The Daily COVID-19 Literature Surveillance Summary

November 10, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Transmission & Prevention

- Pediatricians published best practices for breastfeeding mothers who were positive for or exposed to COVID-19 in JAMA Pediatrics. The authors express that while the literature is uncertain on risk of COVID-19 transmission through breastmilk, this route of transmission seems unlikely, and protective antibodies are likely to be the only SARS-CoV-2 related material to be transmitted. They believe their proposed practices for breastfeeding while infected with COVID-19 will promote safe breastfeeding, although they note these suggestions may change overtime.

Management

- Is there an association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19? Investigators on the STOP-COVID (Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19) team retrospectively analyzed data of 3,924 COVID-19 patients from 68 US hospitals admitted to the ICU. They compared estimated 30-day mortality rates of patients that received tocilizumab (an IL-6 inhibitor) in the first 2 days of ICU admission verses those who did not. The researchers performed inverse probability weighting to ensure that baseline and severity of illness factors were balanced between the study groups. The results revealed an estimated 30-day mortality of 27.5% in patients treated with tocilizumab, compared to 37.1% in patients without tocilizumab, suggesting the drug's benefit in treatment of critically ill COVID-19 patients.

- Investigators affiliated with Yale School of Medicine performed a systematic review of 86 studies worldwide (n=2560 patients) on dermatologic manifestations in COVID-19 patients and found associations with chilblains/pernio like lesions at 51.5%, erythematous maculopapular rashes at 13.3%, and viral exanthem at 7.7%. Average time of skin lesion onset was 7.9 days after upper respiratory infection symptoms in adults and 1.5 days in children. These findings suggest that dermatologic manifestations may be another way to identify COVID-19 and better manage the spread of disease.

R&D: Diagnosis & Treatments

- At what times during infection is SARS-CoV-2 detectable and no longer detectable using RT-PCR-based tests? A systematic review of 32 longitudinal studies examined the accuracy, temporal sensitivity, and optimal sampling sites and strategies for SARS-CoV-2. The authors reported on a total of 1,023 COVID-19 RT-PCR confirmed participants and 1,619 test results for 11 different sampling sites at various times during SARS-CoV-2 infection. They found that the highest rate of virus detection was within 4 days of symptom onset at 89%, which fell to 54% between 10 and 14 days. The authors discuss that the accuracy of RT-PCR is limited, early testing minimizes false negative results, and lower respiratory tract or fecal testing may be preferred sampling sites when testing more than a few days post symptom onset.

- There is clinical impact of monocyte distribution width and neutrophil-to-lymphocyte ratio for distinguishing COVID-19 and influenza from other upper respiratory tract infections according to a cohort study conducted at Taipei Medical University Hospital (Taiwan), that analyzed potential biomarkers of SARS-CoV-2 infection in 174 patients (9 with nasal swab RT-PCR confirmed COVID-19, 24 with influenza confirmed via rapid-test, and 141 determined to have common URIs). The authors found that monocyte distribution width (MDW) greater than or equal to 20 (OR: 8.39, $p = 0.0110$) and neutrophil-to-lymphocyte ratio greater than 3.2 (OR: 4.23, $p = 0.0494$) could independently distinguish COVID-19 from common upper respiratory infections. Further, combing these two markers shows promise for efficient identification of both COVID-19 and influenza infection. For clinicians uncertain about diagnosing COVID-19 or those doubting a test result, this information may become a useful tool in identifying COVID-19.

- A multidisciplinary group of drug development experts from the UK, USA, Switzerland and Italy reviewed literature on effects of antiviral protein binding on in-vivo drug activity by assessing data from antiretroviral drug development and reached a consensus. They found that unbound plasma concentrations could not be compared to in-vitro activity and researchers must instead compare in-vivo and in-vitro free drug concentrations. They cited recent studies investigating remdesivir and lopinavir as possible agents against SARS-CoV-2, which do not account for protein binding. They argue correct interpretation of protein binding data is critical for identification of the most promising drug candidates.

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ADULTS

CHARACTERISTICS AND OUTCOMES OF COVID-19-ASSOCIATED STROKE: A UK MULTICENTRE CASE-CONTROL STUDY

Perry RJ, Smith CJ, Roffe C, Simister RJ, Narayanamoorthi S, Marigold R, Willmot M, Dixit A, Hassan A, Quinn T, Ankolekar S, Zhang L, Banerjee S, Ahmed U, Padmanabhan N, Ferdinand P, McGrane F, Banaras A, Marks IH, Werring DJ; SETICOS collaborators.. J Neurol Neurosurg Psychiatry. 2020 Nov 5:jnnp-2020-324927. doi: 10.1136/jnnp-2020-324927. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

United Kingdom researchers in Cardiovascular, Stroke, and Neurology performed a case control study across 13 hospitals from March 9th 2020 to July 5th 2020 of 2 patient groups:

1) 86 stroke patients (81 ischemic, 5 hemorrhagic) with COVID-19, and
2) 1384 without COVID-19 (1193 ischemic, 191 hemorrhagic).

Findings show “Ischemic strokes which were associated with COVID-19 at onset were more likely to occur in Asian people; more likely to involve multiple large vessel occlusions; more severe; associated with higher D-dimer levels; and more likely to have a worse functional outcome or result in death.” They suggest against anti-coagulating COVID-19 patients for ischemic stroke prevention due to possible increased risk of secondary hemorrhage.

WHAT IS THE SIGNIFICANCE OF THE CONJUNCTIVA AS A POTENTIAL TRANSMISSION ROUTE FOR SARS-COV-2 INFECTIONS?

Lange C, Wolf J, Auw-Haedrich C, Schlecht A, Boneva S, Lapp T, Agostini H, Martin G, Reinhard T, Schlunck G..
Ophthalmologe. 2020 Nov 3. doi: 10.1007/s00347-020-01255-7. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review by physicians from the Department of Ophthalmology at Freiburg University Hospital in Germany found patients with COVID-19 rarely had detectable viral loads in conjunctival smears and tear film samples. Authors also highlight a study showing low expression levels of membrane-bound angiotensin-converting enzyme 2 (ACE2) and the membrane-bound serine protease TMPRSS2 in conjunctival samples (n=38; Figure 2), indicating unlikely transmission via these mediators. Although conjunctivitis has been reported in a small percentage of patients with COVID-19 (1%), authors suggest that conjunctiva may not be a significant transmission route for the SARS-CoV-2 virus.

ABSTRACT

Recent studies have described conjunctivitis in approximately 1% of COVID-19 patients and speculated that SARS-CoV-2 can be transmitted via the conjunctiva. In this article we recapitulate the molecular mechanisms of host cell entry of SARS-CoV-2 and discuss the current evidence for a potential conjunctival transmission of SARS-CoV-2. The current body of evidence indicates that SARS-CoV-2 requires the membrane-bound angiotensin-converting enzyme 2 (ACE2) and the membrane-bound serine protease TMPRSS2 to enter cells. Recent studies suggest that COVID-19 patients rarely exhibit viral RNA in tear film and conjunctival smears and that, ACE2 and TMPRSS2 are only expressed in small amounts in the conjunctiva, making conjunctival infection with SARS-CoV-2 via these mediators unlikely. Nevertheless, we consider the current evidence to be still too limited to provide a conclusive statement and recommend appropriate protective measures for healthcare personnel who are in close contact with suspected and confirmed COVID-19 patients.

FIGURES

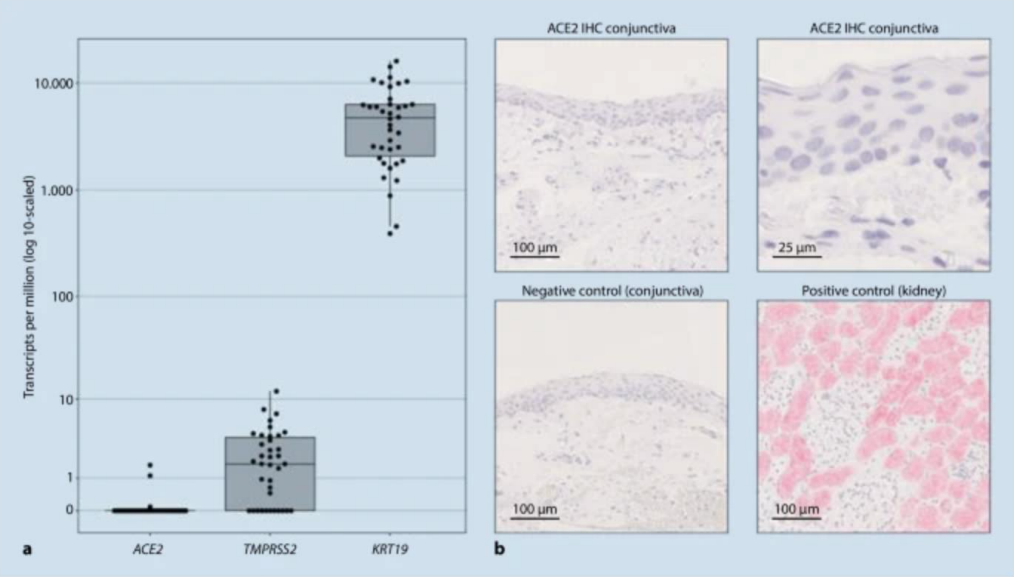


Figure 2. Expression of the SARS-CoV-2 receptor ACE2 and the proteinase TMPRSS2 in the human conjunctiva. a The box plot shows low mRNA expression levels for ACE2 and TMPRSS2 compared to the conjunctival marker keratin 19 in 38 analyzed conjunctival samples. Each dot represents one sample. b Representative immunohistochemical images of ACE2 staining of conjunctival and kidney tissue. While kidney tissue shows strong ACE2 staining, healthy conjunctival samples (n = 8) show negligible immunoreactivity. For the negative control, the primary antibody was omitted. (Image modified from https://www.nature.com/articles/s41433-018-0172-6).

FIRST RESULTS OF INVESTIGATIONS OF SARS-COV-2 RNA IN HUMAN CORNEAL TISSUE

Bayyoud T, Iftner T, Bartz-Schmidt KU, Rohrbach JM, Ueffing M, Schindler M, Thaler S.. Ophthalmologe. 2020 Nov 3. doi: 10.1007/s00347-020-01254-8. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

A review from Eberhard Karls Universität in Tübingen, Germany evaluated a recent study (Bayyoud et al., Cornea, 2020) which found no detectable SARS-CoV-2 viral load in the cadaveric tissue of 10 donor eyes. Limitations discussed were small sample size, variable disease duration, timing and method of sample collection, and absence of validated RT-PCR protocol in cadaveric tissue. Considering these limitations in addition to risk of viral transmission via donor conjunctival and corneal tissue, authors recommend against collecting donor tissue from COVID-19 patients until there is a validated SARS-CoV-2 test for post-mortem tissues.

ABSTRACT

Preliminary investigations of human corneal tissues from coronavirus disease 2019 (COVID-19) cadaveric donors indicated that no severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is present. Current eye banking guidelines do not recommend any type of routine testing for SARS-CoV-2 RNA in post-mortem donor tissue. This is partly based on factors that can influence the test results of the reverse transcription polymerase chain reaction (RT-PCR).

WHY SEVERE COVID-19 PATIENTS ARE AT GREATER RISK OF DEVELOPING DEPRESSION: A MOLECULAR PERSPECTIVE

Bouças AP, Rheinheimer J, Lagopoulos J.. Neuroscientist. 2020 Nov 2:1073858420967892. doi: 10.1177/1073858420967892. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Investigators from the Sunshine Coast Mind and Neuroscience Thompsin Institute in Australia propose a mechanism for which COVID-19 may lead to depression. They pose that COVID-19-induced cytokine storm activates indoleamine 2,3 dioxygenase (IDO-1), which leads to increased kyurenines and chemokine exposure in the brain, eventually resulting in brain impairment and possible depression (Figure 1). These findings provide insight into potential causes of COVID-19-associated depression and ways to surveil and treat these patients as concerns arise.

ABSTRACT

The prevailing evidence suggests that patients with severe COVID-19 seem to have an overreaction of the immune system demonstrating exacerbated levels of inflammation caused by a "cytokine storm." At this early stage, the mechanisms underpinning COVID-19 are still subject to intense scrutiny and the long-term mental health consequences as a result of the disease are unknown. Here we discuss the hypothesis that patients who survive severe COVID-19 and who experience significant activation of the immune system, are at greater risk of developing depression. We posit that a phenomenon known as cytokine storm dramatically activates the enzyme indoleamine 2,3-dioxygenase (IDO-1), resulting in the increase in kynurenine metabolites. Kynurenine is metabolized by IDO-1 in the brain, producing chemokines, in which a prolonged exposure may result long-term brain impairment. In this article, we also propose the possibility that a SARS-CoV-2 neuroinvasion increases the local levels of angiotensin II by angiotensin-converting enzyme 2 down-regulation. Thereby, angiotensin II could increase kynurenine metabolites producing pro-oxidative and pro-inflammatory effects, resulting in impairment of cognitive function, enhanced oxidative stress and decreased brain-derived neurotrophic factor. It is our premise that patients who experience such a cytokine storm may be at increased risk of long-term mental illness, such as depression.

FIGURES

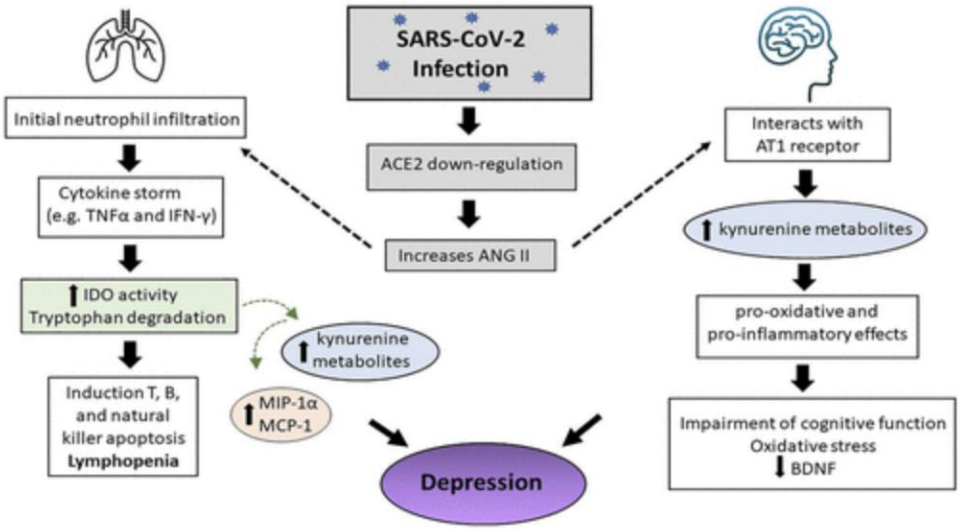


Figure 1. Hypothetical model of depression.

IN SILICO

A COMPREHENSIVE REVIEW ON PROMISING ANTI-VIRAL THERAPEUTIC CANDIDATES IDENTIFIED AGAINST MAIN PROTEASE FROM SARS-COV-2 THROUGH VARIOUS COMPUTATIONAL METHODS

Singh E, Khan RJ, Jha RK, Amera GM, Jain M, Singh RP, Muthukumaran J, Singh AK.. J Genet Eng Biotechnol. 2020 Nov 3;18(1):69. doi: 10.1186/s43141-020-00085-z.
Level of Evidence: Other - Review / Literature Review

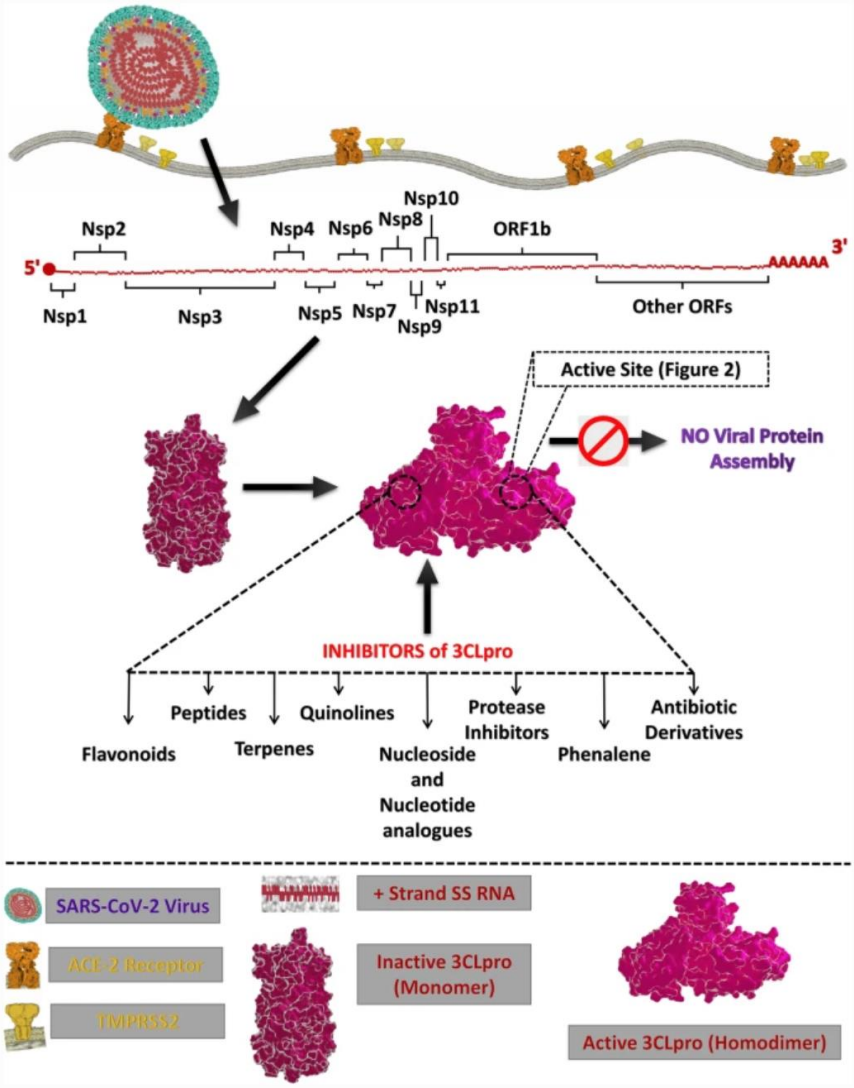
BLUF

Biotechnicians reviewed the potential mechanisms of action identified in silico of a possible anti-viral therapy for SARS-CoV-2 that targets the 3-Chymotrypsin-like protease (3CLpro), a protease that aids in viral replication, and suggests multiple different treatment options and drug classes based on structure, residues, interactions, and stability (see Figure 1 and 2, Table 1) that could all be tested to treat COVID-19.

ABSTRACT

BACKGROUND: The COVID-19 pandemic caused by SARS-CoV-2 has shown an exponential trend of infected people across the planet. Crediting its virulent nature, it becomes imperative to identify potential therapeutic agents against the deadly virus. The 3-chymotrypsin-like protease (3CLpro) is a cysteine protease which causes the proteolysis of the replicase polyproteins to generate functional proteins, which is a crucial step for viral replication and infection. Computational methods have been applied in recent studies to identify promising inhibitors against 3CLpro to inhibit the viral activity. This review provides an overview of promising drug/lead candidates identified so far against 3CLpro through various in silico approaches such as structure-based virtual screening (SBVS), ligand-based virtual screening (LBVS) and drug-repurposing/drug-reprofiling/drug-retasking. Further, the drugs have been classified according to their chemical structures or biological activity into flavonoids, peptides, terpenes, quinolines, nucleoside and nucleotide analogues, protease inhibitors, phenalene and antibiotic derivatives. These are then individually discussed based on the various structural parameters namely estimated free energy of binding (DeltaG), key interacting residues, types of intermolecular interactions and structural stability of 3CLpro-ligand complexes obtained from the results of molecular dynamics (MD) simulations. CONCLUSION: The review provides comprehensive information of potential inhibitors identified through several computational methods thus far against 3CLpro from SARS-CoV-2 and provides a better understanding of their interaction patterns and dynamic states of free and ligand-bound 3CLpro structures.

Fig. 1



Schematic representation for the localization and function of possible inhibitor classes against 3CLpro from SARS-CoV-2

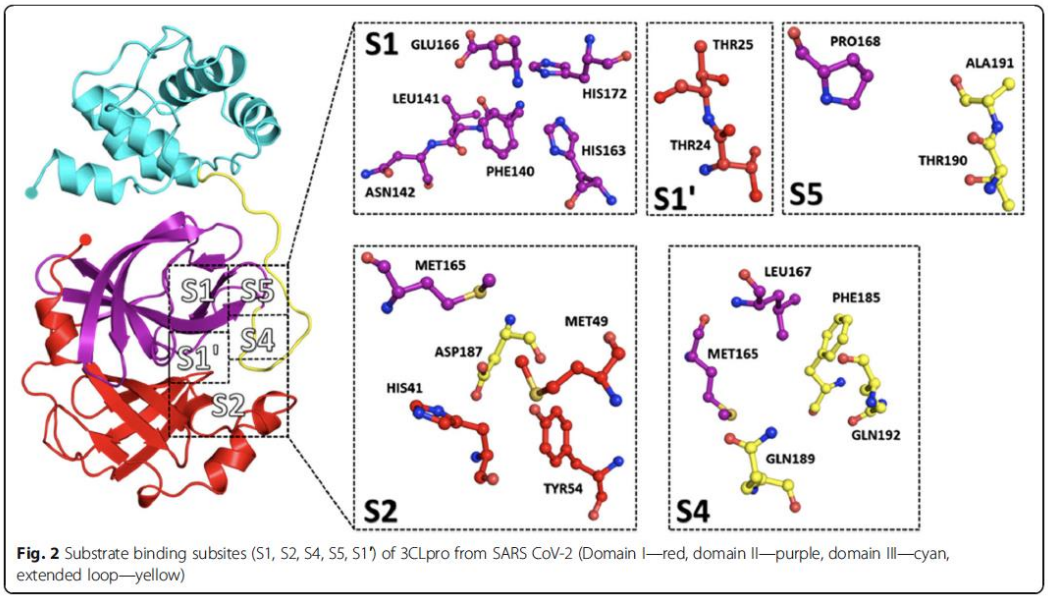


Fig. 2 Substrate binding subsites (S1, S2, S4, S5, S1′) of 3CLpro from SARS CoV-2 (Domain I—red, domain II—purple, domain III—cyan, extended loop—yellow)

Table 1 Existing promising and potential molecules against 3CLpro from SARS CoV-2

S/No	PubChem CID	Binding free energy (kcal/mol)	Tools used	Interacting residues	Refs
1	5,7,3′,4′-Tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone(11610052)	− 29.57	Molecular operating environment (MOE)	Thr25, Thr26, Leu26, His41, Val42, Ser46, Met49, Tyr54, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Leu167, Pro168, Asp187, Arg188, Gln189, Thr190, Ala191, Gln192	[42]
2	Cyanidin 3-glucoside(197081)	− 8.4	Autodock Vina	Glu166, Asn142, His163, Gln189, Asp187, Thr26, Met49, Gly143, His164, Gln189, Cys145	[43]
3	Baicalin(64982)	− 8.1	Autodock Vina	Gly143, Leu141, Gln189, Met165, Asn142, Glu166, Pro168	[43]
4	Glabridin(124052)	− 8.1	Autodock Vina	Leu141, Glu166, Met49, His41, Met165	[43]
5	Quercetin 3-vicianoside(44259139)	− 8.3	Autodock Vina	His163, Glu166, Ser144, Leu114, Gly143, Thr26, Arg188, Asp187, Met165, His164, Gln189, His41, Thr25, Asn142, Phe140, Cys145	[44]
6	Myricitrin(5281673)	− 8.9	Autodock Vina	Tyr54, Asp187, Arg188, Leu141, Phe140, His172, Glu166, Ser144, His164, His163, Leu37, Asn142, Gly143, Thr26, Cys145, Met165, Met49, His41	[45]
7	Oolonghomobisflavan-A(14520989)	− 75.5	CDOCKER	Thr25, Asn142, His163, Glu166, Arg188, His164, Gly143, Met165, His41, Phe140, Leu141, His172, Ser144, Thr24, Cys145, Leu27, Met49, Asp187, Gln189, Gln192, Val186, Thr190, Pro168, Leu167	[46]
8	Birinapant(49836020)	− 8.1	Glide Schrodinger Suite	Thr25, Thr26, Leu26, His41, Val42, Ser46, Met49, Tyr54, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Leu167, Pro168, Asp187, Arg188, Gln189, Thr190, Ala191, Gln192	[47]
9	Carfilzomib(11556711)	− 8.6	Glide Schrodinger Suite	Cys145, His164, Glu166, Gln192, Asn142, Gln189, His41	[48]
10	6-Oxoisoiguesterin(21575473)	− 9.1	Autodock Vina	Arg189, Met49, Met165, Cys145	[49]
11	22-Hydroxyhopan-3-one(21582894)	− 8.6	Autodock Vina	Arg189, Met49, Met165, Cys145	[49]
12	Crocin(5281233)	− 8.2	Autodock 1.5.4 tools	Thr135, Asn133, Thr199, Lys137, Lys5, Phe3, Arg4, Arg131, Asp197	[50]
13	Carnosol(442009)	− 8.2	Autodock 1.5.6 tools	Cys145, His164, Glu166, Gln189, Met165, Arg188, Cys44, Met49, His41, Thr45, Thr25, Thr26, Leu27, Gly143, Ser46, Asn142	[51]
14	Rosmanol(13966122)	− 7.9	Autodock 1.5.6 tools	Cys145, Gly143, Thr25, His41, Met49, Asn142, His143, Glu166, Leu141, Ser144, Met165, Phe140	[51]
15	Withanone(21679027)	− 4.4	Glide Schrodinger Suite	Thr24, Thr25, Thr26, Leu27, His41, Met49, Tyr54, Asn142, Gly143, His164, Met165, Glu166, Arg188, Asp188, Gln189, Cys145	[52]
16	Nelfinavir(64143)	− 7	Autodock Vina	His163, Gln189	[53]
17	CMPD23B	− 118.6	Igemdock	Arg40, Tyr54, Cys85, Phe181, Arg188, Arg40, Tyr54, Glu55, Met82, Asn84	[54]
18	Amodiaquine(2165)	− 7.4	Glide Schrodinger Suite	Leu141, ARG187, Glu166, His41	[55]
19	Remdesivir(121304016)	− 7.9	Glide Schrodinger Suite	Gln191, Ala192, Thr190, Gln189, Arg188, Asp187, Leu141, Asn142, Gly143, Ser144, Cys145, His164, Met165, Glu166, Leu167, Pro168, Thr26, Leu27, Met49, Tyr54, His41	[56]
20	Ribavirin(37542)	2	Glide Schrodinger Suite	Leu4, Gln189, Met49, Val3, Ser46, Cys145, Thr25, Thr24, Thr45	[57]
21	Telbivudine(159269)	2	Glide Schrodinger Suite	Thr190, Leu50, Glu47, Ser46, Met49, Val3, Gln189	[57]
22	Lopinavir(92727)	− 10.8	MMPBSA.py module of AMBER16	Met49, Met165, Pro168, Gln189, His41, Ala46, Met49, Glu166, Leu167, Leu187, Gln189, Ala191, Ala193	[58]
23	Ritonavir(392622)	− 14.9	MMPBSA.py module of AMBER16	Leu27, His41, Met49, Phe140, Asn142, Gly143, His164, Met165, Glu166, Asn142, Gly143, Ser144, Cys145, Met165, Glu166, Asp187, Gln189	[58]
24	Saquinavir(441243)	− 9.8	Glide Schrodinger Suite	His41, Cys44, Tyr54, Met49, His172, Glu166, Met165, His164, His163, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, Thr25, Thr26, Leu27, Asp187, Arg188, Gln189, Thr190, Ala191	[56]
25	Simeprevir(24873435)	− 10	Autodock Vina	Glu166, Met165, Gln189, Phe140, Cys145, Asn142, Leu27, His41, Ser46	[59]

AIRBORNE TRANSMISSION OF SARS-COV-2 VIA AEROSOLS

Comber L, O Murchu E, Drummond L, Carty PG, Walsh KA, De Gascun CF, Connolly MA, Smith SM, O'Neill M, Ryan M, Harrington P.. Rev Med Virol. 2020 Oct 26:e2184. doi: 10.1002/rmv.2184. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A multidisciplinary team from Ireland conducted a rapid review of epidemiological, air sampling, and virological studies (n=28; Figure 1) between January 1 and July 27, 2020. They found that despite epidemiological cluster studies suggesting aerosol transmission via detection in air samples of healthcare/public facilities, clinical infectivity and consistency in viral growth of these samples had not been established. Similarly, virological studies had detected particles possibly representing live virus, but lacked evidence for clinical infectivity. Authors suggest SARS-CoV-2 has potential for transmission via aerosols, but more rigorous studies are needed to determine the extent of its contribution relative to droplet or contact transmission.

ABSTRACT

A key consideration in the Covid-19 pandemic is the dominant modes of transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. The objective of this review was to synthesise the evidence for the potential airborne transmission of SARS-CoV-2 via aerosols. Systematic literature searches were conducted in PubMed, Embase, Europe PMC and National Health Service UK evidence up to 27 July 2020. A protocol was published and Cochrane guidance for rapid review methodology was adhered to throughout. Twenty-eight studies were identified. Seven out of eight epidemiological studies suggest aerosol transmission may occur, with enclosed environments and poor ventilation noted as possible contextual factors. Ten of the 16 air sampling studies detected SARS-CoV-2 ribonucleic acid; however, only three of these studies attempted to culture the virus with one being successful in a limited number of samples. Two of four virological studies using artificially generated aerosols indicated that SARS-CoV-2 is viable in aerosols. The results of this review indicate there is inconclusive evidence regarding the viability and infectivity of SARS-CoV-2 in aerosols. Epidemiological studies suggest possible transmission, with contextual factors noted. Viral particles have been detected in air sampling studies with some evidence of clinical infectivity, and virological studies indicate these particles may represent live virus, adding further plausibility. However, there is uncertainty as to the nature and impact of aerosol transmission of SARS-CoV-2, and its relative contribution to the Covid-19 pandemic compared with other modes of transmission.

FIGURES

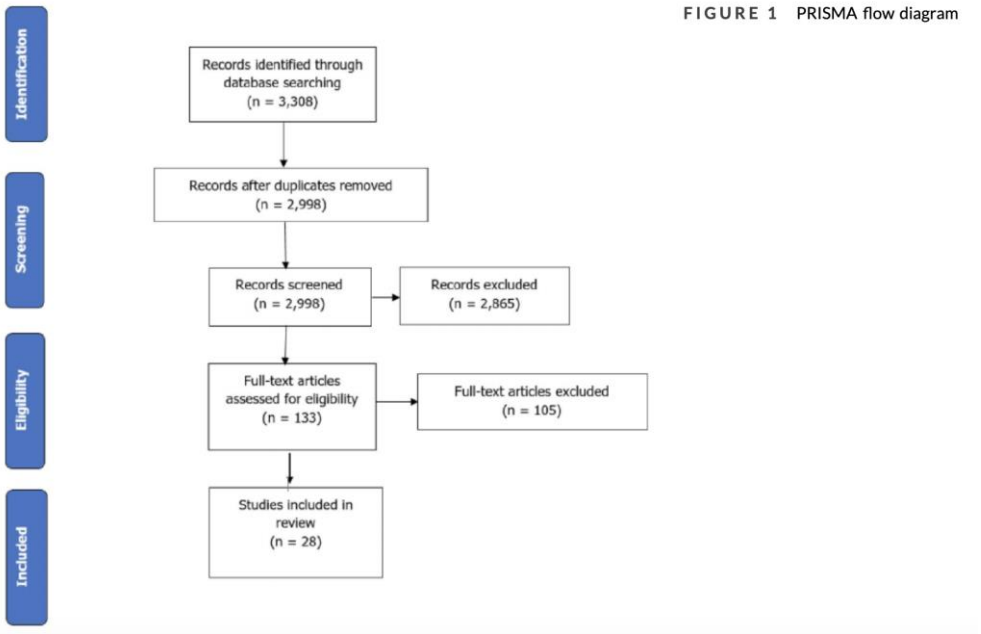


FIGURE 1 PRISMA flow diagram

BEST PRACTICES FOR COVID-19-POSITIVE OR EXPOSED MOTHERS-BREASTFEEDING AND PUMPING MILK

Sullivan SE, Thompson LA.. JAMA Pediatr. 2020 Oct 26. doi: 10.1001/jamapediatrics.2020.3341. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

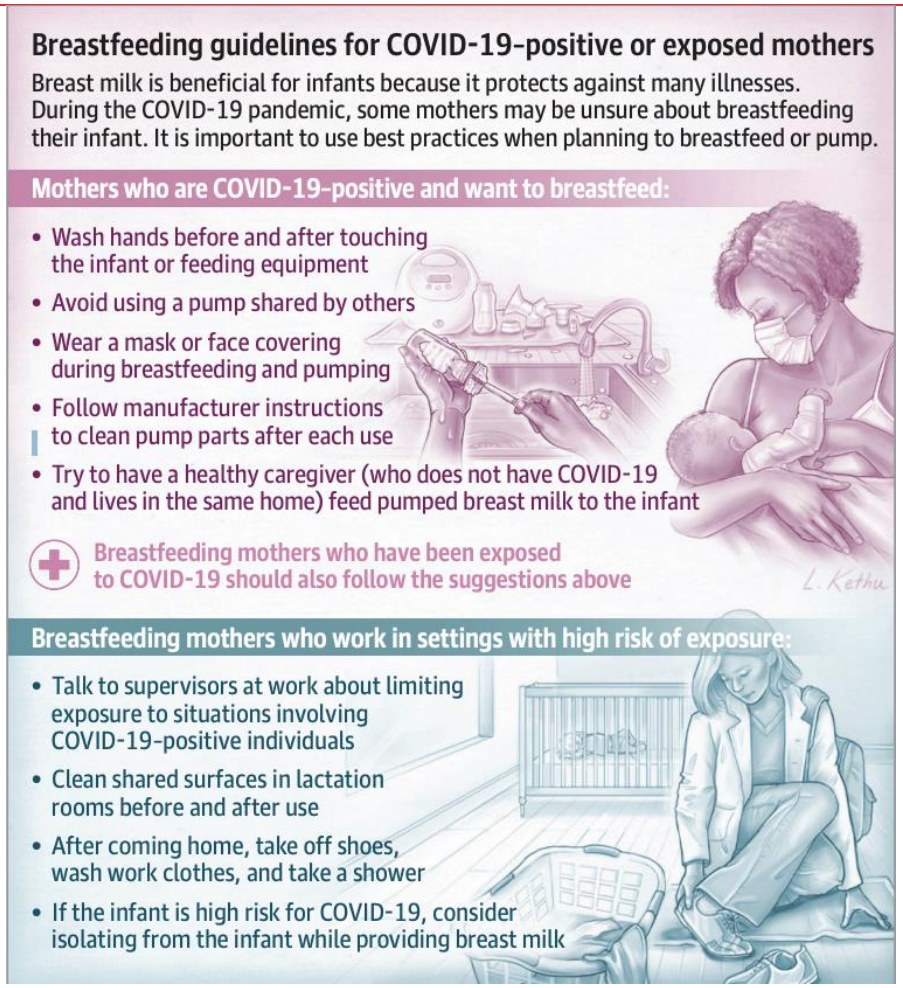
A guidelines paper, composed by University of Florida (U.S.) pediatricians and published by JAMA Pediatrics, proposes guidelines for breastfeeding if the mother is infected with COVID-19 or exposed to COVID-19. The authors express that while the literature is uncertain on risk of COVID-19 transmission through breastmilk, this route of transmission seems unlikely, and protective antibodies are likely to be the only SARS-CoV-2 related material to be transmitted. The authors believe their proposed practices for breastfeeding while infected with COVID-19 (illustrated below) will promote safe breastfeeding, although they note these suggestions may change overtime.

SUMMARY

The authors propose adhering to the following practices of breastfeeding while infected with SARS-CoV-2 (Figure):

1) Wash hands before and after touching your infant or any pump or bottle parts
2) Avoid using a shared pump
3) Wear a face covering during feeding or pumping
4) Follow manufacturer cleaning protocols for pump cleaning between uses
5) Feed pumped breastmilk to the infant from a healthy caregiver if possible

FIGURES



PROTECTION AT THE FRONTLINES: RAPID ORGANIZATION AND DELIVERY OF COVID-19 PERSONAL PROTECTIVE EQUIPMENT TRAINING

Moore M.. J Nurses Prof Dev. 2020 Nov/Dec;36(6):369. doi: 10.1097/NND.0000000000000664.
Level of Evidence: Other - Expert Opinion

BLUF

Molly Moore, MSN, RN, MS, CCRN reports efforts of Hospital of the University of Pennsylvania (HUP) to quickly and efficiently train hospital staff on adequate COVID-19 personal protective equipment (PPE) by Nursing Professional Development Specialists (NPDS). This specialized team has held about 100 interprofessional training sessions with nurses, physicians, advanced practitioners, security personnel, infection control, and others in order to protect frontline employees in the hospital during the COVID-19 pandemic. Their efforts may be a useful resource for other programs organizing COVID-19 PPE training for healthcare workers.

CRITICAL CARE

ASSOCIATION BETWEEN EARLY TREATMENT WITH TOCILIZUMAB AND MORTALITY AMONG CRITICALLY ILL PATIENTS WITH COVID-19

Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, Reiser J, Bansal A, Srivastava A, Zhou Y, Finkel D, Green A, Mallappallil M, Faugno AJ, Zhang J, Velez JCQ, Shaefi S, Parikh CR, Charytan DM, Athavale AM, Friedman AN, Redfern RE, Short SAP, Correa S, Pokharel KK, Admon AJ, Donnelly JP, Gershengorn HB, Douin DJ, Semler MW, Hernán MA, Leaf DE; STOP-COVID Investigators.. JAMA Intern Med. 2020 Oct 20. doi: 10.1001/jamainternmed.2020.6252. Online ahead of print.

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

BLUF

Investigators on the STOP-COVID (Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19) team retrospectively analyzed data of 3924 COVID-19 patients from 68 US hospitals admitted to the ICU between March 4 and May 10, 2020. They compared estimated 30-day mortality rates of patients that received tocilizumab (an IL-6 inhibitor) in the first 2 days of ICU admission verses those who did not. The researchers performed inverse probability weighting to ensure that baseline and severity of illness factors were balanced between the study groups. The results revealed an estimated 30-day mortality of 27.5% in patients treated with tocilizumab, compared to 37.1% in patients without tocilizumab (Figure 2), suggesting the drug's benefit in treatment of critically ill COVID-19 patients.

ABSTRACT

Importance: Therapies that improve survival in critically ill patients with coronavirus disease 2019 (COVID-19) are needed. Tocilizumab, a monoclonal antibody against the interleukin 6 receptor, may counteract the inflammatory cytokine release syndrome in patients with severe COVID-19 illness. Objective: To test whether tocilizumab decreases mortality in this population. Design, Setting, and Participants: The data for this study were derived from a multicenter cohort study of 4485 adults with COVID-19 admitted to participating intensive care units (ICUs) at 68 hospitals across the US from March 4 to May 10, 2020. Critically ill adults with COVID-19 were categorized according to whether they received or did not receive tocilizumab in the first 2 days of admission to the ICU. Data were collected retrospectively until June 12, 2020. A Cox regression model with inverse probability weighting was used to adjust for confounding. Exposures: Treatment with tocilizumab in the first 2 days of ICU admission. Main Outcomes and Measures: Time to death, compared via hazard ratios (HRs), and 30-day mortality, compared via risk differences. Results: Among the 3924 patients included in the analysis (2464 male [62.8%]; median age, 62 [interquartile range {IQR}, 52-71] years), 433 (11.0%) received tocilizumab in the first 2 days of ICU admission. Patients treated with tocilizumab were younger (median age, 58 [IQR, 48-65] vs 63 [IQR, 52-72] years) and had a higher prevalence of hypoxemia on ICU admission (205 of 433 [47.3%] vs 1322 of 3491 [37.9%] with mechanical ventilation and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of <200 mm Hg) than patients not treated with tocilizumab. After applying inverse probability weighting, baseline and severity-of-illness characteristics were well balanced between groups. A total of 1544 patients (39.3%) died, including 125 (28.9%) treated with tocilizumab and 1419 (40.6%) not treated with tocilizumab. In the primary analysis, during a median follow-up of 27 (IQR, 14-37) days, patients treated with tocilizumab had a lower risk of death compared with those not treated with tocilizumab (HR, 0.71; 95% CI, 0.56-0.92). The estimated 30-day mortality was 27.5% (95% CI, 21.2%-33.8%) in the tocilizumab-treated patients and 37.1% (95% CI, 35.5%-38.7%) in the non-tocilizumab-treated patients (risk difference, 9.6%; 95% CI, 3.1%-16.0%). Conclusions and Relevance: Among critically ill patients with COVID-19 in this cohort study, the risk of in-hospital mortality in this study was lower in patients treated with tocilizumab in the first 2 days of ICU admission compared with patients whose treatment did not include early use of tocilizumab. However, the findings may be susceptible to unmeasured confounding, and further research from randomized clinical trials is needed.

FIGURES

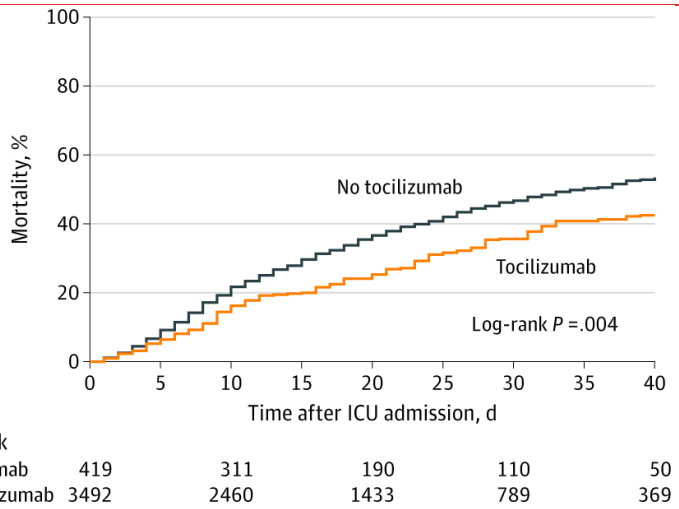


Figure 2. Mortality in Tocilizumab-Treated vs Non-Tocilizumab–Treated Patients.

MEDICAL SUBSPECIALTIES

DERMATOLOGY

DERMATOLOGIC MANIFESTATIONS OF COVID-19: A COMPREHENSIVE SYSTEMATIC REVIEW

Mirza FN, Malik AA, Omer SB, Sethi A.. Int J Dermatol. 2020 Nov 3. doi: 10.1111/ijd.15168. Online ahead of print.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Investigators affiliated with Yale School of Medicine performed a systematic review of 86 studies worldwide (resulting in n=2560 patients) from November 1, 2019 to July 15, 2020 on dermatologic manifestations in COVID-19 patients (Figure 1) and found associated chilblains/pernio like lesions (51.5%), erythematous maculopapular rashes (13.3%) and viral exanthem (7.7%). Average time of skin lesion onset was 7.9 days after upper respiratory infection symptoms in adults and 1.5 days in children. These findings suggest that dermatologic manifestations may be another way to identify COVID-19 and better manage the spread of disease.

ABSTRACT

Recent reports have suggested that there may be dermatologic manifestations of COVID-19. We searched 12 databases for peer-reviewed or pre-print published studies until July 15, 2020, for this PRISMA-compliant review (CRD42020182050). We used the Oxford Center for Evidence-Based Medicine Levels of Evidence to facilitate data synthesis. From 86 retrieved studies, we collated data on 2,560 patients with dermatologic manifestations of COVID-19. The most common findings were chilblains/pernio-like lesion (51.5%), erythematous maculopapular rashes (13.3%), and viral exanthem (7.7%). Average pediatric age was 12.9 years (SD 3.6) and adult was 34.2 years (SD 21.8). Average latency from time of upper respiratory illness symptoms to cutaneous findings was 1.5 days (SD 2.9) in children and 7.9 days (SD 10.7) in adults, ranging from -3 to 38 days. Roughly one-tenth in both populations were otherwise asymptomatic or presented with only skin findings for the entirety of the disease course; 13.3% (pediatrics) and 5.3% (adults) presented with skin issues first. Dermatologic findings may play an important role in identifying cases early and serve as an important proxy to manage spread. Further prospective data collection with international prospective registries is needed.

FIGURES

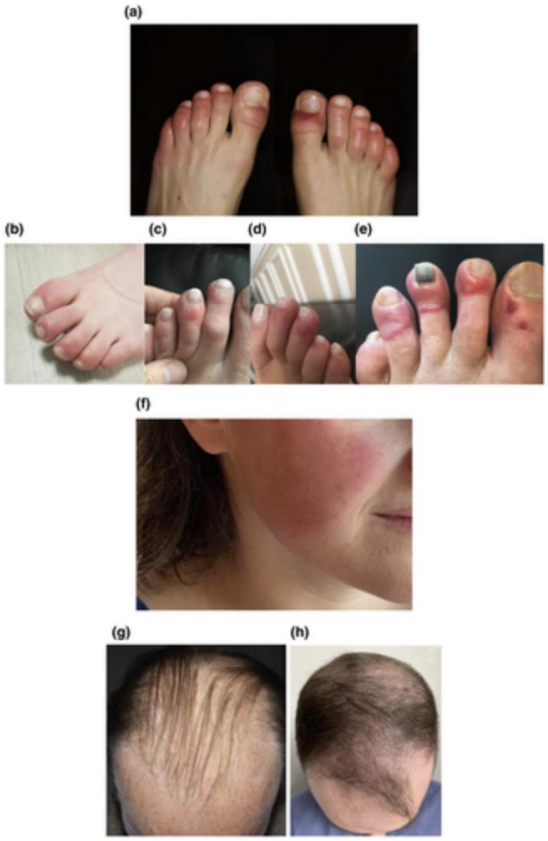


Figure 1. Dermatologic manifestations of COVID-19 and associated skin findings. (a–e) chilblains and pernio-like lesions. Credit: Syndicat National des Dermatologues Vénérologues (SNDV) Dermato-Coronavirus Group. (f) Erythematous rash. Credit: Dr. Marie Masson Regnault and Dr. Odile Debouverie. (g,h) Androgenetic alopecia (Gabrin sign). Credit: Dr. Carlos Wambier

HEMATOLOGY AND ONCOLOGY

COVID-19-INDUCED ATYPICAL PULMONARY LYMPHOCYTES

Vergé V, Soufan R.. Blood. 2020 Nov 5;136(19):2241. doi: 10.1182/blood.2020007613.
Level of Evidence: Other - Case Report

BLUF

A case report, conducted at Gustave Roussy (France), documents COVID-19-related atypical pulmonary lymphocytes in a 39-year-old after after undergoing treatment for a T-cell/histiocyte-rich large B-cell lymphoma–like transformation of nodular lymphocyte-predominant Hodgkin lymphoma. The patient was hospitalized twice for febrile aplasia with subsequent RT-PCR testing revealing the patient was positive for COVID-19 at both time points. Results from bronchoalveolar lavage and flow cytometry revealed atypical reactive lymphocytes (more details illustrated below; Figure 1), demonstrating an aberrant immune process that may be linked to COVID-19 disease processes.

SUMMARY

Additional details of this case are illustrated below:

The patient was hospitalized for fever and aplasia after his 4th treatment cycle for Hodgkin Lymphoma. He subsequently tested positive for COVID-19 via RT-PCR with no presence of severe pulmonary symptoms. CT imaging revealed moderate pulmonary injury. The presence of lymphoma from axillary lymph node biopsy lead to starting a second-line treatment regimen for his lymphoma. Eleven days after the first cycle of this treatment, the patient was hospitalized a second time for febrile aplasia. Bronchoalveolar lavage revealed 160 × 103 cells/mL, 3% neutrophils, 2% eosinophils, 25% lymphocytes, 20%

macrophages, and 50% of larger lymphoid cells. Flow cytometry analysis showed the absence of B CD19- and/or CD20-positive lymphoid cells and 96% of CD3-positive lymphocytes, of which 71% were CD8-positive lymphocytes.

FIGURES

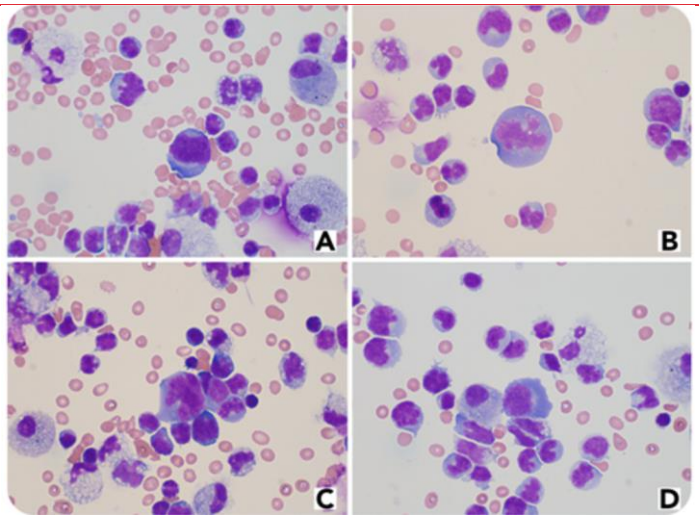


Figure 1. Panels A-D, original magnification ×1000, May-Grünwald-Giemsa stain

OBGYN

RAPID IMPROVEMENT OF A CRITICALLY ILL OBSTETRIC PATIENT WITH SARS-COV-2 INFECTION AFTER ADMINISTRATION OF CONVALESCENT PLASMA

Magallanes-Garza GI, Valdez-Alatorre C, Dávila-González D, Martínez-Reséndez MF, Sánchez-Salazar SS, Castilleja-Leal F, Cardona-Huerta S.. Int J Gynaecol Obstet. 2020 Nov 5. doi: 10.1002/ijgo.13467. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

A case report conducted in Monterrey, Mexico describes a 33-year-old pregnant female in her third trimester with COVID-19 symptoms (fever, weakness, muscle aches, dry cough, loss of smell, and diarrhea) who presented to the hospital on June 21, 2020 with respiratory distress and O2 saturation <90% on room air. Initial therapy of antibiotics and steroids were administered without improvement of symptoms; however, the patient improved clinically with two doses of convalescent plasma. Repeat chest X-ray showed an absence of bilateral interstitial infiltrates and serologic testing detected anti-SARS-CoV-2 IgG (Figure 1). These findings suggest the use of convalescent plasma as a potentially safe alternative treatment for criti cally ill COVID-19 pregnant patients.

ABSTRACT

SARS-CoV-2 (COVID-19) infection in pregnancy increases the likelihood of hospitalization, admission to intensive care, and receipt of mechanical ventilation as compared with nonpregnancy [1]. On June, 21, 2020, a 33-year-old pregnant woman (274 gestational weeks) with SARS-CoV-2 infection presented to Hospital San Jose Tec Salud, Monterrey, Mexico, with respiratory distress and oxygen saturation below 90% (room oxygen). She had developed fever, asthenia, adynamia, myalgia, dry cough, anosmia, and diarrhea 7 days prior to admission. Her past medical history was significant for smoking, which she had stopped at 4 gestational weeks.

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Delivery
Treatments															
Enoxaparin (60 mg)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Azithromycin (250 mg)	X	X	X	X	X										
Ceftaroline (600 mg)	X	X	X	X	X	X	X	X	X	X					
Lopinavir/Ritonavir (200 mg/50 mg) C/12 hrs	X	X	X	X	X	X									
Epinephrine			X	X											
Methylprednisolone (40 mg)	X	X			X	X	X	X	X	X	X	X	X	X	
Convalecent Plasma				Dose 1	Dose 2										
Prednisone			X	X											
Laboratory results															
pH	7.38		7.33	7.43	7.44	7.54	7.52	7.43	7.46	7.43	7.4		7.37	7.37	
PaO2 (mmHg)	53		17	105	77	164	92	46	40	48	44		32	32	
PCO2 (mmHg)	34		45	26	39	35	41	42	41	42	49		49	49	
HCO3 (mEq/L)	20		20	17.3	26	29	29	27	29	27	30		28	28	
Lac (mmol/L)	0.5		2.2	0.6	0.6	2.7	1.2	2.2	0.6	1.2	0.9		1.3	1.3	
SARS-CoV2 RT-PCR Viral Load			512 367 copies									Not Detected			
SARS-Cov2 IgG			Negative											Positive	Positive
RCTG	Reassuring	Reassuring	Non reassuring	Non reassuring	Non reassuring	Non reassuring	Reassuring	Reassuring	Reassuring	Reassuring	Reassuring	Reassuring	Reassuring	Reassuring	

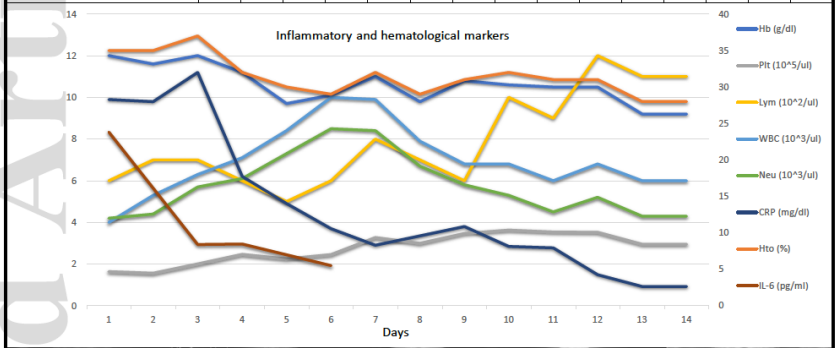


Figure 1. Critically ill obstetric patient with SARS-CoV-2 infection evolution after administration of convalescent plasma.

ASSESSING THE POTENTIAL ASSOCIATION BETWEEN SARS-COV-2 RNA LOAD IN THE RESPIRATORY TRACT AND COVID-19 MORTALITY

Albert E, Bracho MA, Serrano A, Ferrer B, González-Candelas F, Navarro D.. J Med Virol. 2020 Nov 2. doi: 10.1002/jmv.26644. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

This letter to the editor by microbiologists from various institutions in Valencia, Spain assessed use of mRNA from housekeeping β-glucuronidase, E, and N genes rather than SARS-CoV-2 RNA levels alone to quantify viral load in COVID-19 patients (n=40). After normalizing RNA values to specimen cellularity, authors found a significant difference between corrected and uncorrected RNA loads at higher viral loads (Figure 1). Given that high viral load may be associated with poorer outcomes, authors urge for use of more rigorous quantification methods to better estimate COVID-19 disease progression such as viral RNA normalization to specimen cellularity and area under the curve calculations as opposed to single data points.

ABSTRACT

The magnitude of nasopharyngeal (NP) SARS-CoV-2 load either at hospital admission or during the course of hospitalization has been directly associated with mortality of COVID-19 patients.

FIGURES

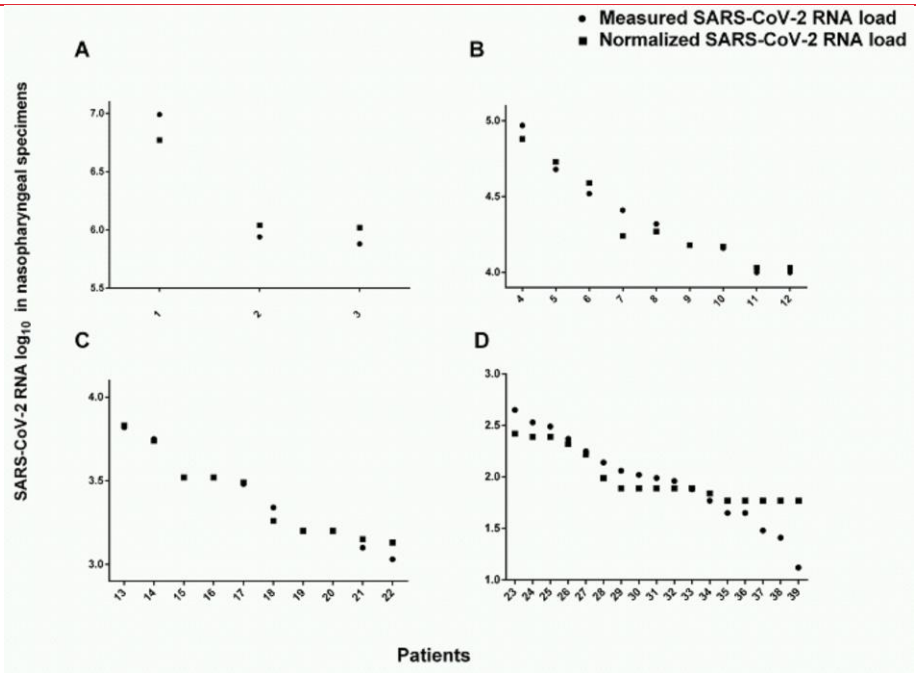


Figure 1. Raw and normalized SARS-CoV-2 RNA loads in 39 hospitalized COVID-19 patients with detectable levels of SARS-CoV-2 RNA and β-glucuronidase mRNA in nasopharyngeal specimens. Raw SARS-CoV-2 RNA load >105 log10 copies/mL (A), load >104 log10 copies/mL (B), load >103 log10 copies/mL (C) and < 103 log10 copies/mL (D). Amplification of β-glucuronidase mRNA gene was not possible in nasopharyngeal exudate from one patient.

AT WHAT TIMES DURING INFECTION IS SARS-COV-2 DETECTABLE AND NO LONGER DETECTABLE USING RT-PCR-BASED TESTS? A SYSTEMATIC REVIEW OF INDIVIDUAL PARTICIPANT DATA

Mallett S, Allen AJ, Graziadio S, Taylor SA, Sakai NS, Green K, Suklan J, Hyde C, Shinkins B, Zhelev Z, Peters J, Turner PJ, Roberts NW, di Ruffano LF, Wolff R, Whiting P, Winter A, Bhatnagar G, Nicholson BD, Halligan S.. BMC Med. 2020 Nov 4;18(1):346. doi: 10.1186/s12916-020-01810-8.

Level of Evidence: 2 - Systematic review of cross sectional studies with consistently applied reference standard and blinding

BLUF

An individual participant data systematic review of 32 longitudinal studies (Figure 1) conducted in the United Kingdom examines the accuracy, temporal sensitivity, and optimal sampling sites and strategies for SARS-CoV-2. The authors reported on a total of 1023 COVID-19 RT-PCR confirmed participants and 1619 test results for 11 different sampling sites at various times during SARS-CoV-2 infection. They found that the highest rate of virus detection was within 4 days of symptom onset (89%), which fell to 54% between 10 and 14 days. The authors discuss that the accuracy of RT-PCR is limited, early testing minimizes false negative results, and lower respiratory tract or fecal testing may be preferred sampling sites when testing more than a few days post symptom onset.

SUMMARY

PubMed, LitCOVID, medRxiv, and COVID-19 Living Evidence Database was consulted to obtain studies for this systematic review. QUADAS-2 adaptation was utilized to assess risk of bias. It was determined that the accuracy of RT-PCR is limited to factors including sampling sites, methods, and the need to test as soon as possible post symptom onset in order to detect the virus. Testing at later times seemed to result in a higher percentage of false negative COVID-19 test results particularly at upper respiratory tract sampling sites. As such, it might be beneficial to utilize other sites such as the lower respiratory tracts or fecal samples after 10 days post symptoms.

ABSTRACT

BACKGROUND: Tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral ribonucleic acid (RNA) using reverse transcription polymerase chain reaction (RT-PCR) are pivotal to detecting current coronavirus disease (COVID-19) and duration of detectable virus indicating potential for infectivity. METHODS: We conducted an individual participant data (IPD) systematic review of longitudinal studies of RT-PCR test results in symptomatic SARS-CoV-2. We searched PubMed, LitCOVID, medRxiv, and COVID-19 Living Evidence databases. We assessed risk of bias using a QUADAS-2 adaptation. Outcomes were the percentage of positive test results by time and the duration of detectable virus, by anatomical sampling sites. RESULTS: Of 5078 studies screened, we included 32 studies with 1023 SARS-CoV-2 infected participants and 1619 test results, from - 6 to 66 days post-symptom onset and hospitalisation. The highest percentage virus detection was from nasopharyngeal sampling between 0 and 4 days post-symptom onset at 89% (95% confidence interval (CI) 83 to 93) dropping to 54% (95% CI 47 to 61) after 10 to 14 days. On average, duration of detectable virus was longer with lower respiratory tract (LRT) sampling than upper respiratory tract (URT). Duration of faecal and respiratory tract virus detection varied greatly within individual participants. In some participants, virus was still detectable at 46 days post-symptom onset. CONCLUSIONS: RT-PCR misses detection of people with SARS-CoV-2 infection; early sampling minimises false negative diagnoses. Beyond 10 days post-symptom onset, lower RT or faecal testing may be preferred sampling sites. The included studies are open to substantial risk of bias, so the positivity rates are probably overestimated.

FIGURES

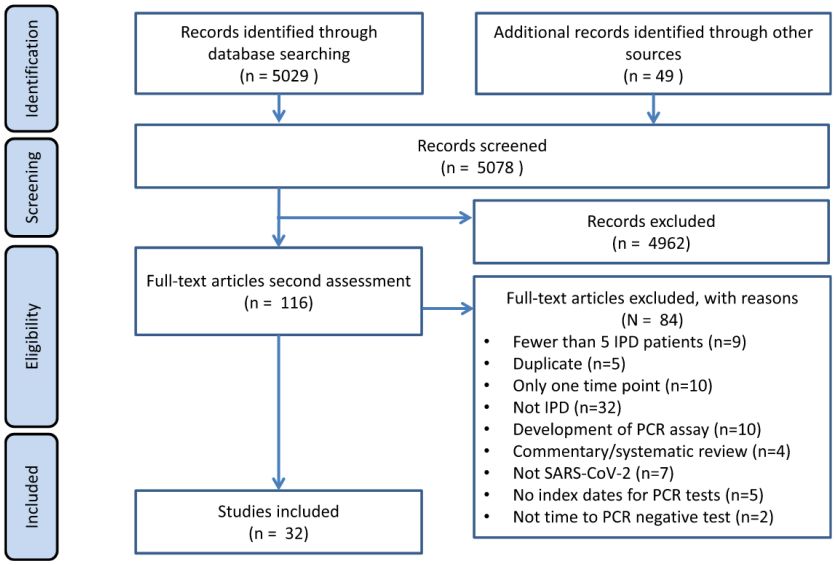


Figure 1. PRISMA flowchart.

DEVELOPMENTS IN DIAGNOSTICS

CLINICAL IMPACT OF MONOCYTE DISTRIBUTION WIDTH AND NEUTROPHIL-TO-LYMPHOCYTE RATIO FOR DISTINGUISHING COVID-19 AND INFLUENZA FROM OTHER UPPER RESPIRATORY TRACT INFECTIONS: A PILOT STUDY

Lin HA, Lin SF, Chang HW, Lee YJ, Chen RJ, Hou SK.. PLoS One. 2020 Nov 2;15(11):e0241262. doi: 10.1371/journal.pone.0241262. eCollection 2020.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

A retrospective cohort study, conducted at Taipei Medical University Hospital (Taiwan), analyzed potential biomarkers of SARS-CoV-2 infection in 174 patients (9 with nasal swab RT-PCR confirmed COVID-19, 24 with influenza confirmed via rapid-test, and 141 determined to have common URIs) who visited the outdoor epidemic prevention screening station for respiratory infections from February 19 to April 30 2020. The authors found that monocyte distribution width (MDW) greater than or equal to 20 (OR: 8.39, p = 0.0110) and neutrophil-to-lymphocyte ratio greater than 3.2 (OR: 4.23, p = 0.0494) could independently distinguish COVID-19 from common upper respiratory infections. Further, combing these two markers shows promise for efficient identification of both COVID-19 and influenza infection (Table 3 and Figure 1). For clinicians uncertain about diagnosing COVID-19 or those doubting a test result, this information may become a useful tool in identifying COVID-19.

ABSTRACT

The coronavirus disease 2019 (COVID-19) has become a pandemic. Rapidly distinguishing COVID-19 from other respiratory infections is a challenge for first-line health care providers. This retrospective study was conducted at the Taipei Medical University Hospital, Taiwan. Patients who visited the outdoor epidemic prevention screening station for respiratory infecti on from February 19 to April 30, 2020, were evaluated for blood biomarkers to distinguish COVID-19 from other respiratory infections. Monocyte distribution width (MDW) >= 20 (odds ratio [OR]: 8.39, p = 0.0110, area under curve [AUC]: 0.703) and neutrophil-to-lymphocyte ratio (NLR) < 3.2 (OR: 4.23, p = 0.0494, AUC: 0.673) could independently distinguish COVID-19 from common upper respiratory tract infections (URIs). Combining MDW >= 20 and NLR < 3.2 was more efficient in identifying COVID-19 (AUC: 0.840). Moreover, MDW >= 20 and NLR > 5 effectively identified influenza infection (AUC: 0.7055). Thus, MDW and NLR can distinguish COVID-19 from influenza and URIs.

FIGURES

	Odds Ratio (95% CI)	pe	Area Under Curve
COVID-19 group			
Univariate			
MDW ≥ 20	8.39 (1.67-∞)	0.0110	0.703 (0.665–0.741)
NLR < 3.2	4.23 (1.07–20.63)	0.0394	0.673 (0.501–0.840)
MDW ≥ 20 + NLR < 3.2	-	-	0.840 (0.739–0.942)
Influenza group			
MDW ≥ 20	3.59 (1.30–9.92)	0.0140	0.628 (0.547–0.708)
NLR ≥ 5	4.05 (1.68–9.77)	0.0018	0.666 (0.574–0.757)
MDW ≥ 20 + NLR ≥ 5	-	-	0.706 (0.622–0.789)

BMI, body mass index; CI, confidence interval; COVID, coronavirus disease; CRP, C-reactive protein; ED, emergency department; MDW, monocyte distribution width; NLR, neutrophil-to-lymphocyte ratio.

Table 3. Diagnostics of blood parameters.

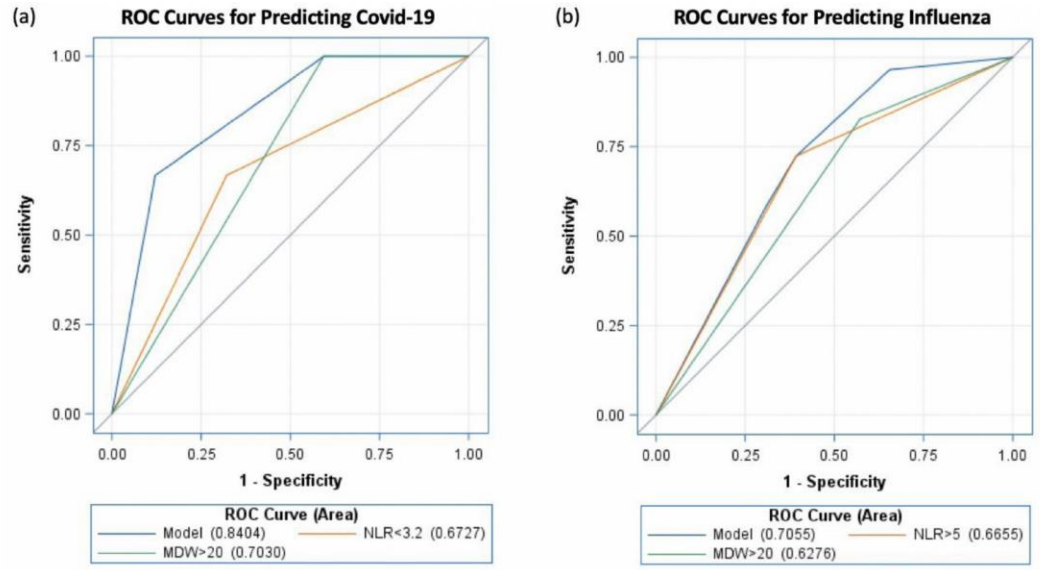


Figure 1

DEVELOPMENTS IN TREATMENTS

A STRATEGY TO TREAT COVID-19 DISEASE WITH TARGETED DELIVERY OF INHALABLE LIPOSOMAL HYDROXYCHLOROQUINE: A PRE-CLINICAL PHARMACOKINETIC STUDY

Tai TT, Wu TJ, Wu HD, Tsai YC, Wang HT, Wang AM, Shih SF, Chen YC.. Clin Transl Sci. 2020 Nov 2. doi: 10.1111/cts.12923. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Product developers from Taiwan Liposome Company, Ltd. administered liposomal hydroxychloroquine (HCQ) to rats and found increased concentration (30-fold) and longer half-life (2.5-fold) in the lungs and lower concentrations in the heart, as compared to intravenously administered HCQ (Table 1, Figure 1). Authors hypothesize that clinical trial data indicating HCQ has no benefit for treatment of COVID-19 may be partially due to insufficient drug delivery to the respiratory tract, suggesting their inhaled product may improve efficacy of HCQ for COVID-19 treatment.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly identified pathogen causing the coronavirus disease 2019 (COVID-19) pandemic. Hydroxychloroquine (HCQ), an antimalarial and anti-inflammatory drug, has been shown to inhibit SARS-CoV-2 infection in vitro and tested in clinical studies. However, achievement of lung concentrations predicted to have in vivo antiviral efficacy might not be possible with the currently proposed oral dosing regimens. Further, high cumulative doses of HCQ raise concerns of systemic toxicity, including cardiotoxicity. Here, we describe a pre-clinical study to investigate the pharmacokinetics of a novel formulation of liposomal HCQ administered by intratracheal (IT) instillation in Sprague-Dawley (SD) rats. Compared to unformulated HCQ administered intravenously (IV), liposomal HCQ showed higher (~30-fold) lung exposure, longer (~2.5-fold) half-life in lung, but lower blood exposure with ~20% of Cmax and 74% of AUC0-72 and lower heart exposure with 23% of Cmax and 58% of AUC0-24 (normalized for dose). Similar results were observed relative to IT administration of unformulated HCQ. These pharmacokinetics results in an animal model demonstrated the proof of concept that inhalable liposomal HCQ may provide clinical benefit and serve as a potential treatment for COVID-19.

FIGURES

T_{max} (h)	0.25	0.25	24	-	-
C_{max} (μg/g)	4.5	3.8	0.5	0.23	0.27
AUC_{0-24}(h*μg/g)	42.6	41.5	11.9	0.58	0.60
AUC_{0-72}(h*μg/g)	67.2	64.2	32.1	0.99	1.04

Table 1. Pharmacokinetic parameters of hydroxychloroquine in lung, blood, and heart after a single administration of liposomal hydroxychloroquine or hydroxychloroquine in rats.

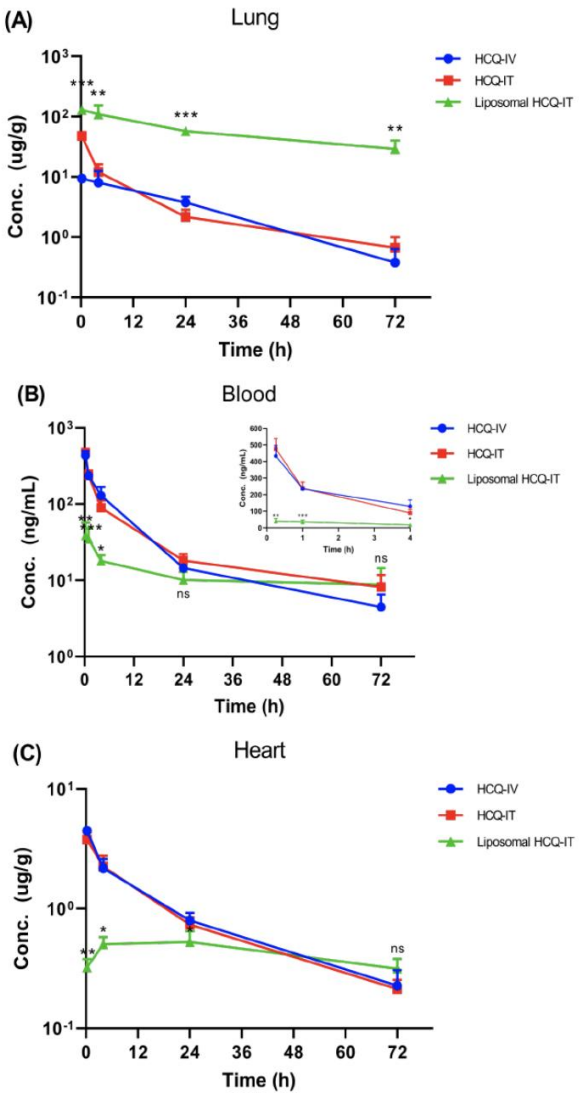


Figure 1. Mean concentration (±SD) - time profiles of HCQ in rat lung (A), blood (B), and heart (C) after a single administration of HCQ through intravenous (IV) or intratracheal (IT) delivery or liposomal HCQ through IT delivery. The inset graph (B) showed mean concentration-time profiles of HCQ in 0.25 to 4 hours. *P < 0.05; **P < 0.01; ***P < 0.001; nsP > 0.05 compared to HCQ-IV.

TOWARDS CONSENSUS ON CORRECT INTERPRETATION OF PROTEIN BINDING IN PLASMA AND OTHER BIOLOGICAL MATRICES FOR COVID-19 THERAPEUTIC DEVELOPMENT

Boffito M, Back DJ, Flexner C, Sjö P, Blaschke TF, Horby PW, Cattaneo D, Acosta EP, Anderson P, Owen A.. Clin Pharmacol Ther. 2020 Oct 28. doi: 10.1002/cpt.2099. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A multidisciplinary group of drug development experts from the UK, USA, Switzerland and Italy reviewed literature on effects of antiviral protein binding on in-vivo drug activity. By assessing data from antiretroviral drug development, they found that unbound plasma concentrations could not be compared to in-vitro activity and researchers must instead compare in-vivo and in-vitro free drug concentrations. Citing recent studies investigating remdesivir and lopinavir as possible agents against SARS-CoV-2 which do not account for protein binding (Figure 1), authors argue correct interpretation of protein binding data is critical for identification of the most promising drug candidates (see summary).

SUMMARY

Authors review the principles of free drug theory, which emphasizes that unbound drug fraction exerts the desired pharmacological effect. Based on this theory, they argue unbound plasma concentration and in-vitro activity cannot be compared due to the following:
1. In-vitro protein binding is rarely zero as it binds culture plastics and media.
2. Most in-vitro studies of drugs for SARS-CoV-2 have included protein in culture media.
3. Small amounts of serum in culture can bind large amounts of drug.
4. Protein binding varies between individual proteins.

Using this framework, pharmacokinetic data of SARS-CoV-2 antivirals were analyzed. While lopinavir demonstrated favorable in-vitro unbound EC50 assuming 93.7% protein binding in 5% free bovine serum (FBS) media (rising to 96.1% in 10% FBS), its showed less favorable anti-SARS-CoV-2 activity in plasma, epithelial fluid, and cerebrospinal fluid (Figure 1A). Similarly, the authors critique the idea that remdesivir's pharmacokinetic profile is accurately represented by its free drug fraction of 12.1% since Remdesivir requires intracellular activation.

Authors use studies of lopinavir's activity against HIV as an example of correct interpretation, where protein adjusted EC50, EC90 or EC95 measurements (inhibitory quotient) both in vitro and in vivo avoided misinterpretation of its potency and efficacy during development. Such methodologies are not yet adapted for SARS-CoV-2 drugs.

ABSTRACT

The urgent global public health need presented by SARS-CoV-2 has brought scientists from diverse backgrounds together in an unprecedented international effort to rapidly identify interventions. There is a pressing need to apply clinical pharmacology principles and this has already been recognised by several other groups. However, one area that warrants additional specific consideration relates to plasma and tissue protein binding that broadly influences pharmacokinetics and pharmacodynamics. The principles of free drug theory have been forged and applied across drug development but are not currently being routinely applied for SARS-CoV-2 antiviral drugs. Consideration of protein binding is of critical importance to candidate selection but requires correct interpretation, in a drug-specific manner, to avoid either under- or over-interpretation of its consequences. This manuscript represents a consensus from international researchers seeking to apply historical knowledge, which has underpinned highly successful antiviral drug development for other viruses such as HIV and HCV for decades.

FIGURES

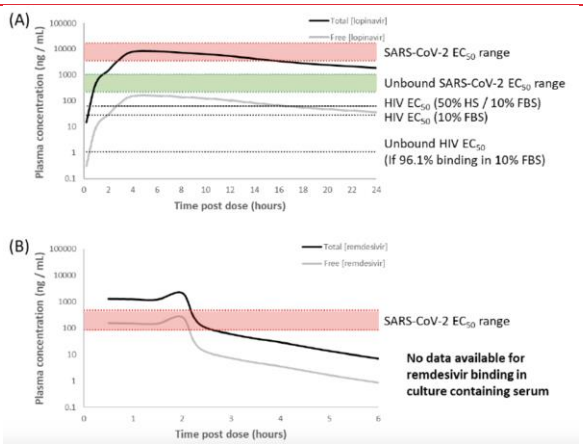


Figure 1: "Comparison of human pharmacokinetics with in vitro derived anti-SARS-CoV-2 activities for single dose lopinavir (A) and remdesivir (B). For illustrative purposes, single dose data are presented because the need for rapid onset of anti-SARS-CoV-2 activity may be needed and drugs like lopinavir take time to reach steady-state pharmacokinetics. For remdesivir it should be noted that while this drug is given every 24h it is cleared rapidly from the plasma and the published study only monitored plasma concentrations for 6h. Solid black lines represent published mean plasma concentrations whereas solid grey lines represent unbound drug concentrations derived from knowledge of the human plasma protein binding. The range of anti-SARS-CoV-2 activities reported as EC50s are shown by the shaded red areas. For lopinavir, where protein binding has been assessed in culture media containing serum, the derived unbound EC50 is shown by the green shaded area. The HIV EC50 values in the presence of human serum (HS) and/or foetal bovine serum (FBS) are also shown, along with an EC50 corrected for the expected free fraction in culture media. Further information and references to the source data are present in the main text".

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CONTRIBUTORS

Ashley Kern
Danika Scott
Diep Nguyen
Ellen Reidy
Eva Shelton
Krithika Kumarasan
Sarala Kal
Sokena Zaidi
Tyler Gallagher
Veronica Graham
Zainab Awan

EDITORS

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