coagulation (D-dimer), cell damage (lactate dehydrogenase) and the inflammatory response (e.g. C-reactive protein) have already been identified as possible predictors of COVID-19 severity or mortality. Proteomics technologies, with their ability to detect many proteins per analysis, have begun to extend these early findings. In order to be effective, proteomics strategies must include not only methods for comprehensive data acquisition (e.g. using mass spectrometry) but also informatics approaches via which to derive actionable information from large data-sets. Here we review applications of proteomics to COVID-19 and SARS, and outline how pipelines involving technologies such as artificial intelligence could be of value for research on these diseases.

PREDICTIVE MODELING BY DEEP LEARNING, VIRTUAL SCREENING AND MOLECULAR DYNAMICS STUDY OF NATURAL COMPOUNDS AGAINST SARS-COV-2 MAIN PROTEASE

Joshi T, Joshi T, Pundir H, Sharma P, Mathpal S, Chandra S.. J Biomol Struct Dyn. 2020 Aug 5:1-19. doi: 10.1080/07391102.2020.1802341. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

In this study, the authors used advanced algorithms inspired by biological brain functions - deep learning - followed by molecular docking analysis (Figure 1) to screen a total of 1611 natural compounds in search of potential natural inhibitors against the main protease (Mpro) enzyme of SARS-CoV-2 in hopes of identifying novel drug candidates to treat COVID-19. The results yielded two natural compounds, Palmatine and Sauchinone, that both formed stable complexes with Mpro with high affinity amino acid binding pockets (Figure 4), suggesting they may be capable of inhibition of the enzyme and have possible applications as therapeutics against SARS-CoV-2.

ABSTRACT

The whole world is facing a great challenging time due to Coronavirus disease (COVID-19) caused by SARS-CoV-2. Globally, more than 14.6 M people have been diagnosed and more than 595 K deaths are reported. Currently, no effective vaccine or drugs are available to combat COVID-19. Therefore, the whole world is looking for new drug candidates that can treat the COVID-19. In this study, we conducted a virtual screening of natural compounds using a deep-learning method. A deep-learning algorithm was used for the predictive modeling of a CHEMBL3927 dataset of inhibitors of Main protease (Mpro). Several predictive models were developed and evaluated based on R2, MAE MSE, RMSE, and Loss. The best model with R2=0.83, MAE = 1.06, MSE = 1.5, RMSE = 1.2, and loss = 1.5 was deployed on the Selleck database containing 1611 natural compounds for virtual screening. The model predicted 500 hits showing the value score between 6.9 and 3.8. The screened compounds were further enriched by molecular docking resulting in 39 compounds based on comparison with the reference (X77). Out of them, only four compounds were found to be drug-like and three were non-toxic. The complexes of compounds and Mpro were finally subjected to Molecular dynamic (MD) simulation for 100 ns. The MMPBSA result showed that two compounds Palmatine and Sauchinone formed very stable complex with Mpro and had free energy of -71.47 kJ mol-1 and -71.68 kJ mol-1 respectively as compared to X77 (-69.58 kJ mol-1). From this study, we can suggest that the identified natural compounds may be considered for therapeutic development against the SARS-CoV-2. Communicated by Ramaswamy H. Sarma.

FIGURES

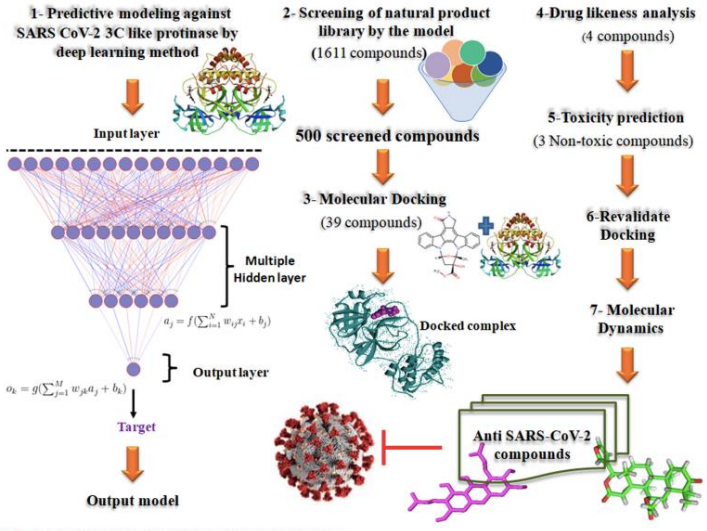

Figure 1. Depiction of the outline of predictive modeling and virtual screening.

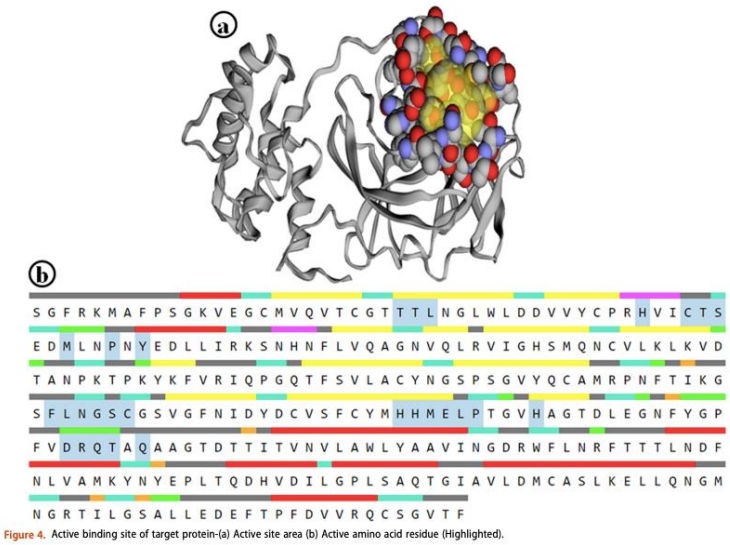

Figure 4. Active binding site of target protein-(a) Active site area (b) Active amino acid residue (Highlighted).

Figure 4. Active binding site of target protein - (a) Active site area (b) Active amino acid residue (Highlighted).

ERRORS IN TRIAL OF EFFECT OF CONVALESCENT PLASMA THERAPY ON TIME TO CLINICAL IMPROVEMENT IN PATIENTS WITH SEVERE AND LIFE-THREATENING COVID-19

Liu Z.. JAMA. 2020 Aug 4;324(5):518-519. doi: 10.1001/jama.2020.12607.
Level of Evidence: Other - Opinion

BLUF

In a letter to the editor, the author apologizes for an erroneous review on an investigation titled “Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial.” The author admits that, although the errors did not affect the interpretation of the article or the results of the study, the reviewers had erroneously utilized relative risk values instead of odds ratio when analyzing clinical outcomes on day 28 of the disease.

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