The Daily COVID-19 Literature Surveillance Summary

July 28, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Climate

- A cross-sectional study surveying 128 researchers, clinicians, and academic personnel showed that 63.3% found social media to be the most important source of information while 67.2% found it to be misinformation. A majority of the respondents supported mandatory peer review and organization of a trustworthy COVID-19 database to combat potentially deadly misinformation.
- A systematic review and meta-analysis evaluating 14 qualifying studies claims to have found that COVID-19 patients with a BMI exceeding 25 kg/m^2 had worse prognosis in all age groups, especially the elderly population, suggesting that this population should be "given special attention to reduce morbidity and mortality associated with COVID-19 infection" to limit their moderate-to-high complication risk.
- A survey study conducted in London, England by Imperial College London found among 167 St. Mary's Hospital healthcare workers, 44% attested to self-quarantining during the past 4 months due to symptoms consistent with COVID-19 and 54% of symptomatic workers tested RT-PCR positive. Since previous infection and positive antibody tests do not necessarily indicate immunity, this study suggests a possible massive shortage of healthcare workers during the anticipated second wave of COVID-19 in November 2020 and calls for the creation of safety guidelines in order to prevent such a shortage.

Transmission & Prevention

- A retrospective study of presumed COVID-19 negative patients (n=103) conducted at four inpatient rehabilitation facilities (IRF) in New Jersey, USA found 6.8% of asymptomatic participants (n=7) tested positive for SARS-CoV-2 on admission (71% [n=5] of this group developed symptoms in 2-5 days), and overall 11.6% (n=12) tested positive within 14 days of admission. Authors suggest SARS-CoV-2 testing on admission to post-acute care settings is worthwhile for appropriate infection control regardless of symptom presence.

Management

- A systematic review of 46 case series and case studies with radiologic findings from 923 symptomatic and asymptomatic pediatric patients diagnosed with COVID-19 by RT-PCR found that:
    1. Chest CT was the most common imagining modality used
    2. Chest CT was able to detect radiological evidence of COVID-19 in 19% of asymptomatic patients.
    3. The most common abnormality seen on scans was ground-glass opacities (39%), and
    4. The most common location of lesions was the lower lobe of the right lung (40%).

  These findings emphasize the need for further investigation of chest CT as a screening tool for COVID-19 in children and for study of other imaging alternatives like lung ultrasound to minimize exposure to radiation.
- A case report conducted at the Department of Internal Medicine at Michigan State University highlights the case of a 29-year-old male who died from COVID-19 acute respiratory distress syndrome (CARDS) and ventilator-induced lung injury (VILI), displaying both phenotypes of CARDS, the milder type L form and the more severe type H form (which resembles full-blown ARDS). The patient's cause of death was a tension pneumothorax from VILI associated with type H CARDS. This case suggests the need for a better understanding of CARDS and transition to type H in order to prevent patients' entry to the VILI vortex and potential death from COVID-19.

R&D: Diagnosis & Treatments

- The Brighton Collaboration developed a standardized template for the assessment of nucleic acid vaccines (NAVs) to answer questions related to safety and benefit-risk issues as well as improve communication and public acceptance of NAVs, particularly in the wake of recent COVID-19 vaccine development efforts
- A study using paper spray mass spectroscopy (PS-MS) to analyze changes in lipid metabolite production by cells infected with SARS-CoV-2 from 30 samples (10 COVID-19 positive, 10 COVID-19 negative, and 10 blind test samples) found significant differences in lipid metabolites between the COVID-19 positive and negative test samples and determined that PS-MS was able to accurately identify 93.3% of these samples when compared to RT-PCR results. These findings demonstrate that PS-MS may aid the development of a new rapid COVID-19 test, although further experimentation is needed.

TABLE OF CONTENTS

CLIMATE

INFORMATION AND MISINFORMATION ON COVID-19: A CROSS-SECTIONAL SURVEY STUDY

Gupta L, Gasparyan AY, Misra DP, Agarwal V, Zimba O, Yessirkepov M.. J Korean Med Sci. 2020 Jul 13;35(27):e256. doi: 10.3346/jkms.2020.35.e256.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

A cross-sectional study surveyed researchers, clinicians, and academic personnel to investigate trustworthy information and misinformation of COVID-19 (Figure 1). Among 128 respondents, 63.3% found social media to be the most important source of information while 67.2% found it to be misinformation (Table 2). The authors report a majority of the respondents support mandatory peer review and organization of a trustworthy COVID-19 database to combat potentially deadly misinformation.

ABSTRACT

BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has led to a large volume of publications, a barrage of non-reviewed preprints on various professional repositories and a slew of retractions in a short amount of time. METHODS: We conducted an e-survey using a cloud-based website to gauge the potential sources of trustworthy information and misinformation and analyzed researchers', clinicians', and academics' attitude toward unpublished items, and pre- and post-publication quality checks in this challenging time. RESULTS: Among 128 respondents (mean age, 43.2 years; M:F, 1.1:1), 60 (46.9%) were scholarly journal editors and editorial board members. Social media channels were distinguished as the most important sources of information as well as misinformation (81 [63.3%] and 86 [67.2%]). Nearly two in five (62, 48.4%) respondents blamed reviewers, editors, and misinterpretation by readers as additional contributors alongside authors for misinformation. A higher risk of plagiarism was perceived by the majority (70, 58.6%), especially plagiarism of ideas (64.1%) followed by inappropriate paraphrasing (54.7%). Opinion was divided on the utility of preprints for changing practice and changing retraction rates during the pandemic period, and higher rejections were not supported by most (76.6%) while the importance of peer review was agreed upon by a majority (80, 62.5%). More stringent screening by journal editors (61.7%), and facilitating open access plagiarism software (59.4%), including Artificial Intelligence (AI)-based algorithms (43.8%) were among the suggested solutions. Most (74.2%) supported the need to launch a specialist bibliographic database for COVID-19, with information indexed (62.3%), available as open-access (82.8%), after expanding search terms (52.3%) and following due verification by academics (66.4%), and journal editors (52.3%). CONCLUSION: While identifying social media as a potential source of misinformation on COVID-19, and a perceived high risk of plagiarism, more stringent peer review and skilled post-publication promotion are advisable. Journal editors should play a more active role in streamlining publication and promotion of trustworthy information on COVID-19.

Table 2. Analysis of survey results on COVID-19 information and misinformation

Questions	Respondents (n = 128)
On which resources/platforms have you found information on COVID-19?	
TV	58 (41.4)
Digital libraries	12 (51.6)
Publishers' repositories	13 (46.9)
Information Aggregators	21 (22.7)
Social media channels	86 (63.3)
Other	5 (6.3)
On which resources/platforms have you found misinformation on COVID-19?	
TV	58 (45.3)
Digital libraries	12 (9.4)
Publishers' repositories	13 (10.2)
Information aggregators	21 (16.4)
Social media channels	86 (67.2)
Other	5 (3.9)
All of these	34 (26.6)
Who is responsible for misinformation in scholarly journals during the pandemic?	
Authors	83 (64.8)
Reviewers	61 (47.7)
Editors	62 (48.4)
Commercial editing agencies involved in editing and submitting manuscripts	62 (48.4)
Social media accounts of scholarly journals	54 (42.2)
Misinterpretation by readers	61 (47.7)
No one	8 (6.3)
Other	3 (2.3)
Can we rely on non-reviewed (unpublished) items posted on preprints (e.g. medRxiv, bioRxiv) and amend our preventative and curative approaches?	
Yes	3 (2.3)
No	65 (50.8)
Sometimes	38 (29.7)
I am not sure	18 (14.1)
What are pre-prints?	4 (3.1)
In changing times like this, where rapid dissemination of scientific information is vital, what are your thoughts on peer review at scholarly journals?	
It is mandatory for quality control	80 (62.5)
Causes unnecessary delay in the publication of potentially valuable data	8 (6.3)
Somewhat helpful-should be at the discretion of the editor-in-chief	25 (19.5)
I am not sure	15 (11.7)
Do you think plagiarism may become more rampant in the current pandemic, with the publish or perish dictum?	
Yes	75 (58.6)
No	11 (8.6)
I am not sure	42 (32.8)
What kind of plagiarism do you expect the most in these times?	
Self-plagiarism	36 (28.1)
Paraphrasing plagiarism	70 (54.7)
Verbatim plagiarism	29 (22.7)
Graphics copying	45 (35.2)
Plagiarism of ideas	82 (64.1)
Mosaic plagiarism	28 (21.9)
Incorrect citation	46 (35.9)
I am not aware of these	3 (2.3)
I am not sure	15 (11.7)
None	1 (0.8)
Who do you feel is more likely to plagiarize?	
Prolific researchers	21 (16.4)
Novice researchers	56 (43.8)
Agents of commercial editing companies	66 (51.6)
Everyone	47 (36.7)
No-one	4 (3.1)

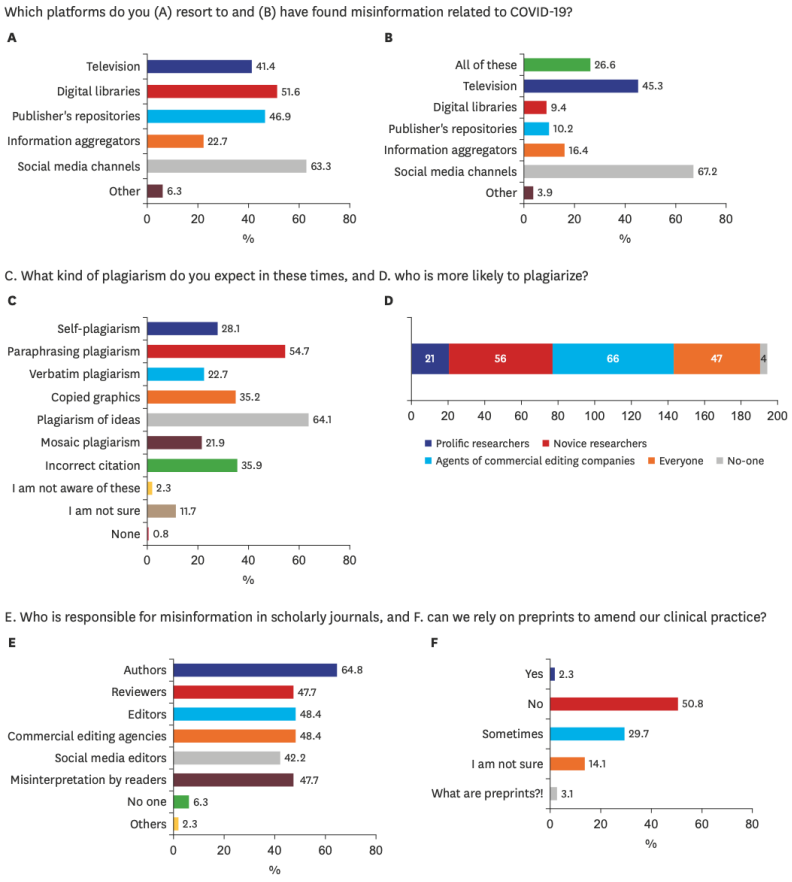


Fig. 1. Perception of sources of misinformation, plagiarism, and reliability of preprints by physicians and academics.
COVID-19 = coronavirus disease 2019.

HIGHER BODY MASS INDEX IS AN IMPORTANT RISK FACTOR IN COVID-19 PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Malik VS, Ravindra K, Attri SV, Bhadada SK, Singh M.. Environ Sci Pollut Res Int. 2020 Jul 24. doi: 10.1007/s11356-020-10132-4. Online ahead of print.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A systematic review and meta-analysis evaluating 14 qualifying studies (Figure 1) claims to have found that COVID-19 patients with a BMI exceeding 25 kg/m^2 had worse prognosis in all age groups (53.45% heterogeneity; Figure 2, Table 3), especially the elderly population, suggesting that this population should be "given special attention to reduce morbidity and mortality associated with COVID-19 infection" to limit their moderate-to-high complication risk.

ABSTRACT

Globally, both obesity and underweight are severe health risks for various diseases. The current study systematically examined the emerging evidence to identify an association between body mass index (BMI) and COVID-19 disease outcome. Online literature databases (e.g., Google Scholar, PubMed, MEDLINE, EMBASE, Scopus, Medrixv and BioRixv) were screened following standard search strategy having the appropriate keyword such as "Obesity", "Underweight", "BMI", "Body Mass Index", "2019-nCov", "COVID-19, "novel coronavirus", "coronavirus disease". Studies published till 20th April 2020 were included without language restriction. These studies include case reports, case series, cohort, and any other which reported BMI, overweight/obesity or underweight, and its complication with COVID-19 disease. This study observed COVID-19 infection among BMI < 25 kg/m2 with prevalence of 0.60 (95%CI: 0.34-0.86, I2 = - 76.77) as compared to the 0.34 (95%CI: 0.23-0.44, I2 = 53.45% heterogeneity) having BMI > 25 kg/m2. The results of the current study show that BMI plays a significant role in COVID-19 severity in all age groups, especially the older individuals. A panel of doctors and nursing staff should review COVID-19 patients with higher BMI with other co-morbidities (diabetes and hypertension), and they should be given increased vigilance, priority in testing, and treatment to control the associated co-morbidities. Further, the COVID-19

patients whose illness entered 7-10 days, age > 50 years, and elevated CRP levels should be given additional medical considerations. Our finding showed that the population and patients with high BMI have moderate to high risk of medical complications with COVID-19, and hence, their health status should be monitored more frequently including monitoring of blood pressure and blood glucose.

FIGURES

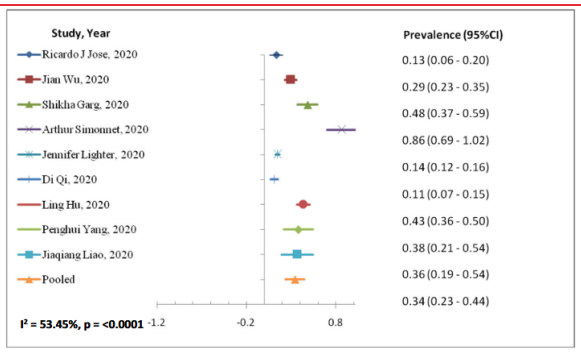


Figure 2. Forest plot of risk factor BMI > 25 kg/m2with COVID-19 patients

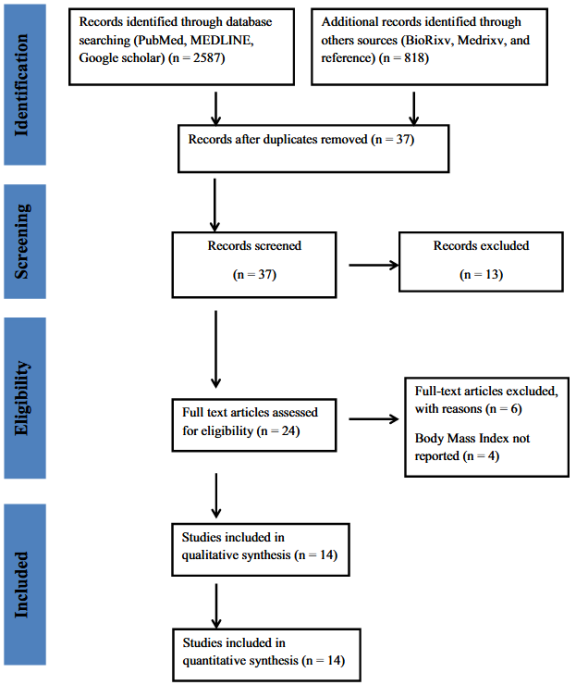


Figure 1. PRISMA chart.

Risk factor	Variable	Number of studies	Size (*n*)	Prevalence (95%CI)	I^2
Body mass index					
< 25 kg/m^2	Continuous	6	769	0.60 (0.34–0.86)	0% (– 76.77)
> 25 kg/m^2	Continuous	9	689	0.34 (0.23–0.44)	53.45%

Table 3. The meta-analysis of body mass index for COVID-19 patients.

THE CONSEQUENCES OF THE COVID-19 PANDEMIC ON NON-COVID-19 CLINICAL TRIALS

Bagiella E, Bhatt DL, Gaudino M.. J Am Coll Cardiol. 2020 Jul 21;76(3):342-345. doi: 10.1016/j.jacc.2020.05.041. Epub 2020 May 26.
Level of Evidence: Other - Expert Opinion

BLUF

Public health experts reported a shift in priority of clinical trials which favors COVID-19 based research while non-COVID-19 studies are experiencing issues that may affect the validity and outcome of the study (see below) and believe these issues will persist throughout the duration of the pandemic.
- Social distancing policies interference with procedures and monitoring.
- The decrease in sample sizes could lead to a decrease in statistical power.
- Compromise validity and increased the chance of Type II error.

THE IMPACT OF THE GLOBAL COVID-19 PANDEMIC ON THE CONDUCT OF CLINICAL TRIALS. RETURN TO NORMALCY BY CONSIDERING THE PRACTICAL IMPACT OF A STRUCTURED ETHICAL ANALYSIS

Vissers MFJM, Cohen AF, van Gerven JMA, Groeneveld GJ.. Br J Clin Pharmacol. 2020 Jul 15. doi: 10.1111/bcp.14480. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Researchers in the Netherlands make a case for continuing clinical drug trials during the COVID-19 pandemic era based on autonomy, beneficence, non-maleficence, and justice commitments (see summary; Table 1). They suggest clinical trials should operate in pre-COVID standards without the need for an overcautious approach.

SUMMARY

Four moral commitments:
Autonomy
- Societal lock-down during COVID-19 has hindered the approval process for clinical trials but urgent safety measures were implemented to resolve this issue without the need for ethics/IRB approval.

Beneficence + Non-maleficence
- The risk/benefit analysis can be negatively and/or positively affected by the pandemic.
- Risks are heightened due to the risk of contracting SARS-CoV2, especially in immunocompromised populations or alter the ability of a person to fight off infection, so risk mitigation strategies need to be in place to resume clinical trials.

Justice
- Resources and PPE should be available to participants and a subjects' rights, including the right to withdraw from a trial at any time, will not change due to the pandemic.
- Guidelines should maintain a balance of caution and rationality in allowing appropriate and essential trials to be performed.

ABSTRACT

During the outbreak of the COVID-19 pandemic many clinical trials were abruptly halted. Measures to contain the pandemic are currently taking effect and societies in general and health care systems in particular are considering how to return to normalcy. This opens-up the discussion when and how clinical trials should be restarted while the COVID-19 pandemic has not yet resolved, and what should happen in case of a resurgence of the virus in the coming months. This article uses the Four Ethical Principles framework as a structured approach to come to a set of practical, ethically grounded guidelines for halting and relaunching clinical trials during the SARS-CoV-2 pandemic. The framework applied provides a structured approach for all clinical trials stakeholders and thereby prevents unclear reasoning in a complex situation. While it is essential to prevent the virus from resurging and focus on developing a COVID-19 treatment as soon as possible, it is just as important to our society that we continue developing new drugs for other conditions. In this article we argue that the situation for clinical trials is not essentially different from the pre-COVID-19 era and that an overcautious approach will have negative consequences.

TABLE 1 Ethical guidelines for continuing clinical trials during a pandemic

	Consider suspending trials when:	Consider relaunching trials when:
Autonomy	Timely autonomous decisions are not possible, eg, as a result of new information about the virus or significant changes to trial conduct	An upfront autonomous decision can be made by trial participants
Non-maleficence	The pandemic is spreading ($R \geq 1$)	The pandemic is controlled ($R < 1$)
	The risk of contracting SARS-CoV-2 in the trial is elevated compared to the background risk for demographically comparable nontrial participants	Risk mitigation strategies have been implemented that reduce the risk of contracting SARS-CoV-2 to the same or less than the background risk for demographically comparable nontrial participants and without causing undue burden for trial participants
	The trial intervention could increase the risk of contracting SARS-CoV-2 or worsen COVID-19 symptoms or outcomes	The trial intervention is unlikely to increase the risk of contracting SARS-CoV-2 or worsen COVID-19 symptoms or outcomes, or the trial beneficence continuous to outweighs these risks, such as for life-threatening conditions
Distributive justice	The trial negatively impacts essential care by using up scarce resources	Adequate resources are available for elective healthcare and clinical trials
Legal justice	Trial conduct conflicts with government restrictions to contain the COVID-19 pandemic	Trial conduct has been adapted to government pandemic restrictions and/or COVID-19 related trial guidance

GLOBAL

CROSS-COUNTRY COMPARISON OF PUBLIC AWARENESS, RUMOURS, AND BEHAVIOURAL RESPONSES TO THE COVID-19 EPIDEMIC: AN INTERNET SURVEILLANCE STUDY

Hou Z, Du F, Zhou X, Jiang H, Martin S, Larson H, Lin L.. J Med Internet Res. 2020 Jul 23. doi: 10.2196/21143. Online ahead of print.

Level of Evidence: Other – Modeling

BLUF

An internet surveillance study by researchers in Shanghai, China, and London across 12 countries between December 1, 2019, and April 11, 2020, compared search data to COVID-19 incidence rates. In East Asian countries, searches for "coronavirus" and hygienic products peaked in late January and followed trends in China's cases, while these searches reached a peak in the US and Europe following the spread of the virus to Italy in late February. Several rumored treatments in China were widely searched in late January to early February, while searches of hydroxychloroquine and chloroquine peaked worldwide on March 20. The data reveals that internet searches tended to follow increases in local case increases, indicating a possible missed opportunity for civilians to protect themselves in a timely manner. Search results could inform countries' governments on public awareness and purchasing behaviors related to COVID-19, which would alert the government to ensure pertinent, accurate information is disseminated.

SUMMARY

- Countries included in the study were as follows: China, Japan, South Korea, Singapore, Italy, France, UK, Spain, US, Brazil, South Africa, India.
- In China, searches for "coronavirus" reached a small peak on December 31 following the announcement of 27 pneumonia cases of unknown cause, then stayed low until January 19, and increased dramatically following the government's confirmation of human-to-human transmission on January 20.
- In other countries, searches reached a small peak around January 20 but increased dramatically in late February, when the disease began to spread to Italy.
- Shortly after January 21, searches for, and purchases of, hygiene products in China rapidly increased. In Japan, Singapore, and South Korea, searches and purchases for masks and hand sanitizer increased around this time also; in Japan and Singapore, the peak was reached at the end of January and then searches declines with decreased cases, while in South Korea, searches continued to increase with increases in cases and peaked again in late February. Searches in these three countries tended to be correlated with changes in China's cases than local cases.
- Google trends for mask and hand sanitizer in Europe and the US began to increase when COVID-19 cases increased from 11 to 123 in Italy on February 23. Searches in India, South Africa, and Brazil did not significantly increase until early March. Google trends in the aforementioned countries tended to follow local case trends.
- Some rumored treatments that gained search popularity in China from late January to early February included radix isatidis (traditional Chinese medicine for fever), Shuanghuanglian (another Chinese medicine), and garlic (rumored to prevent the disease).
- Asian and European countries had a small peak in Google searches for chloroquine in late February. Worldwide, searches for hydroxychloroquine and choroquine peaked on March 20.

ABSTRACT

BACKGROUND: Understanding the public's behavioural response to COVID-19 and accompanied infodemic is crucial to control an epidemic. OBJECTIVE: To assess real-time public awareness and behavioural responses to the COVID-19 epidemic across 12 selected countries. METHODS: Internet surveillance was used to collect real-time data from the general public to assess public awareness and rumours (China: Baidu; Worldwide: Google Trends) and behaviour response (China: Ali; Worldwide: Google Shopping). These indices measured the daily number of searching or purchasing, and were compared with daily COVID-19 cases. The trend comparisons across selected countries were observed from December 2019 (pre-pandemic baseline) to 11 April 2020 (when the lockdown lifted in Wuhan, China). RESULTS: We identified the squandered windows of opportunity for early epidemic control in 12 countries, when public awareness was very low despite the emerging epidemic. China's epidemic and the declaration of a public health emergency of international concern did not prompt a worldwide public reaction to adopt public health protective measures; instead, most only responded to the epidemic after case counts mounted in their own country/region. Rumours and misinformation led to a surge of sales in herbal remedies in China and antimalarial drugs worldwide, and timely clarification of rumours mitigated the rush to buy unproven remedies. CONCLUSIONS: Our comparative study highlighted the urgency of international coordination to promote mutual learning on epidemic characteristics as well as effective control measures, and to trigger early and timely response in individual countries. The early release of official guidelines and timely clarification of rumours led by government are necessary to guide the public to take rational actions.

IMPACT OF COVID-19 SECOND WAVE ON HEALTHCARE WORKERS STAFFING LEVELS

Abuown A, Taube C, Koizia LJ.. Infect Control Hosp Epidemiol. 2020 Jul 22:1-5. doi: 10.1017/ice.2020.353. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A survey study conducted in London, England by Imperial College London found among 167 St. Mary's Hospital healthcare workers, 44% attested to self-quarantining during the past 4 months due to symptoms consistent with COVID-19. 54% of symptomatic workers tested RT-PCR positive. Since previous infection and positive antibody tests do not necessarily indicate immunity, this study suggests a possible massive shortage of healthcare workers during the anticipated second wave of COVID-19 in November 2020 and calls for the creation of safety guidelines in order to prevent such a shortage.

DISSEMINATED INTRAVASCULAR COAGULATION: A DEVASTATING SYSTEMIC DISORDER OF SPECIAL CONCERN WITH COVID-19

Singh P, Schwartz RA.. Dermatol Ther. 2020 Jul 23. doi: 10.1111/dth.14053. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

The authors describe how disseminated intravascular coagulation (DIC) is found in patients with severe cases of COVID-19 and presents as petechiae, cyanosis of the toes and/or fingers, dry gangrene, and skin bulla. They also explain that it is also associated with increased D-dimer levels and a hypercoagulable state. Diagnosis is primarily clinical, although a skin biopsy can confirm diagnosis with fibrin thrombi seen capillary walls. The recommend that treatment for COVID-19 patients with DIC should include standard supportive treatment, supplemented with thromboembolic prophylaxis.

ABSTRACT

Disseminated intravascular coagulation (DIC) is linked with severe COVID-19, prompting considerable concern. DIC can be a devastating systemic disorder. It is often markedly manifest on the skin as acrocyanosis or as petechiae and purpura with progression to hemorrhagic bullae. Subcutaneous hematomas may occur, as may thrombotic findings including necrosis and gangrene. This article is protected by copyright. All rights reserved.

ADULTS

ORAL MANIFESTATIONS ASSOCIATED TO COVID-19

Díaz Rodríguez M, Jimenez Romera A, Villarroel M.. Oral Dis. 2020 Jul 22. doi: 10.1111/odi.13555. Online ahead of print.
Level of Evidence: Other - Case report

BLUF

Authors within the field of dentistry present 3 cases (summarized below) involving COVID-19 patients who developed oral manifestations such as dry mouth, aphthous-like lesions, pseudomembranous candidiasis, angular cheilitis, and commissural cheilitis. Although a cause-effect relationship has not been identified with COVID-19 and oral symptoms, the authors propose that these oral findings may be a consequence of immunosuppression and suggest performing precise intraoral examinations on patients with COVID-19.

SUMMARY

This report included the following three COVID-19 cases:
1) A 43 year-old female, who tested positive for COVID-19 for 56 days, developed aphthous-like lesions (Figure 1), dysgeusia, and anosmia and was treated with triamcinolone acetonide 0.05% (3 times daily for 10 days).
2) A 53 year-old male with COVID-19 developed a burning mouth sensation and commissural fissures (Figure 2) several days after hospital discharge and was treated with an ointment of neomycin, nystatin, and triamcinolone acetonide (3 times daily)
3) A 78 year-old female with COVID-19 developed dry mouth, tongue lesions, pseudomembranous candidiasis, and angular cheilitis (Figure 3) during hospitalization. She was treated with an ointment of nystatin, neomycin, and triamcinolone acetonide and nystatin solution rinses (4 times daily)

ABSTRACT

The appearance in December of a new coronavirus has caused an unprecedented pandemic in the modern era. Undoubtedly, the disease produced by the novel Coronavirus and its consequences have posed a challenge for health authorities worldwide. The way of contagion through direct contact, through saliva in the form of small drops and the production of aerosols have facilitated the rapid spread worldwide. In Spain the authorities declared the confinement for the majority of population in March 14th , therefore most of dental clinics were closed except for emergencies. Dentists were considered at high risk due to two factors: all procedures are obviously performed in the mouth with direct contact with saliva and the exposure to aerosols

produced by rotatory instruments. Many articles have been published regarding to the spread of the virus and the role that saliva plays in its transmission and diagnosis. (Li et al.,2020) (Sabino-Silva, R.,2020) (Xu et al., 2020) (Zhong et al.,2020) (Chen et al., 2020).

FIGURES

Figure 1: Bilateral atrophy of the surface of the tongue located in the lateral sides. Lateral dorsum appears depapillated with a simetrical distribution.

Figure 2: Commissural cheilitis. Notice the fissure and bleeding located in the commissure.

Figure 3: Atrophy of the surface of the tongue including white fungal patches, distributed mainly in the left lateral side, and a red plate located in the hard and soft palate. Notice the fissures located in the dorsum of the tongue.

PERSISTENT PSYCHOTIC SYMPTOMS FOLLOWING COVID-19 DISEASE

Lim ST, Janaway B, Costello H, Trip SA, Price G.. BJPsych Open. 2020 Jul 22:1-11. doi: 10.1192/bjo.2020.76. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

Authors present the case of a 55-year-old female with no prior history of mental illness admitted to the University College Hospital in London initially for COVID-19 management and readmitted due to persistent psychotic behaviors. Concurrently, the patient had elevated TNF-alpha which was suggestive of a pro-inflammatory state, leading to the potential association between pro-inflammatory cytokines and psychosis in patients with COVID-19.

SUMMARY

A 55-year-old Caucasian female with no history of mental illness presented with 14 days of COVID-19 symptoms (fever, cough, anosmia, and ageusia) improved after hospitalization and returned after two days for ongoing auditory hallucinations and delusional misperception. The patient received Lorazepam and Haloperidol for acute agitation, and Risperidone as delusional symptoms persisted. On day 20, the patient's cognition and behavior improved and was discharged home despite having persistent paranoid thoughts. Outpatient follow-up reported paranoid thoughts persisted for 34 days and reassessment of the patient's hospital records showed elevation of TNF-alpha consistent with a pro-inflammatory state. This led to the proposal that pro-inflammatory cytokines may have been associated with acute psychosis in COVID-19 patients.

UNDERSTANDING THE PATHOLOGY

ASSESSMENT OF SERUM FERRITIN AS A BIOMARKER IN COVID-19: BYSTANDER OR PARTICIPANT? INSIGHTS BY COMPARISON WITH OTHER INFECTIOUS AND NON-INFECTIOUS DISEASES

Kappert K, Jahić A, Tauber R.. Biomarkers. 2020 Jul 23:1-36. doi: 10.1080/1354750X.2020.1797880. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

This literature review assessed the evidence of the role of serum ferritin in COVID-19 disease progression and other viral infections. The investigators found that following:
- Previous studies reported an association between high serum ferritin and more severe COVID-19 complications, indicating that ferritin might serve as a diagnostic biomarker of COVID-19 severity.
- Investigators also found that while serum ferritin was not commonly reported in SARS, MERS, Avian flu, or Swine flu, high ferritin was commonly reported in Influenza A and B infections, Ebola, Crimean-Congo hemorrhagic fever, and Dengue fever.

The authors note that the poorly understood association between ferritin and COVID-19 warrants further study to determine whether serum ferritin can be used to track disease progression or severity.

ABSTRACT

BACKGROUND: The 2019 coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus has an impact on all aspects of patient care. Serum ferritin generally represents a biomarker of choice when iron deficiency is suspected. However, ferritin is also an acute-phase-protein exhibiting elevated serum concentrations in various inflammatory diseases. Here we focus on the role of serum ferritin for diagnostic and clinical management of patients with COVID-19 in comparison with other infectious and non-infectious diseases.METHODS: We examined scientific articles listed in PubMed reporting on ferritin in various infectious and non-infectious diseases. We then compared these results with nine current COVID-19 ferritin reports published in 2020.RESULTS: Several non-infectious as well as non-COVID-19 infectious diseases are characterized by a partly dramatic elevation of serum ferritin levels. All COVID-19 studies published between February and May 2020, which documented laboratory serum ferritin, indicate ferritin as a diagnostic biomarker of COVID-19 severity in hospitalized patients.CONCLUSIONS: Serum ferritin may be considered both a prognostic and stratifying biomarker that can also contribute to therapeutic decision-making concerning patients with COVID-19. It should be emphasized, however, that most scientific reports refer to cohorts in the Asian region. Further validation in other cohorts is urgently required.

CYTOKINE STORM SYNDROME IN CORONAVIRUS DISEASE 2019: A NARRATIVE REVIEW

Gao YM, Xu G, Wang B, Liu BC.. J Intern Med. 2020 Jul 22. doi: 10.1111/joim.13144. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Researchers from Zhongda Hospital and Tongji Hospital in China summarized the pathogenesis, clinical manifestations, and potential therapeutics for cytokine storm syndrome (CSS) in this narrative review (see summary) and believe additional research is beneficial to further improve the outcomes of CSS in COVID-19 patients.

SUMMARY

The researchers noted:
• Clinical manifestations of CSS may include fever, respiratory symptoms (cough, dyspnea, and ARDS), hepatosplenomegaly, coagulation dysfunction, and pancytopenia.
• Currently there are no known criteria that differentiate CSS between COVID-19 and non-COVID 19 patients.
• A proposed mechanism for CSS in COVID 19 is diagramed in Figure 2.
• Elevation in inflammatory cytokines (IL-6) are higher in ICU patients than non-ICU patients.
• A specific target of IL-6 or GM-CSF may be effective in blocking inflammatory storm in COVID-19 patients.
• There is no supportive evidence from randomized clinical trials on the use of glucocorticoids in patients with COVID-19.
• Alternative therapeutic such as blood purification, IL-1, and JAK inhibiting agents are currently being studied at this time.

ABSTRACT

Cytokine storm syndrome (CSS) is a critical clinical condition induced by a cascade of cytokine activation, characterized by overwhelming systemic inflammation, hyperferritinaemia, haemodynamic instability and multiple organ failure (MOF). At the end of 2019, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, and rapidly developed into a global pandemic. More and more evidence shows that there is a dramatic increase of inflammatory cytokines in patients with COVID-19, suggesting the existence of cytokine storm in some critical illness patients. Here, we summarize the pathogenesis, clinical manifestation of CSS, and highlight the current understanding about the recognition and potential therapeutic options of CSS in COVID-19.

FIGURES

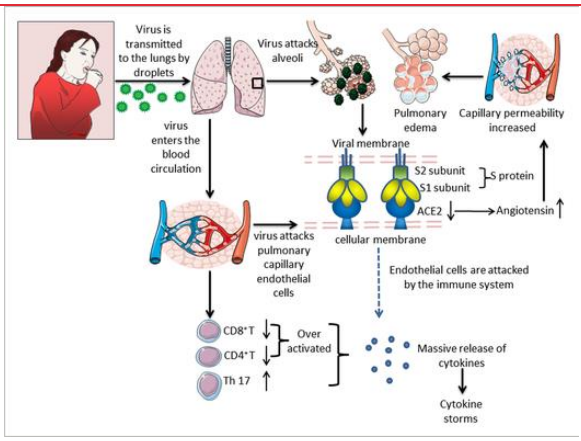


Figure 2. Possible mechanisms of cytokine storms in COVID-19. SARS-CoV-2 transmitted by air droplets reaches the lungs. On the one hand, the S protein on the surface of the virus binds to the ACE2 receptor in alveolar epithelial cells, resulting in the down-regulation of ACE2 expression and an increase of angiotensin level, which leads to increased pulmonary capillary permeability and pulmonary oedema. On the other hand, SARS-CoV-2 reaches the lungs again through blood circulation and interacts with ACE2 receptors on the surface of alveolar capillary endothelial cells, making the alveolar capillary endothelium the target of attack by the immune system, thus inducing a series of immune responses and aggravating lung injury. The imbalance of lymphocyte subsets characterized by the decrease of CD4+, CD8+ T cells, the increase of the number of proinflammatory Th17 cells and the increase of CD8+ cytotoxic particles, aggravated the disorder of host immune system. Inflammatory monocytes amplify cytokines production. In addition, many kinds of cytokines are released in patients with COVID-19, which contribute to the formation of a cytokine storm. Abbreviations: ACE2: angiotensin-converting enzyme 2 and NK cell: natural killer cell.

SCREENING TESTING FOR SARS-COV-2 UPON ADMISSION TO REHABILITATION HOSPITALS IN A HIGH COVID-19 PREVALENCE COMMUNITY

Kirshblum SC, DeLauter G, Lopreiato MC, Pomeranz B, Dawson A, Hammerman S, Gans BM.. PM R. 2020 Jul 23. doi: 10.1002/pmrj.12454. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective study of presumed COVID-19 negative patients (n=103; Table 1) conducted at four inpatient rehabilitation facilities (IRF) in New Jersey, United States between 4 April and 27 April 2020 found 6.8% of asymptomatic participants (n=7) tested positive for SARS-CoV-2 (via reverse transcription polymerase chain reaction [RT-PCR]) on admission (71% [n=5] of this group developed symptoms in 2-5 days), and overall 11.6% (n=12) tested positive within 14 days of admission (Tables 2, 3). Authors suggest SARS-CoV-2 testing on admission to post-acute care settings is worthwhile for appropriate infection control regardless of symptom presence.

ABSTRACT

INTRODUCTION: While planning for the care of COVID-19 patients during the pandemic crisis has dominated the focus of leaders of inpatient rehabilitation facilities (IRF), patients with injuries/ illnesses unrelated to COVID-19 continue to need inpatient rehabilitation admission. To maintain a safe environment for all patients and staff, we established an admission screening plan of testing for SARS-CoV-2 to determine the presence of asymptomatic patients who were infected with the virus upon admission. OBJECTIVE: To determine the prevalence of patients who test positive for SARS-CoV-2 but were presumed to be COVID-19 negative at the time of admission to IRF in New Jersey. DESIGN: Retrospective analysis of SARS-CoV-2 testing results. SETTING: Four freestanding IRFs in New Jersey operated as one system. PATIENTS: All (N=103) patients sequentially admitted from April 4 -27, 2020 with no symptoms or evidence of COVID-19 disease at the time of transfer from the acute hospital. INTERVENTIONS: Specimens were collected for SARS-CoV-2 analysis at the time of admission to the IRF and patients were monitored for subsequent symptom development over the next 14 days. MAIN OUTCOME MEASURES: Results of SARS-CoV-2 testing upon admission and evidence of development of clinical signs or symptoms of COVID-19. RESULTS: Seven asymptomatic persons (6.8% of admissions) without clinical signs/symptoms of COVID-19 tested positive on admission. Of these, five developed symptoms of COVID-19, with a mean onset of 3.2 (range of 2-5) days. Five additional patients became symptomatic and tested positive within the next 3-10 days (mean of 5.2 days). Overall, 11.6% of admissions (12/103) had a positive test within 14 days of admission. CONCLUSIONS: Admission testing to post-acute centers for SARS-CoV-2 can help identify pre-symptomatic or asymptomatic individuals, especially in areas where COVID-19 is prevalent. Negative results however, do not preclude COVID-19 and should not be used as the sole basis for patient management decisions.

FIGURES

	All (n=103)	Tests negative (n=91)	Tests initially positive (n=7)	Re-tested SARS-CoV-2 positive (n=5)	All tested SAR-CoV-2 positive (n=12)
Age (years) Mean (range):	66.3 (27-99)	65.4 (27-99)	72.1 (47-84)	76.4 (67-92)	73.9 (47-92)*
Sex (Females: Males)	54:49	48:43	3:4	3:2	6:6
Race					
White	69	59	5	5	10
Black	31	29	2	0	2
Other	3	3	0	0	0
BMI					
Mean	27.7	27.3	32.1	28.3	30.5
Median	26.5	26.2	30.1	28.6	29.6
Range	15.2-47.1	15.2-44.3	22.4-47.1	22.9-30.6	22.4-47.1
Medical comorbidities					
HTN	76	70	6	4	10
DM	36	34	2	2	4
Kidney Disease	21	19	2	1	3
Resp Disease	36	34	2	3	5
Immunosuppression	10	10	0	1	2
Cardiac Disease	41	40	1	2	3
Pre-screened negative at acute care hospital	63	52	3	4	7
If yes, days prior to transfer (mean)	8	8	5	7	6
Duration of stay at acute care hospital Mean (range)	20.5 (2-214)	21.0 (2-214)	23.4 (5-93)	6.8 (3-14)	16.6 (3-93)
Primary ICD dx					
CIM	1	1	0	1	1
General debility	14	12	2	0	2
NT - SCI	7	6	1	0	1
NT - TBI (incl. stroke)	46	44	2	2	4
LE amputation	3	3	0	0	0
Orthopedic fracture	17	17	0	2	2
Other Neurologic	5	4	1	0	1
TBI	7	6	1	0	1
Traumatic SCI	3	3	0	0	0

Table 1. Demographics of Sample.

Patient	Admitting Diagnosis	Symptoms	Days from admission	Outcomes
1	CVA	Asymptomatic	Up to 14 days	Still in IRF (post day #14)
2	CVA	Fever >100.4^{0}F; altered mental status	2 days; 5 days	ACT day # 5 for altered mental status changes
3	General Debility	Asymptomatic	Up to 14 days	D/C home day #14
4	General Debility	Fever 101.2^{0}F, dyspnea	4 days	ACT for worsening resp and renal issues
5	NT-SCI	Fever-101.1^{0}F; 103.4^{0}F	3 days; 5 days	D/C home day # 21.
6	TBI	Cough and congestion	2 days	No further complications. Still in IRF (post day #14)
7	Other Neurologic	Congestion; flu-like symptoms	5 days; 6 days	Day #13 still in IRF

Table 2. Clinical follow up of asymptomatic persons on admission who tested positive for RT-PCR SARS-CoV-2 to IRF.

Patient	Admitting diagnosis	Reasons for testing	Days post admission	Outcomes
1	Orthopedic fracture	Fever (Tmax = 101.6^{0}F)	4	D/C home day # 19
2	CMI	Dyspnea; Low grade temp (Tmax = 100.1^{0}F)	10	D/C nursing home day # 17
3	NT-TBI	Cough; lethargy, Fever (Tmax = 100.9^{0}F)	8	D/C home day # 19
4	NT-TBI	Lethargy; cough.	10	ACT on day # 19 for worsening resp needs
5	Orthopedic fracture	Shortness of breath and lethargy	3	ACT for pneumonia day # 3

Table 3. Patient who became symptomatic and retested positive for RT-PCR SARS-CoV-2 during their rehabilitation stay.

DIAGNOSTIC RADIOLOGY

RADIOLOGICAL FINDINGS OF COVID-19 IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Kumar J, Meena J, Yadav A, Yadav J.. J Trop Pediatr. 2020 Jul 21:fmaa045. doi: 10.1093/tropej/fmaa045. Online ahead of print.

Level of Evidence: 1 - Systematic review of cross sectional studies with consistently applied reference standard and blinding

BLUF

This systematic review of 46 case series and case studies (Figure 1) with radiologic findings from 923 symptomatic and asymptomatic pediatric patients diagnosed with COVID-19 by RT-PCR found that:

1. Chest CT was the most common imagining modality used
2. Chest CT was able to detect radiological evidence of COVID-19 in 19% of asymptomatic patients.
3. The most common abnormality seen on scans was ground-glass opacities (39%; Table 2)
4. The most common location of lesions was the lower lobe of the right lung (40%).

These findings emphasize the need for further investigation of chest CT as a screening tool for COVID-19 in children and for study of other imaging alternatives like lung ultrasound to minimize exposure to radiation.

ABSTRACT

BACKGROUND: The majority of the children with SARS-CoV-2 infection present with respiratory symptoms, hence various chest imaging modalities have been used in the management. Knowledge about the radiological findings of coronavirus disease (COVID-19) in children is limited. Hence, we systematically synthesized the available data that will help in better management of COVID-19 in children. METHODS: Four different electronic databases (MEDLINE, EMBASE, Web of Science and CENTRAL) were searched for articles reporting radiological findings in children with COVID-19. Studies reporting thoracic radiological findings of COVID-19 in patients aged <19 years were included. A random-effect meta-analysis (wherever feasible) was performed to provide pooled estimates of various findings. RESULTS: A total of 1984 records were screened of which forty-six studies (923 patients) fulfilled the eligibility criteria and were included in this systematic review. A chest computed tomography (CT) scan was the most frequently used imaging modality. While one-third of the patients had normal scans, a significant proportion (19%) of clinically asymptomatic children had radiological abnormalities too. Unilateral lung involvement (55%) was frequent when compared with bilateral and ground-glass opacities were the most frequent (40%) definitive radiological findings. Other common radiological findings were non-specific patchy shadows (44%), consolidation (23%), halo sign (26%), pulmonary nodules and prominent bronchovascular marking. Interstitial infiltration being the most frequent lung ultrasound finding. CONCLUSION: CT scan is the most frequently used imaging modality for COVID-19 in children and can detect pneumonia before the appearance of clinical symptoms. Undefined patchy shadows, grand-glass opacities and consolidation are commonly observed imaging findings in COVID-19 pneumonia.

FIGURES

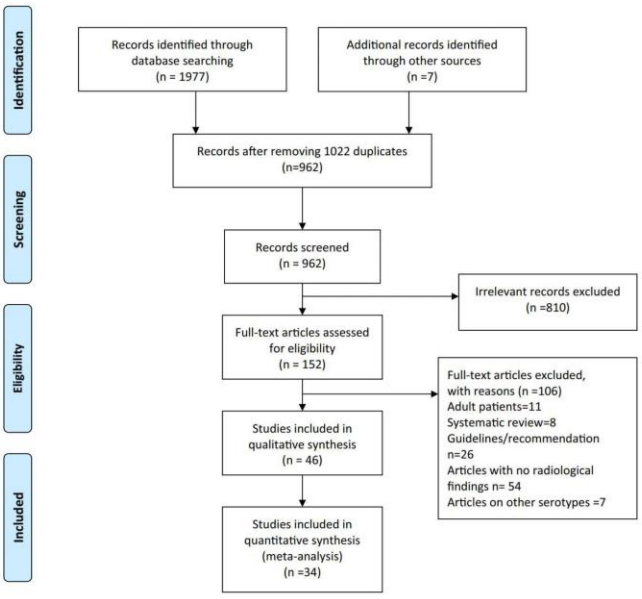


Figure 1. PRISMA flowchart.

Radiological finding	No. of studies (patients)	Pooled estimates % (95% CI)	Heterogeneity % (I^2)	*P*-value for heterogeneity
Ground glass opacity	32 (706)	39 (31–48)	82	0.00
Consolidation	12 (192)	23 (12–34)	82	0.00
Halo sign	6 (78)	26 (11–41)	51	0.09
Patchy shadow	13 (246)	44 (32–55)	62	0.00
Prominent bronchiovascular markings	5 (97)	17 (09–24)	0.0	0.83
Bronchial wall thickening	4 (36)	11 (1–21)	0.0	1.00
Pleural effusion	5 (187)	2 (0.1–4)	0.0	0.60
Interstitial pattern	4 (187)	12 (1–23)	82	0.00
Nodules	5 (63)	25 (9–41)	62	0.03

Table 2. Common radiological findings in children with SARS-CoV-2 infection.

CRITICAL CARE

COVID-19 AND COAGULATION: BLEEDING AND THROMBOTIC MANIFESTATIONS OF SARS-COV-2 INFECTION

Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP.. Blood. 2020 Jul 23;136(4):489-500. doi: 10.1182/blood.2020006520.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

In this multicenter retrospective study conducted in Boston, MA from March 1st-April 5th, 2020 investigators examined the rate of bleeding and thrombosis in 400 hospitalized COVID-19 patients in critically and non-critically ill conditions (see summary for results). Additionally, researchers found elevated D-dimer levels were associated with a higher risk for bleeding and thrombotic complications and caution clinicians when increasing prophylactic doses of anticoagulants.

SUMMARY

The multicenter retrospective study of 400 hospital admitted COVID-19 patients found:
- The rate of radiographically confirmed venous thromboembolism (VTE) was 4.8% (3.1% in non-critically ill patients and 7.6% in critically ill patients).
- The rate of arterial thrombosis was 2.8% (1.2% in non-critically ill patients and 5.6% in critically ill patients).
- The overall rate of thrombotic complication was 9.5% (4.7% in non-critically ill patients and 18.1% in critically ill patients).
- The overall rate of bleeding was 4.8% (3.1% in non-critically ill patients and 7.6% in critically ill patients).

- The rate of major bleeding rate was 2.3%.
- When comparing patient with bleeding and thrombotic complications to those without these complications, patients with thrombotic complications had "higher D-dimer, fibrinogen, CRP, ferritin, and procalcitonin" and patients with bleeding complications had "higher procalcitonin and peak D-dimer, and lower platelet counts."

ABSTRACT

Patients with coronavirus disease 2019 (COVID-19) have elevated D-dimer levels. Early reports describe high venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC) rates, but data are limited. This multicenter, retrospective study described the rate and severity of hemostatic and thrombotic complications of 400 hospital-admitted COVID-19 patients (144 critically ill) primarily receiving standard-dose prophylactic anticoagulation. Coagulation and inflammatory parameters were compared between patients with and without coagulation-associated complications. Multivariable logistic models examined the utility of these markers in predicting coagulation-associated complications, critical illness, and death. The radiographically-confirmed VTE rate was 4.8% (95% CI, 2.9-7.3%) and the overall thrombotic complication rate was 9.5% (6.8-12.8%). The overall and major bleeding rates were 4.8% (2.9-7.3%) and 2.3% (1.0-4.2%). In the critically ill, radiographically-confirmed VTE and major bleeding rates were 7.6% (3.9-13.3%) and 5.6% (2.4-10.7%). Elevated D-dimer at initial presentation was predictive of coagulation-associated complications during hospitalization [D-dimer >2,500 ng/mL, adjusted OR for thrombosis, 6.79 (2.39-19.30), adjusted OR for bleeding, 3.56 (1.01-12.66)], critical illness, and death. Additional markers at initial presentation predictive of thrombosis during hospitalization included platelet count >450x109/L [adjusted OR, 3.56 (1.27-9.97)], C-reactive protein (CRP) >100 mg/L [adjusted OR, 2.71 (1.26-5.86)], and erythrocyte sedimentation rate >40 mm/h [adjusted OR, 2.64 (1.07-6.51)]. ESR, CRP, fibrinogen, ferritin, and procalcitonin were higher in patients with thrombotic complications than those without. DIC, clinically-relevant thrombocytopenia, and reduced fibrinogen were rare and were associated with significant bleeding manifestations. Given the observed bleeding rates, randomized trials are needed to determine any potential benefit of intensified anticoagulant prophylaxis in COVID-19 patients.

THE ROLE OF HYPERBARIC OXYGEN TREATMENT FOR COVID-19: A REVIEW

Paganini M, Bosco G, Perozzo FAG, Kohlscheen E, Sonda R, Bassetto F, Garetto G, Camporesi EM, Thom SR.. Adv Exp Med Biol. 2020 Jul 22. doi: 10.1007/5584_2020_568. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

This review illustrates the mechanism of action in hyperbaric oxygen (HBO) therapy and examines current protocols to summarize successful practices in its use as a treatment for COVID-19. While the authors recognize that the pulmonary and neurological adverse effects of HBO must be considered, they found multiple studies describing HBO's potential to limit viral replication, decrease pro-inflammatory IL-6, increase anti-inflammatory IL-10, and prevent immune system impairment (Figure 1). They advocate for clinicians to consider HBO treatment in severe COVID-19 patients.

ABSTRACT

The recent coronavirus disease 2019 (COVID-19) pandemic produced high and excessive demands for hospitalizations and equipment with depletion of critical care resources. The results of these extreme therapeutic efforts have been sobering. Further, we are months away from a robust vaccination effort, and current therapies provide limited clinical relief. Therefore, several empirical oxygenation support initiatives have been initiated with intermittent hyperbaric oxygen (HBO) therapy to overcome the unrelenting and progressive hypoxemia during maximum ventilator support in intubated patients, despite high FiO2. Overall, few patients have been successfully treated in different locations across the globe. More recently, less severe patients at the edge of impending hypoxemia were exposed to HBO preventing intubation and obtaining the rapid resolution of symptoms. The few case descriptions indicate large variability in protocols and exposure frequency. This summary illustrates the biological mechanisms of action of increased O2 pressure, hoping to clarify more appropriate protocols and more useful application of HBO in COVID-19 treatment.

FIGURES

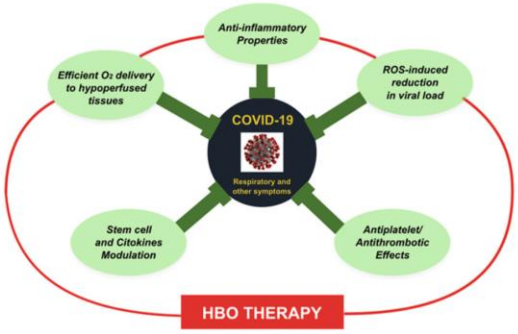


Figure 1: Possible effects of hyperbaric oxygen (HBO) therapy in coronavirus disease 19 (COVID-19) patients

A 29-YEAR-OLD MALE WITH A FATAL CASE OF COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME (CARDS) AND VENTILATOR-INDUCED LUNG INJURY (VILI)

Deliwala SS, Ponnapalli A, Seedahmed E, Berrou M, Bachuwa G, Chandran A.. Am J Case Rep. 2020 Jul 23;21:e926136. doi: 10.12659/AJCR.926136.
Level of Evidence: Other - Case Report

BLUF

A case report conducted at the Department of Internal Medicine at Michigan State University highlights the case of a 29-year-old male who died from COVID-19 acute respiratory distress syndrome (CARDS) and ventilator-induced lung injury (VILI). This patient displayed both phenotypes of CARDS, the milder type L form and the more severe type H form (which resembles full-blown ARDS). Ultimately, the patient's cause of death was a tension pneumothorax from VILI associated with type H CARDS. This case suggests the need for a better understanding of CARDS and transition to type H in order to prevent patients' entry to the VILI vortex and potential death from COVID-19.

SUMMARY

A 29-year-old obese male with history of asthma and prior gunshot wound presented to the emergency department with complaints of shortness of breath, fatigue, cough, and diffuse myalgias. Exam was positive for fever, tachycardia, and tachypnea, and he was subsequently placed on a ventilator. His labs were positive for lymphopenia and thrombocytopenia. Chest x-ray (CXR) on day of admission revealed mild bilateral interstitial changes consistent with type L CARDS (Figure 1). A nasopharyngeal swab and RT-PCR test for SARS-CoV-2 came back positive, confirming a case of COVID-19 pneumonia. By day 8, the patient's respiratory function continued to decline, requiring mechanical ventilation as well as a therapeutic dose of enoxaparin due to formation of a DVT in the left upper extremity. CXR was repeated at this point, which revealed progression of his bilateral consolidations, consistent with a conversion to type H CARDS (Figure 2). Despite all the appropriate ARDS treatment strategies, the patient continued to decline until sudden desaturation on day 17 resulted in a tension pneumothorax that was ultimately the cause of death (Figure 3).

ABSTRACT

BACKGROUND COVID-19 patients that develop acute respiratory distress syndrome (ARDS) "CARDS" behave differently compared to patients with classic forms of ARDS. Recently 2 CARDS phenotypes have been described, Type L and Type H. Most patients stabilize at the milder form, Type L, while an unknown subset progress to Type H, resembling full-blown ARDS. If uncorrected, phenotypic conversion can induce a rapid downward spiral towards progressive lung injury, vasoplegia, and pulmonary shrinkage, risking ventilator-induced lung injury (VILI) known as the "VILI vortex". No cases of in-hospital phenotypic conversion have been reported, while ventilation strategies in these patients differ from the lung-protective approaches seen in classic ARDS. CASE REPORT A 29-year old male was admitted with COVID-19 pneumonia complicated by severe ARDS, multi-organ failure, cytokine release syndrome, and coagulopathy during his admission. He initially resembled CARDS Type L case, although refractory hypoxemia, fevers, and a high viral burden prompted conversion to Type H within 8 days. Despite ventilation strategies, neuromuscular blockade, inhalation therapy, and vitamin C, he remained asynchronous to the ventilator with volumes and pressures beyond accepted thresholds, eventually developing a fatal tension pneumothorax. CONCLUSIONS Patients that convert to Type H can quickly enter a spiral of hypoxemia, shunting, and dead-space ventilation towards full-blown ARDS. Understanding its nuances is vital to interrupting phenotypic conversion and entry into VILI vortex.

Tension pneumothorax represents a poor outcome in patients with CARDS. Further research into monitoring lung dynamics, modifying ventilation strategies, and understanding response to various modes of ventilation in CARDS are required to mitigate these adverse outcomes.

FIGURES

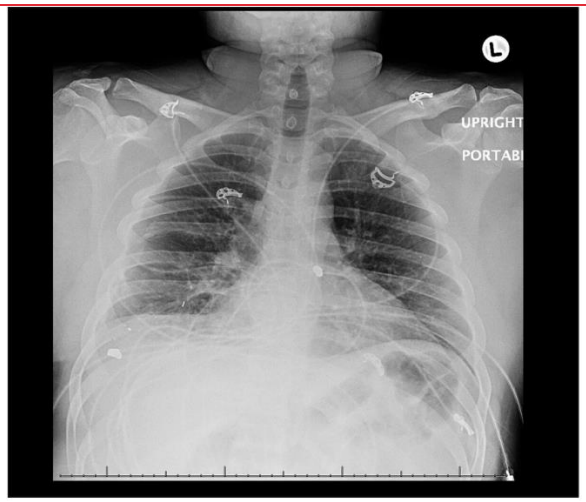


Figure 1. Chest radiograph revealing mild bilateral interstitial changes consistent with CARDS Type L on day 1.

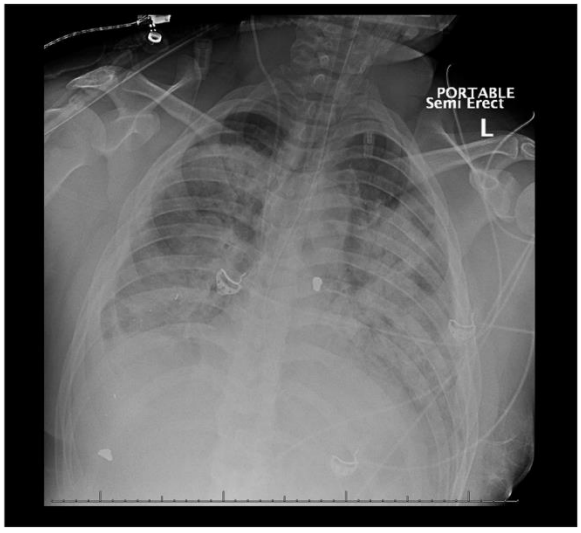


Figure 2. Chest radiograph revealing extensive bilateral consolidations consistent with CARDS Type H on day 8.

Figure 3. Chest radiograph revealing pneumothorax with near collapse of the left lung and placement of a chest tube on day 18 of admission.

OTOLARYNGOLOGY

SARS-COV-2 VIRUS ISOLATED FROM THE MASTOID AND MIDDLE EAR: IMPLICATIONS FOR COVID-19 PRECAUTIONS DURING EAR SURGERY

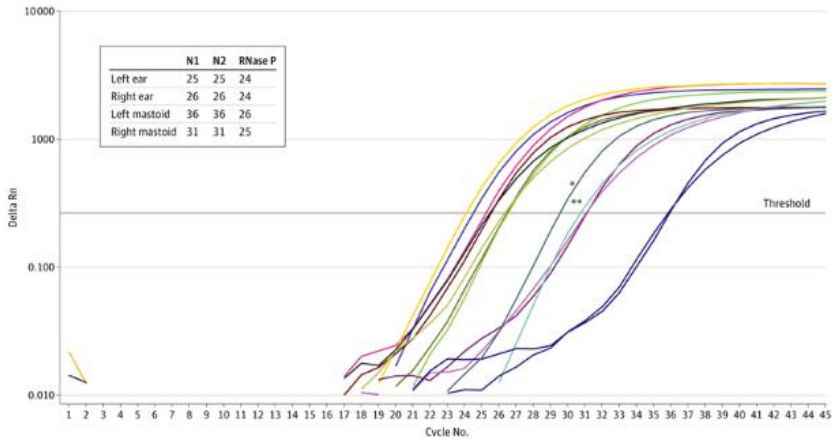
Frazier KM, Hooper JE, Mostafa HH, Stewart CM.. JAMA Otolaryngol Head Neck Surg. 2020 Jul 23. doi: 10.1001/jamaoto.2020.1922. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

This letter from authors in the Departments of Otolaryngology and Pathology at John Hopkins School of Medicine reports autopsy findings of 3 decedents (all COVID-19 positive by real-time reverse transcriptase polymerase chain reaction [rRT-PCR]) with SARS-CoV-2 colonization of the middle ear or mastoid. Post-bilateral corticoid mastoidectomy and rRT-PCR, 2 of the 3 cases tested positively for N1, N2, and internal control viral target genes (Figure 1) with viral isolation in 2 of 6 mastoids and 3 of 6 middle ears. The authors suggest screening and droplet protection prior to otolaryngology procedures involving likely aerosol and droplet transmission risk to clinicians.

FIGURES

Figure. Amplification Plot of Patient 3



R&D: DIAGNOSIS & TREATMENTS

THE BRIGHTON COLLABORATION STANDARDIZED TEMPLATE FOR COLLECTION OF KEY INFORMATION FOR BENEFIT-RISK ASSESSMENT OF NUCLEIC ACID (RNA AND DNA) VACCINES

Kim D, Robertson JS, Excler JL, Condit RC, Fast PE, Gurwith M, Pavlakis G, Monath TP, Smith J, Wood D, Smith ER, Chen RT, Kochhar S; Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG).. Vaccine. 2020 Jul 22;38(34):5556-5561. doi: 10.1016/j.vaccine.2020.06.017. Epub 2020 Jun 19.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

The Brighton Collaboration, an international initiative that formed the Viral Vector Vaccines Safety Working Group (V3SWG), has created a standardized template for the assessment of nucleic acid vaccines (NAVs), including both DNA and RNA vaccines. Their standardized template aims to answer questions related to safety and benefit-risk issues as well as improve communication and public acceptance of NAVs, particularly in the wake of recent COVID-19 vaccine development efforts.

ABSTRACT

Nucleic acid (DNA and RNA) vaccines are among the most advanced vaccines for COVID-19 under development. The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) has prepared a standardized template to describe the key considerations for the benefit-risk assessment of nucleic acid vaccines. This will facilitate the assessment by key stakeholders of potential safety issues and understanding of overall benefit-risk. The structured assessment provided by the template can also help improve communication and public acceptance of licensed nucleic acid vaccines.

DEVELOPMENTS IN DIAGNOSTICS

PAPER SPRAY MASS SPECTROMETRY UTILIZING TESLIN® SUBSTRATE FOR RAPID DETECTION OF LIPID METABOLITE CHANGES DURING COVID-19 INFECTION

De Silva IW, Nayek S, Singh V, Reddy J, Granger JK, Verbeck GF.. Analyst. 2020 Jul 22. doi: 10.1039/d0an01074j. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or “poor or non-independent reference standard

BLUF

An investigation conducted at the University of North Texas utilized paper spray mass spectroscopy (PS-MS) to analyze changes in lipid metabolite production by cells infected with SARS-CoV-2 from 30 samples (10 COVID-19 positive, 10 COVID-19 negative, and 10 blind test samples). They found significant differences in lipid metabolites between the COVID-19 positive and negative test samples (Figure 2, Table 1), categorized these metabolites between positive and negative samples with linear discriminant analysis (LDA; Figure 3A, 3B), and determined that PS-MS was able to accurately identify 93.3% of these samples when compared to RT-PCR results (Figure 3C). These findings demonstrate that PS-MS may aid the development of a new rapid COVID-19 test, although further experimentation is needed.

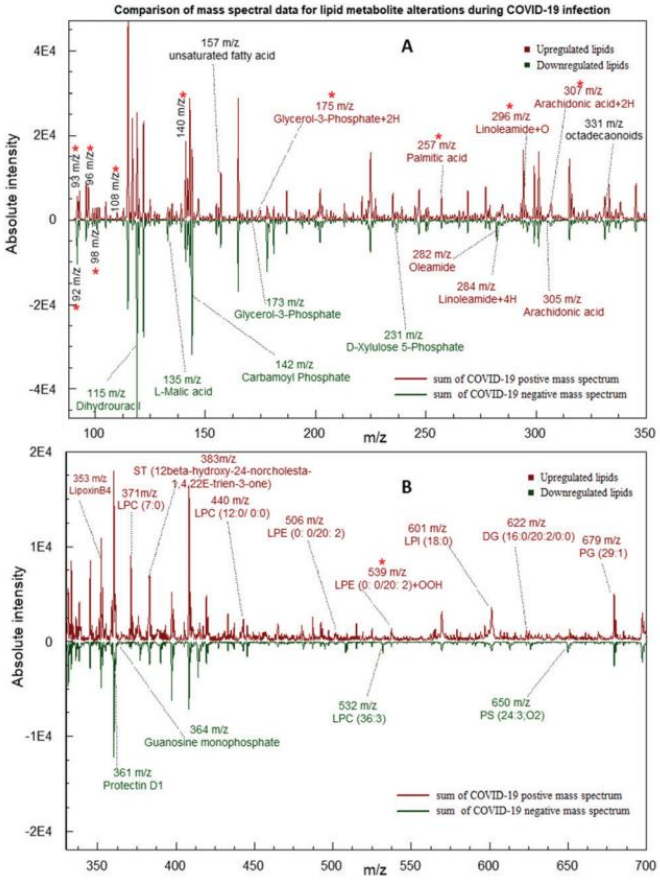
ABSTRACT

The SARS-CoV-2 virus is known as the causal agent for the current COVID-19 global pandemic. The majority of COVID-19 patients develop acute respiratory distress syndrome (ARDS), while some experience a cytokine storm effect, which is considered as one of the leading causes of patient mortality. Lipids are known to be involved in the various stages of the lifecycle of a virus functioning as receptors or co-receptors that controls viral propagation inside the host cell. Therefore, lipid-related metabolomics aims to provide insight into the immune response of the novel coronavirus. Our study has focused on determination of the potential metabolomic biomarkers utilizing a Teslin Substrate in paper spray mass spectrometry (PS-MS) for the development of a rapid detection test within 60 seconds of analysis time. In this study, results were correlated with PCR tests to reflect that the systemic responses of the cells were affected by the COVID-19 virus.

Metabolite	*m/z* $[M + H]^+$	Expression during COVID-19 infection
Aminooxyacetic acid[a]	92	Downregulated
Hydroxyethyl methyl sulfide[a]	93	Upregulated
3-Hydroxypyridine[a]	96	Upregulated
N-Pyrrylcarbinol[a]	98	Upregulated
Benzylamine[a]	108	Upregulated
Dihydrouracil	115	Downregulated
L-Malic acid	135	Downregulated
3-Hydroxypicolinic acid[a]	140	Upregulated
Carbamoyl phosphate	142	Downregulated
Glycerol-3-phosphate	173	Downregulated
Glycerol-3-phosphate + 2H[a]	175	Upregulated
D-Xylulose 5-phosphate	231	Downregulated
Palmitic acid	257	Upregulated
Oleamide	282	Upregulated
Linoleamide + 4H[a]	284	Upregulated
Linoleamide + O[a]	296	Upregulated
Arachidonic acid	305	Upregulated
Arachidonic acid + 2H[a]	307	Upregulated
LipoxinB4	353	Upregulated
Protectin D1	361	Downregulated
Guanosine monophosphate	364	Downregulated
LPC (7:0)	371	Upregulated
ST (12β-hydroxy-24-norcholesta-1,4,22*E*-trien-3-one)	383	Upregulated
LPC (12:0/0:0)	440	Upregulated
LPE (0:0/20:2)	506	Upregulated
LPC (36:3)	532	Upregulated
LPE (0:0/20:2) + OOH[a]	539	Upregulated
LPI (18:0)	601	Upregulated
DG (16:0/20:2/0:0)	622	Upregulated
PS (24:3; O2)	650	Downregulated
PG (29:1)	679	Upregulated

[a] Metabolites that expressed with oxidative degradation indicating 2, 4, 16, or 32 *m/z* mass shifts and used as the variables in the statistical analysis. LPC – Lysophosphatidylcholines/lysoPC; ST – Sterol Lipids; LPE – Lysophosphatidylethanolamine; LPI – Lysophosphatidylinositol; PS – Phosphatidylserine; PG – Phosphatidylglycerol.

Table 1. The potential small metabolites and lipid alterations during COVID-19 infection



C Summary of PS-MS Classification

Sample Number	PCR Confirmation	PS-MS Clasification (Function2)	
Positive 1	COVID-19 Positive	2.380	Positive
Positive 2	COVID-19 Positive	2.780	Positive
Positive 3	COVID-19 Positive	2.390	Positive
Positive 4	COVID-19 Positive	2.960	Positive
Positive 5	COVID-19 Positive	1.330	Positive
Positive 6	**COVID-19 Positive**	**-0.650**	**Negative**
Positive 7	COVID-19 Positive	0.550	Positive
Positive 8	COVID-19 Positive	2.260	Positive
Positive 9	COVID-19 Positive	3.040	Positive
Positive10	COVID-19 Positive	1.820	Positive
Negative1	COVID-19 Negative	-3.310	Negative
Negative2	COVID-19 Negative	-1.470	Negative
Negative3	COVID-19 Negative	-1.970	Negative
Negative4	COVID-19 Negative	-1.930	Negative
Negative5	COVID-19 Negative	-2.460	Negative
Negative6	COVID-19 Negative	-0.540	Negative
Negative7	COVID-19 Negative	-1.540	Negative
Negative8	COVID-19 Negative	-0.070	Negative
Negative9	COVID-19 Negative	-2.560	Negative
Negative10	COVID-19 Negative	-1.650	Negative
Blind1	COVID-19 Negative	-0.180	Negative
Blind2	COVID-19 Negative	-1.760	Negative
Blind3	COVID-19 Negative	-0.800	Negative
Blind4	COVID-19 Negative	-0.650	Negative
Blind5	COVID-19 Negative	-0.240	Negative
Blind6	COVID-19 Positive	0.910	Positive
Blind7	COVID-19 Positive	0.220	Positive
Blind8	COVID-19 Positive	0.240	Positive
Blind9	**COVID-19 Positive**	**-0.260**	**Negative**
Blind10	COVID-19 Positive	1.000	Positive

* Positive 6 and blind test 9 was predicted as 6.7% false positive out of 30 samples.

Figure 3. Linear discriminant analysis for (LDA) for best possible classification of metabolites between COVID-19 positive and negative samples. The x-axis represents the prediction components function 2, and the y-axis represents the orthogonal component function 1 differences within the group. Each dot represents an individual sample, and each patient group is differently colored (green – negative, red – positive, and blue – blind samples). (A) LDA for COVID-19 positive and negative group classification. (B) LDA for COVID-19 positive and negative group classification with the blind test samples indicating the function 2 mean values as the determining factor for positive and negative groups. (C) Indicate the summary of classification using PS-Ms metabolite data set correlation to the PCR analysis.

DEVELOPMENTS IN TREATMENTS

STEM CELL THERAPIES FOR COVID-19: STRATEGY AND APPLICATION

Darabi R, Li Y.. J Cell Biochem. 2020 Jul 21. doi: 10.1002/jcb.29816. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

Two authors affiliated with McGovern Medical School's Center for Stem Cell and Regenerative Medicine and Western Michigan University's Department of Orthopaedic Surgery discuss the potential therapeutic role of mesenchymal stem cells (MSCs) in

treating COVID-19 patients with acute respiratory distress syndrome (ARDS) or pneumonia. They believe the immunomodulatory effects of MSCs may indirectly or directly suppress activation and proliferation of immune cells. Although existing studies are limited, the authors suggest MSCs may be a useful adjunct to acutely treating COVID-19 associated pneumonia, multi-organ failure, and sepsis and in reducing long-term, inflammation-related complications such as pulmonary fibrosis through alveolar regeneration.

SUMMARY

Based on previous research, the authors indicate that MSCs exert their immunomodulatory abilities and are useful in addressing multi-organ failure and sepsis by:
- secreting regulatory cytokines such as IL-1 RA or directly interacting with immune cells to suppress activation or multiplication of immune cells and cytokine-releasing cells.
- entrapment of MSCs in the lung and local secretion of cytokines in combination reduce inflammation, increase phagocytosis in alveolar macrophages, control capillary permeability, and restore clearance of alveolar fluid.
- improving CRP and tumor necrosis factor-α levels.
- MSC fusion and differentiation into damaged tissue.
- inhibiting cell death and damage.
- facilitating organelle and molecule transportation in damaged tissues.
- secreting antimicrobial peptides or increase phagocytosis of infectious agents.

ABSTRACT

In this perspective, the potential application of stem cells for the treatment of COVID-19 related pneumonia and their potential mechanism of action have been overviewed.

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