The Daily COVID-19 Literature Surveillance Summary

February 09, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Epidemiology

- What have we learned about clinical characteristics and outcomes of pregnant women with COVID-19. Investigators from various institutions from Iran, Canada, and United States conducted a meta-analysis and systematic review of 349 studies, of which 121 were studies involving 10,000 pregnant patients (both COVID-19 positive and negative), and 228 were studies involving 128,176 non-pregnant COVID-19 patients. The results revealed that pregnant COVID-19 positive patients are less likely to show classic symptoms (cough, sore throat, headache, or diarrhea), and have a propensity towards different imaging diagnostics, different laboratory results, and higher rate of gestational complications when compared to the two control groups (non-pregnant COVID-19 patients and pregnant COVID-19 negative patients). This study concludes that pregnant patients and their support system warrant additional preventative measures and education in order to mitigate gestational COVID-19 infection in order to reduce the risk of maternal and neonatal complications.

Adjusting Practice During COVID-19

- Mortality is not increased in SARS-CoV-2 infected persons with Hepatitis C virus infection. This retrospective study from the University of Pittsburgh Medical Center examines the impact of concurrent hepatitis C (HCV) and COVID-19 infections on hospitalization and ICU admission using the Electronically Retrieved Cohort of HCV Infected Veterans database. The authors found that while patients with both COVID-19 and HCV are more likely to be hospitalized, especially patients with higher FIB-4 scores, the rate of ICU admission and mortality is not significantly affected by HCV status.

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CLIMATE

GLOBAL

GENERAL MEDICAL PUBLICATIONS DURING COVID-19 SHOW INCREASED DISSEMINATION DESPITE LOWER VALIDATION

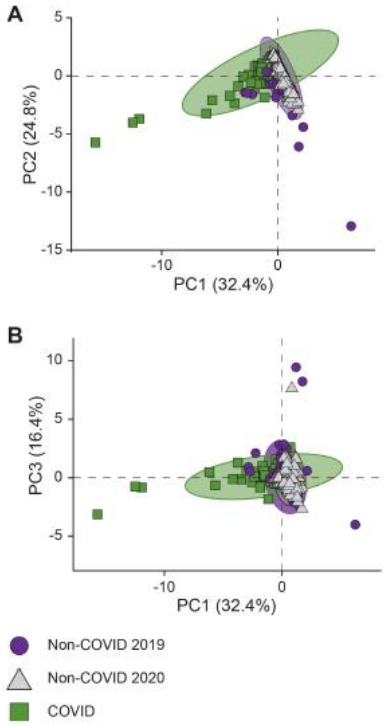
Gai N, Aoyama K, Faraoni D, Goldenberg NM, Levin DN, Maynes JT, McVey MJ, Munshey F, Siddiqui A, Switzer T, Steinberg BE.. PLoS One. 2021 Feb 2;16(2):e0246427. doi: 10.1371/journal.pone.0246427. eCollection 2021.
Level of Evidence: 5 - Review / Literature Review

BLUF

A cross-sectional bibliometric study compared research articles about COVID-19 published in March-April 2020 (n=402) to non-COVID-19 articles published in March-April 2019 (n=154) and 2020 (n= 172). Results demonstrated a substantial difference between the quality of evidence, with COVID-19-related articles comprising of more observational studies and case series with lower word counts and fewer citations (Table 1). However, this decrease in quality was balanced by shorter time to publishing and more diverse access to research via reads, tweets, and citations (Table 1). The authors conclude that the pandemic has prompted a shift toward faster dissemination of lower quality evidence in response to a need for quickly available information about of an emerging infectious disease, though this comes at a cost of diluting the quality of evidence and may delay higher-level trials.

ABSTRACT

BACKGROUND: The COVID-19 pandemic has yielded an unprecedented quantity of new publications, contributing to an overwhelming quantity of information and leading to the rapid dissemination of less stringently validated information. Yet, a formal analysis of how the medical literature has changed during the pandemic is lacking. In this analysis, we aimed to quantify how scientific publications changed at the outset of the COVID-19 pandemic. METHODS: We performed a cross-sectional bibliometric study of published studies in four high-impact medical journals to identify differences in the characteristics of COVID-19 related publications compared to non-pandemic studies. Original investigations related to SARS-CoV-2 and COVID-19 published in March and April 2020 were identified and compared to non-COVID-19 research publications over the same two-month period in 2019 and 2020. Extracted data included publication characteristics, study characteristics, author characteristics, and impact metrics. Our primary measure was principal component analysis (PCA) of publication characteristics and impact metrics across groups. RESULTS: We identified 402 publications that met inclusion criteria: 76 were related to COVID-19; 154 and 172 were non-COVID publications over the same period in 2020 and 2019, respectively. PCA utilizing the collected bibliometric data revealed segregation of the COVID-19 literature subset from both groups of non-COVID literature (2019 and 2020). COVID-19 publications were more likely to describe prospective observational (31.6%) or case series (41.8%) studies without industry funding as compared with non-COVID articles, which were represented primarily by randomized controlled trials (32.5% and 36.6% in the non-COVID literature from 2020 and 2019, respectively). CONCLUSIONS: In this cross-sectional study of publications in four general medical journals, COVID-related articles were significantly different from non-COVID articles based on article characteristics and impact metrics. COVID-related studies were generally shorter articles reporting observational studies with less literature cited and fewer study sites, suggestive of more limited scientific support. They nevertheless had much higher dissemination.



DELETE

Table 1. Publication characteristics and impact.

	Non-COVID publications		COVID publications	*P* value [a]	
	2019	2020		*COVID vs non-COVID 2019*	*COVID vs non-COVID 2020*
Articles (n)	172	154	76		
Article type, No. (%)					
Meta-analysis	6 (3.5)	4 (2.6)	0 (0)	<0.0001	<0.0001
Systematic review	4 (2.3)	6 (3.9)	2 (2.6)		
Narrative review	17 (9.9)	16 (10.4)	4 (5.3)		
RCT	63 (36.6)	50 (32.5)	1 (1.3)		
Cohort / prospective	30 (17.4)	29 (18.8)	24 (31.6)		
Case-control	3 (1.7)	4 (2.6)	2 (2.6)		
Case report or series	14 (8.1)	17 (11.0)	31 (40.8)		
Basic biomedical research / preclinical	18 (10.5)	18 (11.7)	5 (6.6)		
Other	17 (9.9)	10 (6.5)	7 (9.2)		
Study characteristics [b], No. (%)					
Registered trial	75 (47.5)	54 (35.5)	0 (0)	<0.0001	<0.0001
Industry funding	37 (22.2)	48 (31.2)	2 (2.7)	<0.0001	<0.0001
Publication characteristics					
Author number, median (IQR)	15 (17)	12 (16)	10.5 (12.75)	0.4499	1
Author affiliations, median (IQR)	8 (7)	7 (13)	4 (4)	<0.0001	<0.0001
Female corresponding or first author [b], No. (%)	59 (36.4)	56 (36.8)	24 (33.8)	0.7671	0.7646
Time to publication, days, mean (SD) [c]	305.3 (124.2)	288.3 (99.7)	35.1 (4.6)	<0.0001	0.0001
Word count, median (IQR)	3816 (2063)	3746 (2061)	914 (2139)	<0.0001	<0.0001
References, median (IQR)	33 (19.75)	33 (24.5)	6 (22)	<0.0001	<0.0001
Publication impact [d], median (IQR)					
Reads [e]	17 648 (21 959)	9 652 (15 110)	224 714 (389 243)	<0.0001	<0.0001
Tweets	168.5 (250.5)	81.5 (149.5)	1202 (4014	<0.0001	<0.0001
Times cited	25 (33.75)	2 (4)	50.5 (125.3)	0.1414	<0.0001

Table 1. Publication characteristics and impact.

Abbreviations: COVID, Coronavirus Disease; JAMA, Journal of the American Medical Association; NEJM, New England Journal of Medicine; RCT, Randomized Controlled Trial. a P values, adjusted for multiple comparison, shown for comparison between COVID and non-COVID publications from the indicated year. b Articles in which study characteristic was not reported or in which gender of author was unknown were excluded from calculation of the proportion. c Includes only Nature Medicine publications as submission dates not reported for JAMA, The Lancet, or NEJM. d Reads, tweets and times cited are reported as absolute numbers and are not normalized to their time since publication. e Excludes articles published in The Lancet, which does not list article reads as part of their Altmetrics.

EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

HOST GENOMICS OF COVID-19: EVIDENCE POINT TOWARDS ALPHA 1 ANTITRYPSIN DEFICIENCY AS A PUTATIVE RISK FACTOR FOR HIGHER MORTALITY RATE

Dutta AK, Goswami K.. Med Hypotheses. 2021 Jan 9;147:110485. doi: 10.1016/j.mehy.2021.110485. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

An in silico study conducted at All India Institute of Medical Sciences in Kalyani, India found that alpha-1 antritrypsin can interact with TMPRSS2, a protein found in the human lung and liver known to increase SARS-CoV-2 viral entry into host cells. The authors also analyzed a dataset to find that Europeans and Latinos are both known to have higher carrier frequency of alpha-1 antritrypsin deficiency and hypothesized that alpha-1 antitrypsin deficiency is a risk factor of poor prognosis with SARS-CoV-2.

ABSTRACT

Corona Virus Disease 2019 (COVID-19) has emerged as a pandemic leading to unprecedented disruption of global health and economy. Transmembrane protease serine 2 (TMPRSS2) has been found to be critical in priming the viral spike protein and the host ACE2 receptor before the virus enters into the host cell. Recent studies have experimentally demonstrated that Alpha 1 antitrypsin (encoded by SERPINA1 gene) is an inhibitor of TMPRSS2 and provided support to the already approved therapy as a candidate for COVID-19. Interestingly Alpha 1 antitrypsin deficiency is common among Europeans. Here we have provided in silico evidence that Alpha 1 antitrypsin can interact with TMPRSS2 and both of them are co-expressed in the human liver and lung. We then analyzed the gnomAD dataset to show that Europeans and Latinos have a substantially higher carrier frequency of Alpha 1 Antitrypsin Deficiency (~12%) compared to other large ethnicities. Therefore, we hypothesize that Alpha 1 antitrypsin deficiency might be a risk factor for severe infection with SARS-CoV-2. We propose Alpha 1 antitrypsin status as a potential prognostic predictor of COVID-19 outcome.

ADULTS

ASSESSMENT OF THIRTY-DAY READMISSION RATE, TIMING, CAUSES, AND PREDICTORS AFTER HOSPITALIZATION WITH COVID-19

Yeo I, Baek S, Kim J, Elshakh H, Voronina A, Lou MS, Vapnik J, Kaler R, Dai X, Goldbarg S.. J Intern Med. 2021 Jan 16. doi: 10.1111/joim.13241. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers from New York-Presbyterian Queens, NY and the Icahn School of Medicine at Mount Sinai, NY conducted a retrospective observational study of 1062 patients hospitalized between March 13 - April 9, 2020 with COVID-19 and subsequently discharged, measuring 30-day readmission data, found that 79 (7.4%) returned to emergency department, of which 48 (4.5% of total) were readmitted. Of those that were readmitted, the majority had a diagnosis of hypoxic respiratory failure (Figure 3) and presented within a week of initial discharge; readmitted patients in general had higher serum creatine levels during initial admission (Figure 4) and had an overall mortality rate of 22.9%. The authors call for additional research regarding COVID-19 readmission, with the relatively low rates suggestive of uncomplicated recovery versus the current strain on the health care system and lack of seeking medical care.

ABSTRACT

BACKGROUND: There is limited data on the characteristics of 30-day readmission after hospitalization with coronavirus disease 2019 (COVID-19). OBJECTIVES: To examine the rate, timing, causes, predictors, and outcomes of 30-day readmission after COVID-19 hospitalization. METHODS: From March 13 to April 9, 2020, all patients hospitalized with COVID-19 and

discharged alive were included in this retrospective observational study. Multivariable logistic regression was used to identify the predictors of 30-day readmission, and a restricted cubic spline function was utilized to assess the linearity of the association between continuous predictors and 30-day readmission. RESULTS: A total of 1062 patients were included in the analysis, with a median follow-up time of 62 days. The mean age of patients was 56.5 years, and 40.5% were women. At the end of the study, a total of 48 (4.5%) patients were readmitted within 30 days of discharge, and a median time to readmission was 5 days. The most common primary diagnosis of 30-day readmission was a hypoxic respiratory failure (68.8%) followed by thromboembolism (12.5%) and sepsis (6.3%). The patients with a peak serum creatinine level of >= 1.29 mg/dL during the index hospitalization, compared to those with a creatinine of < 1.29 mg/dL, had 2.4 times increased risk of 30-day readmission (adjusted odds ratio: 2.41; 95% CI: 1.23-4.74). The mortality rate during the readmission was 22.9%. CONCLUSION: With 4.5% of the thirty-day readmission rate, COVID-19 survivors were readmitted early after hospital discharge, mainly due to morbidities of COVID-19. One in five readmitted COVID-19 survivors died during their readmission.

FIGURES

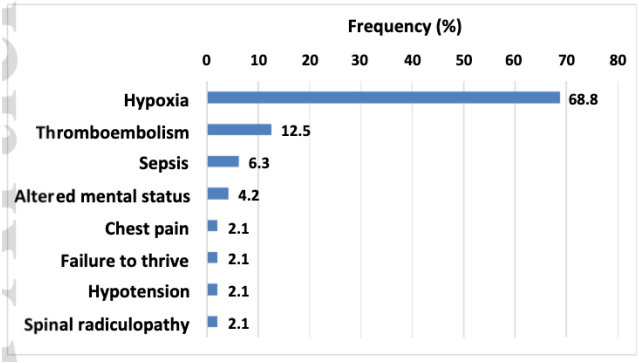


Figure 3. Primary Diagnosis of 30-Day Readmission after Index Hospitalization Related to COVID-19.

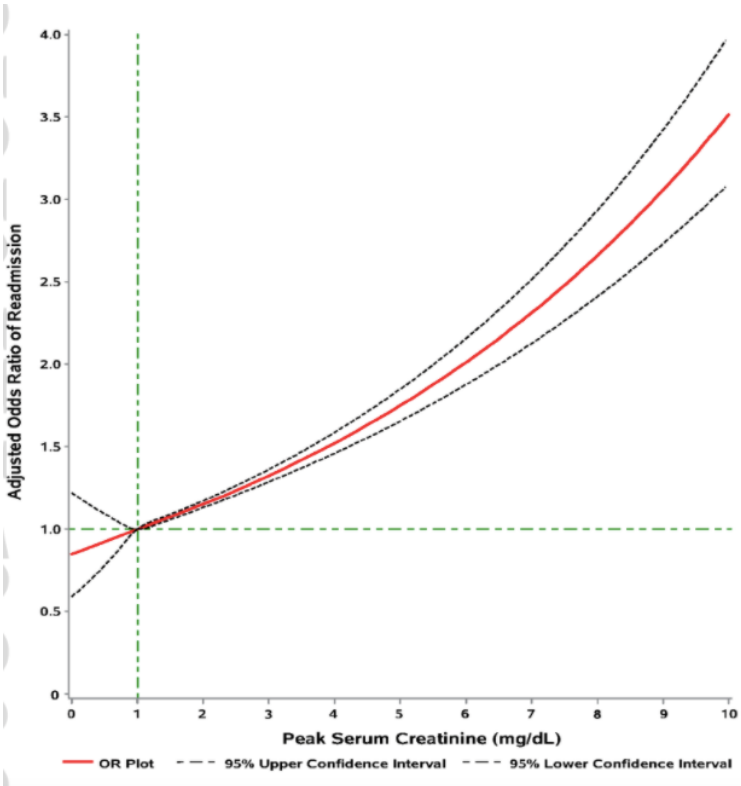


Figure 4. Association between Peak Serum Creatinine Level during Index Hospitalization Related to COVID-19 and 30-Day Readmission. A restricted cubic spline function was used adjusting for covariates including age, body-mass index, hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease /asthma, lactate dehydrogenase, troponin, and discharge disposition.

POTENTIAL LATE EFFECTS OF SARS-COV-2 (COVID-19) INFECTION: PARALLELS TO CANCER LATE EFFECTS

Phipps RP, Sime PJ, Phipps CR.. Cancer Metastasis Rev. 2021 Feb 4. doi: 10.1007/s10555-021-09954-6. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

An expert opinion study penned by doctorates in Richmond, Virginia discusses the potential of SARS-CoV-2 to cause late effects such as cardiomyopathy and lung fibrosis months to years after illness and treatment, similar to the long-term damage seen in cancer patients (Figure 1). This article suggests that long-term follow up and increased monitoring is needed in order to assess the late effects caused by the inflammation and resolution processes associated with COVID-19 and treatment.

FIGURES

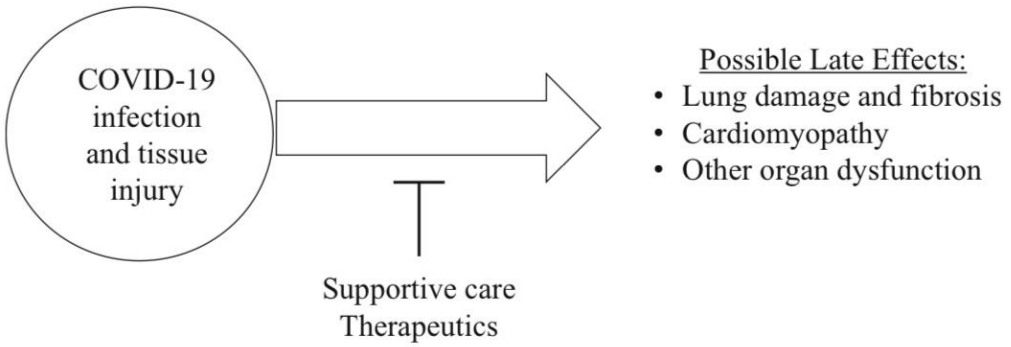


Fig. 1 Following infection with COVID-19, tissue injury is incited by the virus and host immune and inflammatory responses causing organ dysfunction. We postulate in certain cases this may lead to late effects, similar to those seen in oncology. How this is modified by therapies will become evident as data is collected

PREGNANT PERSONS

CLINICAL CHARACTERISTICS AND OUTCOMES OF PREGNANT WOMEN WITH COVID-19 AND COMPARISON WITH CONTROL PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Jafari M, Pormohammad A, Sheikh Neshin SA, Ghorbani S, Bose D, Alimohammadi S, Basirjafari S, Mohammadi M, Rasmussen-Ivey C, Razizadeh MH, Nouri-Vaskeh M, Zarei M.. Rev Med Virol. 2021 Jan 2:e2208. doi: 10.1002/rmv.2208. Online ahead of print.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Investigators from various institutions from Iran, Canada, and United States conducted a meta-analysis and systematic review of 349 studies, of which 121 were studies involving 10,000 pregnant patients (both COVID-19 positive and negative), and 228 were studies involving 128,176 non-pregnant COVID-19 patients. The results revealed that pregnant COVID-19 positive patients are less likely to show classic symptoms (cough, sore throat, headache, or diarrhea), and have a propensity towards different imaging diagnostics, different laboratory results, and higher rate of gestational complications when compared to the two control groups (non-pregnant COVID-19 patients and pregnant COVID-19 negative patients) (Table 1 and 2). This study concludes that pregnant patients and their support system warrant additional preventative measures and education in order to mitigate gestational COVID-19 infection in order to reduce the risk of maternal and neonatal complications.

SUMMARY

In regards to imaging studies conducted, both the majority of pregnant COVID-19 and non-pregnant COVID-19 patients had abnormal lung manifestations, with 89%, and 83.5% respectively. Some of the notable imaging difference between the groups included pregnant COVID-19 patients with 68% bilateral involvement, 41% with consolidation, and 57% with ground-glass opacities. For non-pregnant COVID-19 patients, there was increased rates with 77.2% with bilateral involvement, 76% with consolidation, and 72% with ground-glass opacities. When comparing pregnant patients without COVD-19 verses pregnant patients with COVID-19, there was a significantly higher rate of cesarian delivery in COVID-19 pregnant patients.

ABSTRACT

In a large-scale study, 128176 non-pregnant patients (228 studies) and 10000 pregnant patients (121 studies) confirmed COVID-19 cases included in this Meta-Analysis. The mean (confidence interval [CI]) of age and gestational age of admission (GA) in pregnant women was 33 (28-37) years old and 36 (34-37) weeks, respectively. Pregnant women show the same manifestations of COVID-19 as non-pregnant adult patients. Fever (pregnant: 75.5%; non-pregnant: 74%) and cough (pregnant: 48.5%; non-pregnant: 53.5%) are the most common symptoms in both groups followed by myalgia (26.5%) and chill (25%) in pregnant and dysgeusia (27%) and fatigue (26.5%) in non-pregnant patients. Pregnant women are less probable to show cough (odds ratio [OR] 0.7; 95% CI 0.67-0.75), fatigue (OR: 0.58; CI: 0.54-0.61), sore throat (OR: 0.66; CI: 0.61-0.7), headache (OR: 0.55; CI: 0.55-0.58) and diarrhea (OR: 0.46; CI: 0.4-0.51) than non-pregnant adult patients. The most common imaging found in pregnant women is ground-glass opacity (57%) and in non-pregnant patients is consolidation (76%). Pregnant women have higher proportion of leukocytosis (27% vs. 14%), thrombocytopenia (18% vs. 12.5%) and have lower proportion of raised C-reactive protein (52% vs. 81%) compared with non-pregnant patients. Leucopenia and lymphopenia are almost the same in both groups. The most common comorbidity in pregnant patients is diabetes (18%) and in non-pregnant patients is hypertension (21%). Case fatality rate (CFR) of non-pregnant hospitalized patients is 6.4% (4.4-8.5), and mortality due to all-cause for pregnant patients is 11.3% (9.6-13.3). Regarding the complications of pregnancy, postpartum hemorrhage (54.5% [7-94]), caesarean delivery (48% [42-54]), preterm labor (25% [4-74]) and preterm birth (21% [12-34]) are in turn the most prevalent complications. Comparing the pregnancy outcomes show that caesarean delivery (OR: 3; CI: 2-5), low birth weight (LBW) (OR: 9; CI: 2.4-30) and preterm birth (OR: 2.5; CI: 1.5-3.5) are more probable in pregnant woman with COVID-19 than pregnant women without COVID-19. The most prevalent neonatal complications are neonatal intensive care unit admission (43% [2-96]), fetal distress (30% [12-58]) and LBW (25% [16-37]). The rate of vertical transmission is 5.3% (1.3-16), and the rate of positive SARS-CoV-2 test for neonates born to mothers with COVID-19 is 8% (4-16). Overall, pregnant patients present with the similar clinical characteristics of COVID-19 when compared with the general population, but they may be more asymptomatic. Higher odds of caesarean delivery, LBW and preterm birth among pregnant patients with COVID-19 suggest a possible association between COVID-19 infection and pregnancy complications. Low risk of vertical transmission is present, and SARS-CoV-2 can be detected in all conception products, particularly placenta and breast milk. Interpretations of these results should be done cautiously due to the heterogeneity between studies; however, we believe our findings can guide the prenatal and postnatal considerations for COVID-19 pregnant patients.

	Non-pregnant (total of 328 studies, 138,176 patients)					Pregnant (total 121 studies, 15 000 patients)				
Variables	Proportion % /Mean* (95% CI)	Number of included studies	Number of included patients	I^2	p-Value**	Proportion% /Mean* (95% CI)	Number of included studies	Number of included patients	I^2	p-Value**
Age (years)*	51.2 [45–57]	189	125,160	98	<0.001	33 [28–37]	56	3348	90	<0.001
Male sex	52.2 [50–53.2]	236	127,743	61	<0.001	-	-	-	-	-
Fever	74 [72.5–75]	182	125,237	89	<0.001	75.5 [36–589]	55	3302	75	<0.001
Chill	15.5 [9–21]	34	9577	89	<0.001	25 [17–87]	5	302	77	0.01
Body temperature (°C)	37.2 [37.1–37.3]	28	7691	53	0.01	36.7 [mean 35–38.5]	27	159	99	<0.001
Fatigue	39.5 [34–30]	143	121,643	92	<0.001	21 [17–25.5]	25	2330	66	<0.001
Myalgia	19.5 [17–24]	145	93,077	91	<0.001	20.5 [19–28]	30	5196	79	<0.001
Dyspnea	14.5 [13–15]	128	78,761	89	<0.001	22 [16–28]	26	2836	86	<0.001
Cough	52.5 [50–58]	183	125,162	89	<0.001	48.5 [42–55]	52	3175	84	<0.001
Sputum	19.5 [18–24]	134	83,506	83	<0.001	13 [5–31.5]	33	1209	93	<0.001
Sore throat	10.5 [9.5–14]	98	52,969	89	<0.001	9 [6–14]	30	315	0	0.7
Dysgeusia	37 [10–60]	14	1020	0	0.9	6 [3–10]	2	221	0	0.09
Anosmia	35 [13–46]	18	1220	0	0.9	15.5 [5–31.5]	9	1260	90	<0.001
Headache	11 [9–12]	123	72,311	81	<0.001	15 [5–46]	8	240	69	0.02
Chest pain	11 [9–12.5]	78	42,759	89	<0.001	13 [9–19]	13	216	0	0.09
Diarrhoea	8 [6.6–11]	131	83,403	93	<0.001	9 [6–12.5]	24	2109	73	<0.001
Nausea and vomiting	6 [4–8.5]	81	52,608	89	<0.001	11 [7–16]	13	950	75	<0.001
Homocystein	3 [1.5–4.5]	28	7754	71	<0.001	3.5 [3.5–19]	7	696	69	0.07
Renal injury	5.5 [4–14.5]	58	6577	92	<0.001	3 [1–8.5]	12	1301	73	0.06
Risk factors and comorbidities										
Non-pregnant						Pregnant				
Proportion% (95% CI)		Number of included studies	Number of included patients	I^2	p-Value**	Proportion% (95% CI)	Number of included studies	Number of included patients	I^2	p-Value**
Contact history*	41 [35–52]	65	11,126	94	<0.001	35 [20–54]	26	6365	97	<0.001
Healthcare worker	23.5 [9–42]	43	89,667	92	<0.001	17 [6.5–31]	5	125	64	0.02
Hypertension	21 [16–24]	186	119,461	94	<0.001	9 [6–13]	26	8126	96	<0.001
Diabetes	13 [10.5–16.5]	203	96,565	94	<0.001	10 [13–37]	23	8267	0	0.4
Non gestational diabetes	-	-	-	-	-	8 [4.5–13]	25	8432	82	<0.001
Gestational diabetes						10 [7.5–13.5]	28	1263	37	0.07
Chronic respiratory disease	10.5 [7–16.5]	67	88,478	96	<0.001	4.3 [3–10]	14	8066	93	<0.001
Risk factors and comorbidities										
Non-pregnant						Pregnant				
Proportion% (95% CI)		Number of included studies	Number of included patients	I^2	p-Value**	Proportion% (95% CI)	Number of included studies	Number of included patients	I^2	p-Value**
Bacterial co-infection	4.3 [1.4–11]	31	3767	89	<0.001	16 [2.5–61]	10	5467	84	<0.001
Viral co-infection	4.5 [2–11]	28	5875	84	<0.001	14 [7.5–25]	17	5134	0	0.6
Chest x-ray and CT scan findings										
Non-pregnant						Pregnant				
Proportion% (95% CI)		Number of included studies	Number of included patients	I^2	p-Value**	Proportion% (95% CI)	Number of included studies	Number of included patients	I^2	p-Value**
Maternal abnormal chest imaging	83.5 [77–80]	29	3765	89	<0.001	89 [75–95]	30	2361	96	<0.001
Bilateral involvement	77.2 [61.5–86]	35	86,156	91	<0.001	68 [54–79]	22	3477	85	<0.001
Unilateral involvement	16 [12–21.5]	63	8436	89	<0.001	26 [21–32]	14	1387	34	0.11
Consolidation	76 [50.5–93]	56	3454	91	<0.001	41 [30–53]	9	771	85	<0.001
Ground glass opacity	73 [61–82]	37	97,768	82	<0.001	57 [39–73]	7	1470	94	<0.001
Neonatal abnormal chest X-ray	-	-	-	-	-	49 [13–91]	9	109	69	0.09
Outcome										
Non-pregnant						Pregnant				
Proportion% (95% CI)		Number of included studies	Number of included patients	I^2	p-Value**	Proportion% (95% CI)	Number of included studies	Number of included patients	I^2	p-Value**
Case fatality rate*	6.4 [4.4–8.5]	153	98,997	89	<0.001	11.3 [9.6–13.3]	38	2660	82	<0.001

Table 1. Demographics and clinical manifestations of CVOID-19 in pregnant women compared with non-pregnant adult patients with confirmed SARS-CoV-2 infection.

Variables	Odds ratio (95% CI)	Number of studies	I^{2**}	p-value***	Pregnant Women with COVID-19 (Case) *n/N*	Non-pregnant patients with COVID-19 (Control) *n/N*
Fever	0.8 (0.6–1.1)	5	95	<0.001	4562/31,871	87,090/470,092
Cough	0.7 (0.67–0.75)	5	85	<0.001	23,114/241,238	41,570/121,240
Sore throat	0.66 (0.61–0.7)	5	82	<0.001	543/14,238	1682/41,240
Headache	0.55 (0.55–0.58)	5	65	0.007	2710/14,138	41,899/121,240
Fatigue	0.58 (0.54–0.61)	5	91	<0.001	1929/13,238	30,505/98,240
Diarrhoea	0.46 (0.4–0.51)	4	87	<0.001	872/14,138	18,121/142,240
Nausea and vomiting	1 (0.94–1.1)	3	0	0.8	2737/31,672	35,798/469,268
	Odds ratio (95% CI)	**Number of studies**	I^{2**}	**p-Value*** **	**Pregnant women with COVID-19 (Case) *n/N***	**Pregnant women without COVID-19 (Control) *n/N***
Non-gestational diabetes	1.3 (0.87–1.9)	5	0	0.9	36/638	120/2671
Singleton	0.11 (−0.2–0.68)	3	0	0.4	118/121	414/415
Medical comorbidities	8.4 (0.7–92)	3	49	0.16	4/32	5/242
Preterm birth	2.5 (1.5–3.5)	8	0	0.8	45/295	694/12,634
Low birth weight	9 (2.4–30)	2	0	0.99	6/32	6/242
Fetal distress	2.7 (0.6–9)	2	0	0.99	4/32	12/242
Caesarean delivery	3 (2–5)	7	28	0.21	179/257	6399/12,060
Lab findings						
Odds ratio (95% CI)		**Number of study**	I^{2**}	**p-Value*** **	**Pregnant women with COVID-19 (Case) *n/N***	**Pregnant Women without COVID-19 (Control) *n/N***
Leucocyte (mean)	0.7 (0.3–1)	2	0	0.54	32	242
Neutrophil (mean)	0.53 (0.15–0.9)	2	0	0.4	32	242
Lymphocyte (mean)	0.4 (0.15–0.8)	2	0	0.6	32	242
Lymphocytes decreased*	1 (0.3–3)	2	0	0.9	4/32	29/242
CRP (mean)	0.37 (0.01–0.7)	2	0	0.4	32	242
CRPIncreased*	0.4 (0.2–0.9)	2	0	0.65	10/32	125/242
ALT (mean)	0.05 (−0.36–0.4)	2	0	0.9	32	242
AST (mean)	0.3 (0.02–0.9)	2	0	0.56	32	242

Table 2. Association of clinical symptoms, pregnancy, outcomes and laboratory findings between case and control groups.

INPATIENT MEDICINE

MORTALITY IS NOT INCREASED IN SARS-COV-2 INFECTED PERSONS WITH HEPATITIS C VIRUS INFECTION

Butt AA, Yan P, Chotani RA, Shaikh OS.. Liver Int. 2021 Feb 3. doi: 10.1111/liv.14804. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

This retrospective study from the University of Pittsburgh Medical Center examines the impact of concurrent hepatitis C (HCV) and COVID-19 infections on hospitalization and ICU admission using the Electronically Retrieved Cohort of HCV Infected Veterans database. The authors found that while patients with both COVID-19 and HCV are more likely to be hospitalized, especially patients with higher FIB-4 scores, the rate of ICU admission and mortality is not significantly affected by HCV status.

ABSTRACT

BACKGROUND: Impact of SARS-CoV-2 infection upon hospitalization, intensive care unit (ICU) admissions and mortality in persons with hepatitis C virus (HCV) infection is unknown METHODS: We used the Electronically Retrieved Cohort of HCV infected Veterans (ERCHIVES) database to determine the impact of HCV infection upon the rates of acute care hospitalization, ICU admission and all-cause mortality. We identified Veterans with chronic HCV infection and propensity-score matched controls without HCV in ERCHIVES. We excluded those with HIV or hepatitis B virus coinfection, RESULTS: We identified 975 HCV+ and 975 propensity-score matched HCV- persons with SARS-CoV-2 infection. Mean FIB-4 score (+-SD) was higher in those with HCV (1.9+-2.1 vs. 1.2+-0.9; P<0.0001) and a larger proportion of those with HCV had cirrhosis (8.1% vs. 1.4%; P<0.0001). A larger proportion of HCV+ were hospitalized compared to HCV- (24.0% vs. 18.3%; p=0.002); however, those requiring ICU care and mortality was also similar in both groups (6.6% vs. 6.5%; P=0.9). Among those with FIB-4 score of 1.45-3.25, hospitalization rate/1,000-person-years was 41.4 among HCV+ and 20.2 among HCV-, while among those with a FIB-4>3.25, the rate- was 9.4 and 0.6 (P<0.0001). There was no difference in all-cause mortality by age, sex, FIB-4 score, number of comorbidities or treatment with remdesivir and/or systemic corticosteroids. CONCLUSIONS: HCV+ persons with SARS-CoV-2 infection are more likely to be admitted to a hospital. The hospitalization rate also increased with higher FIB-4 score. However, admission to an ICU and mortality are not different between those with and without HCV infection.

DIAGNOSTIC VALUE OF PATIENT-REPORTED AND CLINICALLY TESTED OLFACTORY DYSFUNCTION IN A POPULATION SCREENED FOR COVID-19

Villerabel C, Makinson A, Jaussent A, Picot MC, Nègre-Pagès L, Rouvière JA, Favier V, Crampette L, Morquin D, Reynes J, Le Moing V, Tuaillon E, Venail F.. JAMA Otolaryngol Head Neck Surg. 2021 Jan 7. doi: 10.1001/jamaoto.2020.5074. Online ahead of print.
Level of Evidence: 2 - Individual cross sectional studies with consistently applied reference standard and blinding

BLUF

Investigators from various institutions in Montpellier, France evaluated the diagnostic value of olfactory test Clinical Olfactory Dysfunction Assessment (CODA) in a prospective double blinded survey of 809 people who were referred for COVID-19 testing from March 23 - April 22, 2020, concluding 35% of those with subsequently confirmed SARS-CoV-2 had self-reported acute olfactory dysfunction (OD) and/or gustatory dysfunction (GD). These results suggest the utility of CODA as a screening tool for those that are asymptotic or have mild COVID-19 symptoms prior to additional testing.

SUMMARY

This prospective, observer and participant blinded study consisted of a preliminary assessment to determine degree of OD and/or GD, followed by confirmatory SARS-CoV-2 testing. The study included 809 participants who were referred for SARS-CoV-2 testing that were either asymptomatic or had mild symptoms. They were first asked to complete a survey of "yes" or "no" responses to hyposmia (decreased smell), anosmia (no smell), or decreased ability to taste sweet, salty, bitter, sour, or umami, as well as certain and flavors that corresponded to the olfactory component of taste, such as coffee or strawberry flavors. They then completed an assessment adapted from the University of Pennsylvania Smell Identification Test, using strips dipped in 3 different fragrant oils (lavender, lemongrass, and mint), asking subjects to identify each scent with corresponding score of intensity. Each subject was then tested for SARS-CoV-2 by rtPCR. They found that 58 participants had positive SARS-CoV-2 results, with 35% of those also had an acute decrease in OD and/or GD, as compared to only 4% of those that tested negative. The authors suggest the utility of CODA, or similar assessments, as useful screening tools for the sensitivity and specificity of COVID-19 (Table 2, Figure 2), especially in populations that may be asymptomatic or have more mild symptoms.

ABSTRACT

Importance: Recent studies have suggested that olfactory dysfunction and gustatory dysfunction are associated with coronavirus disease 2019 (COVID-19). However, olfaction has been evaluated solely on reported symptoms, after COVID-19 diagnosis, and in both mild and severe COVID-19 cases, but rarely has it been assessed in prospectively unselected populations. Objective: To evaluate the diagnostic value of a semiobjective olfactory test developed to assess patient-reported chemosensory dysfunction prior to testing for the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients attending a COVID-19 screening facility. Design, Setting, and Participants: This prospective diagnostic study with participants and observers blinded to COVID-19 status was conducted in a COVID-19 screening center of a tertiary university hospital in France from March 23 to April 22, 2020. Participants were 854 consecutively included health care workers or outpatients with symptoms or with close contact with an index case. Exclusion criteria were prior chemosensory dysfunction, testing inability, or contraindications (n = 45). Main Outcomes and Measures: Participants were interviewed to ascertain their symptoms and then underwent Clinical Olfactory Dysfunction Assessment (CODA), an ad hoc test developed for a simple and fast evaluation of olfactory function. This assessment followed a standardized procedure in which participants identified and rated the intensity of 3 scents (lavender, lemongrass, and mint) to achieve a summed score ranging from 0 to 6. The COVID-19 status was assessed using reverse transcriptase-polymerase chain reaction to detect the presence of SARS-CoV-2 in samples collected via nasopharyngeal swab (reference standard) to calculate the diagnostic values of patient-reported chemosensory dysfunction and CODA. Results: Of 809 participants, the female to male sex ratio was 2.8, and the mean (SD) age was 41.8 (13.0) years (range, 18-94 years). All participants, if symptomatic, had mild disease at the time of testing, and 58 (7.2%) tested positive for SARS-CoV-2. Chemosensory dysfunction was reported by 20 of 58 participants (34.5%) with confirmed COVID-19 vs 29 of 751 participants (3.9%) who tested negative for COVID-19 (absolute difference, 30.6% [95% CI, 18.3%-42.9%]). Olfactory dysfunction, either self-reported or clinically ascertained (CODA score <=3), yielded similar sensitivity (0.31 [95% CI, 0.20-0.45] vs 0.34 [95% CI, 0.22-0.48]) and specificity (0.97 [95% CI, 0.96-0.98) vs 0.98 [95% CI, 0.96-0.99]) for COVID-19 diagnosis. Concordance was high between reported and clinically tested olfactory dysfunction, with a Gwet AC1 of 0.95 (95%

CI, 0.93-0.97). Of 19 participants, 15 (78.9%) with both reported olfactory dysfunction and a CODA score of 3 or lower were confirmed to have COVID-19. The CODA score also revealed 5 of 19 participants (26.3%) with confirmed COVID-19 who had previously unperceived olfactory dysfunction. Conclusions and Relevance: In this prospective diagnostic study of outpatients with asymptomatic or mild to moderate COVID-19, systematically assessed anamnesis and clinical testing with the newly developed CODA were complementary and specific for chemosensory dysfunction. Olfactory dysfunction was suggestive of COVID-19, particularly when clinical testing confirmed anamnesis. However, normal olfaction was most common among patients with COVID-19.

FIGURES

Table 2. Diagnostic Values of Suggestive Patient-Reported COVID-19 Symptoms and CODA Total Score

Clinical feature	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR	NLR
Cough	0.45 (0.32-0.58)	0.70 (0.67-0.73)	0.10 (0.07-0.15)	0.94 (0.92-0.96)	1.50	0.79
Fever	0.34 (0.22-0.48)	0.81 (0.78-0.84)	0.12 (0.08-0.18)	0.94 (0.92-0.96)	1.82	0.81
Headache	0.30 (0.18-0.43)	0.83 (0.80-0.86)	0.12 (0.07-0.18)	0.94 (0.92-0.96)	1.75	0.85
Myalgia	0.21 (0.11-0.34)	0.92 (0.90-0.94)	0.17 (0.09-0.28)	0.94 (0.92-0.96)	2.72	0.86
OD	0.31 (0.20-0.45)	0.97 (0.96-0.98)	0.47 (0.31-0.64)	0.95 (0.93-0.96)	11.65	0.71
Flavor-GD	0.26 (0.15-0.39)	0.98 (0.96-0.99)	0.47 (0.29-0.65)	0.94 (0.93-0.96)	11.42	0.76
Taste-GD	0.07 (0.02-0.17)	0.99 (0.98-0.99)	0.31 (0.09-0.61)	0.93 (0.91-0.95)	5.75	0.94
OD and/or GD	0.34 (0.22-0.48)	0.96 (0.95-0.97)	0.41 (0.27-0.56)	0.95 (0.93-0.96)	8.93	0.68
CODA total score						
0	0.19 (0.10-0.31)	1.00 (0.99-1.00)	0.85 (0.55-0.98)	0.94 (0.92-0.96)	71.22	0.81
≤1	0.26 (0.15-0.39)	1.00 (0.99-1.00)	0.88 (0.64-0.99)	0.95 (0.93-0.96)	97.11	0.74
≤2	0.31 (0.20-0.45)	0.99 (0.98-1.00)	0.72 (0.51-0.88)	0.95 (0.93-0.96)	33.30	0.70
≤3	0.34 (0.22-0.48)	0.98 (0.96-0.99)	0.53 (0.36-0.69)	0.95 (0.93-0.96)	14.39	0.67
≤4	0.47 (0.33-0.60)	0.87 (0.85-0.90)	0.22 (0.15-0.31)	0.95 (0.94-0.97)	3.72	0.61
≤5	0.66 (0.52-0.78)	0.54 (0.50-0.57)	0.10 (0.07-0.13)	0.95 (0.93-0.97)	1.41	0.64
≤6	1.00	0.00	0.07	NA	1.00	NA

Abbreviations: CODA, Clinical Olfactory Dysfunction Assessment; COVID-19, coronavirus disease 2019; GD, gustatory dysfunction; NA, not applicable; NLR, negative likelihood ratio; NPV, negative predictive value; OD, olfactory dysfunction; PLR, positive likelihood ratio; PPV, positive predictive value.

Table 2. Diagnostic Values of Suggestive Patient-Reported COVID-19 Symptoms and CODA Total Score.

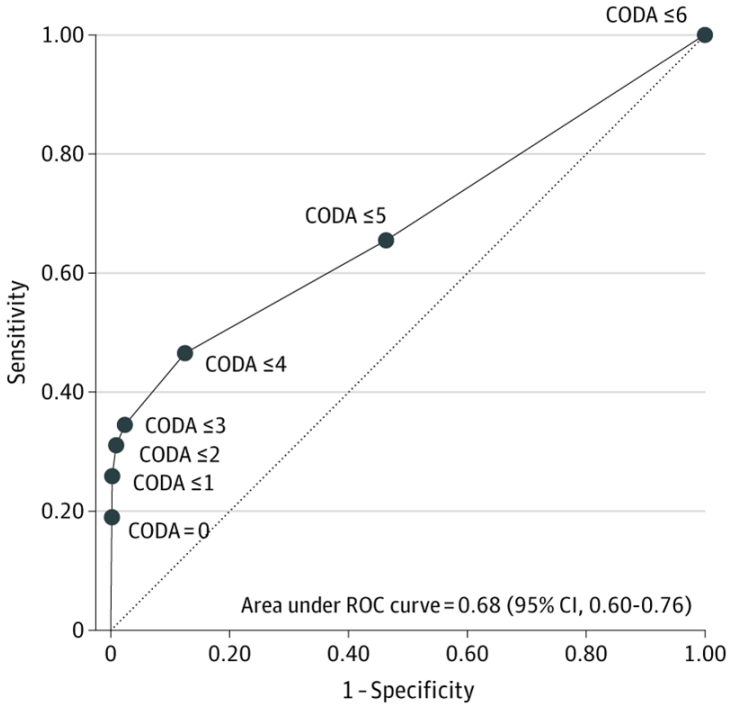


Figure 2. Receiver Operating Characteristic (ROC) Curve Depicting the Performances of the Clinical Olfactory Dysfunction Assessment (CODA) to Detect Confirmed Cases of Coronavirus Disease 2019.

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