The Daily COVID-19 Literature Surveillance Summary

August 22, 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

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EXECUTIVE SUMMARY

Climate

- Infectious disease doctors affiliated with the University of Turin, Italy discussed the ambiguity and dismay among the scientific community in response to COVID-19. They identify pitfalls regarding standardization of diagnostics including RT-PCR, antibody lateral flow immunoassays and ELISA; prevention--citing a paper by Zhang et al, 2020 asserting airborne transmission as the dominant route while quarantine was not in place in many parts of the world; and therapy stating that many articles were retracted possibly due to rushed publishing followed by uncertainty.

Transmission and Prevention

- A cross sectional study conducted in Spain found that in 23 household pets owned by people with confirmed COVID-19, one female cat had a positive SARS-CoV-2 RT-qPCR result from oropharyngeal swab, suggesting that the virus may be transmitted from humans to cats. The authors acknowledge the limitation of their small sample size and recommend further study into animal models as hosts for SARS-CoV-2

R&D: Diagnosis and Treatment

- A single-center randomized controlled trial investigated the efficacy of combination therapy with 400 mg sofosbuvir, 60 mg daclatasvir, and 1200 mg ribavirin among 48 patients (24 in intervention group, 24 controls) with moderate COVID-19 infection. Data revealed a shorter time to recovery in the intervention group, but no significant difference in ICU admission rates, number of deaths, or median duration of hospital stay.

Understanding the Pathology

- A review by the European Association for the Study of Obesity (EASO) discussed the immunological basis by which obese patients may be more susceptible to COVID-19 via mechanisms including decreased CD4/CD8 T cell activation and increased renin-angiotensin-aldosterone system (RAAS) activity. The authors advocate for COVID-19 patient phenotyping to identify subgroups at increased risk and urge further research into this area.
- Cardiologists in the United States examined the potential association of viral myocarditis with SARS-CoV-2 by assessing angiotensin-converting enzyme 2 (ACE2) in the left ventricles of patients with previous heart disease. Their findings showed:
    - ACE2 expression was highest in pericytes but was also observed in vascular smooth muscle cells, fibroblasts, and cardiomyocytes.
    - No significant changes in ACE2 expression were observed in patients with dilated or hypertrophic cardiomyopathy.
    - ACE2 expression in patients with hypertrophic cardiomyopathy was increased in all cell types.

TABLE OF CONTENTS

CLIMATE

GLOBAL

COVID-19: IN THE UNCERTAINTY, DO NOT TRY THIS AT HOME

Lupia T, Corcione S, De Rosa FG.. Intern Emerg Med. 2020 Aug 17. doi: 10.1007/s11739-020-02471-4. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A letter to the editor by authors affiliated with Infectious Diseases at University of Turin, Italy discussed the ambiguity and dismay among the scientific community in response to COVID-19. They identify pitfalls regarding standardization of diagnostics including RT-PCR, antibody lateral flow immunoassays and ELISA; prevention--citing a paper by Zhang et al, 2020 asserting airborne transmission as the dominant route while quarantine was not in place in many parts of the world; and therapy stating that many articles were retracted possibly due to rushed publishing followed by uncertainty. Authors suggest a lack of treatment safety data and efficacy highlights the importance of caution when caring for COVID-19 patients to avoid treating with ineffective or harmful drugs.

DISPARITIES

EXPANDING BILINGUAL SOCIAL WORKERS FOR THE EAST ASIAN OLDER ADULTS BEYOND THE "COVID-19 RACISM"

Lee S.. J Gerontol Soc Work. 2020 Aug 19:1-3. doi: 10.1080/01634372.2020.1802635. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

A professional opinion piece by an American doctoral student found that older East Asian adults, who were already prone to worse health outcomes due to high poverty rates, low Social Security benefits, and high vulnerability to mental health issues, are facing more issues of discrimination and targeted violence due to COVID-19 stigmatization. Since many of these issues are brought about by cultural and linguistic barriers, the author advocates for the support of Asian bilingual social workers and volunteers in the healthcare system to assist the Asian community against COVID-19 racism.

UNDERSTANDING THE PATHOLOGY

OBESITY AND COVID-19: A PERSPECTIVE FROM THE EUROPEAN ASSOCIATION FOR THE STUDY OF OBESITY ON IMMUNOLOGICAL PERTURBATIONS, THERAPEUTIC CHALLENGES, AND OPPORTUNITIES IN OBESITY

Goossens GH, Dicker D, Farpour-Lambert NJ, Frühbeck G, Mullerova D, Woodward E, Holm JC.. Obes Facts. 2020 Aug 13:1-14. doi: 10.1159/000510719. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review article by the European Association for the Study of Obesity (EASO) discussed the immunological basis by which obese patients may be more susceptible to COVID-19 and have worse clinical outcomes upon infection via mechanisms including decreased CD4/CD8 T cell activation and increased renin-angiotensin-aldosterone system (RAAS) activity. Authors advocate for COVID-19 patient phenotyping to identify subgroups at increased risk in addition to further clinical research, suggesting improved understanding of concomitant obesity and COVID-19 may inform on disease progression/outcomes and help develop strategies for prevention, care access, and future therapeutics.

ABSTRACT

Accumulating evidence suggests that obesity is a major risk factor for the initiation, progression, and outcomes of coronavirus disease 2019 (COVID-19). The European Association for the Study of Obesity (EASO), as a scientific and medical society dedicated to the promotion of health and well-being, is greatly concerned about the concomitant obesity and COVID-19 pandemics and their impact on health and society at large. In this perspective, we will address the inherent immunological perturbations and alterations in the renin-angiotensin-aldosterone system in patients with obesity and COVID-19, and discuss how these impairments may underlie the increased susceptibility and more detrimental outcomes of COVID-19 in people with obesity. Clearly, this has important implications for preventive measures, vaccination, and future therapeutic strategies to combat COVID-19. Furthermore, we will highlight important knowledge gaps and provide suggestions for future research and recommendations for policy actions. Since many new reports on COVID-19 rapidly appear, the present perspective should be seen as a focus for discussion to drive forward further understanding, research initiatives, and clinical management of COVID-19.

IN VITRO

MYOCYTE-SPECIFIC UPREGULATION OF ACE2 IN CARDIOVASCULAR DISEASE: IMPLICATIONS FOR SARS-COV-2-MEDIATED MYOCARDITIS

Tucker NR, Chaffin M, Bedi KC Jr, Papangeli I, Akkad AD, Arduini A, Hayat S, Eraslan G, Muus C, Bhattacharyya RP, Stegmann CM; Human Cell Atlas Lung Biological Network, Margulies KB, Ellinor PT; Human Cell Atlas Lung Biological Network Consortium Members.. Circulation. 2020 Aug 18;142(7):708-710. doi: 10.1161/CIRCULATIONAHA.120.047911. Epub 2020 Jun 22.
Level of Evidence: 3 - Local non-random sample

BLUF

A group of cardiologists across the United States examined the potential association of viral myocarditis with SARS-CoV-2 by assessing angiotensin-converting enzyme 2 (ACE2) expression via bulk and single nucleus RNA-sequencing on the left ventricles of patients with previous heart disease (n=26). Their findings showed:

1) ACE2 expression was highest in pericytes but was also observed in vascular smooth muscle cells, fibroblasts, and cardiomyocytes (Figure A).
2) No significant changes in ACE2 expression were observed in patients with dilated (n=11) or hypertrophic (n=15) cardiomyopathy (Figure B) compared to controls with nonfailing hearts (n=16).
3) ACE2 expression in patients with hypertrophic cardiomyopathy was increased in all cell types (Figure D).

This study suggests that a history of cardiovascular disease can lead to increased ACE2 expression and provides a pathologic

link between SARS-CoV-2 and viral myocarditis. However, the authors acknowledge it is important to also consider the limitations on statistical analysis of single nucleus sequencing data.

FIGURES

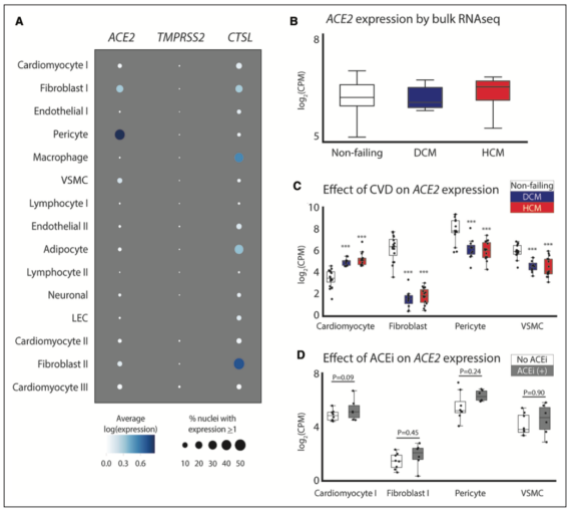

Figure: Assessment of ACE2 expression in the human myocardium.

A, Dot plot representing the relative expression of ACE2, CTSL, and TMPRSS2 in the left ventricle. Size and hue of the dot indicate the percent of nuclei expressing and the mean of the log-transformed, normalized counts for all nuclei in each cell type. B, Expression of ACE2 by bulk RNA-Seq from nonfailing, dilated cardiomyopathy (DCM), and hypertrophic cardiomyopathy (HCM) ventricles. C, Single nucleus RNA-Seq from the same tissue samples as in B with mean expression of ACE2 in cell subtypes with appreciable expression. D, Effects of angiotensin-converting enzyme inhibitors (ACEis) on ACE2 expression across cell types in individuals with HCM. Boxes represent 25% to 75% and whiskers represent the minimum-maximum range, excluding outliers. ***P<0.001. CVD indicates cardiovascular disease; LEC, lymphatic endothelial cell; and VSMC, vascular smooth muscle cell.

DETECTION OF SARS-COV-2 IN PETS LIVING WITH COVID-19 OWNERS DIAGNOSED DURING THE COVID-19 LOCKDOWN IN SPAIN: A CASE OF AN ASYMPTOMATIC CAT WITH SARS-COV-2 IN EUROPE

Ruiz-Arrondo I, Portillo A, Palomar AM, Santibáñez S, Santibáñez P, Cervera C, Oteo JA.. Transbound Emerg Dis. 2020 Aug 18. doi: 10.1111/tbed.13803. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A cross sectional study conducted in La Rioja, Spain by researchers at The Center of Rickettsiosis and Arthropod-Borne Diseases found that in 23 household pets owned by people with confirmed COVID-19 from April to May 2020 (Table 1), one female cat had a positive SARS-CoV-2 RT-qPCR result from oropharyngeal swab, suggesting that the virus may be transmitted from humans to cats. The authors acknowledge the limitation of their small sample size and recommend further study into animal models as hosts for SARS-CoV-2.

ABSTRACT

Pets from COVID-19 owners were screened for SARS-CoV-2 (April-May 2020). From 23 pets, an asymptomatic cat showed positive RT-qPCRs results from oropharyngeal swab (negative rectal swab). Remaining pets were negative. This suggests that cats can contract the virus from their infected owners and may act as potential hosts for SARS-CoV-2. Their role in carrying live or infectious viruses and disseminating them needs more investigation.

FIGURES

Table 1. Characteristics of pets screened for SARS-CoV-2 living with owners diagnosed with COVID-19 during the quarantine (April-May 2020), in La Rioja (Spain).

Sample ID	Pet	Breed	Age (years)	Gender	SARS-CoV-2 RT-qPCR results		Disease severity of COVID-19 in pet owners	Days from owner's COVID-19 diagnosis to pet sample collection
					Oropharyngeal swab	Rectal swab		
covid1	Guinea pig	Indeterminate	<1	Male	Negative	Negative	Moderate	6
covid2	Cat	European	11	Male	Negative	Negative	Moderate	9
covid3	Cat	European	9	Male	Negative	Negative		
covid4	Dog	Spanish mastiff	<1	Male	Negative	Negative	Moderate	11
covid5	Cat	European	6	Male	Negative	Negative	Mild	9
covid6	Dog	Bichon maltese	11	Female	Negative	Negative	Severe	10
covid7	Dog	Bichon maltese	11	Male	Negative	Negative		
covid8	Cat	European	8	Female	Positive	Negative	Severe	4
covid9	Cat	European	7	Male	Negative	Negative		
covid10	Dog	Yorkshire	3	Female	Negative	Negative	Moderate	3
covid11	Dog	Mixed mastiff	10	Male	Negative	Negative	Moderate	3
covid12	Cat	European	15	Male	Negative	Negative	Moderate	3
covid13	Dog	Gos d'atura	5	Male	Negative	Negative	Moderate	20
covid14	Rabbit	Super toy	2	Macho	Negative	Negative	Mild	32
covid15	Rabbit	Teddy	1	Macho	Negative	Negative		
covid16	Dog	Labrador retriever	4	Female	Negative	Negative	Mild	17
covid17	Dog	Mixed breed	6	Female	Negative	Negative	Mild†	29
							Moderate†	26
covid18	Cat	Toyger	6	Male	Negative	Negative	Mild	18
covid19	Cat	European	4	Female	Negative	Negative		
covid20	Dog	Mixed Villano-Alano	<1	Female	Negative	Negative	Mild	16
covid21	Dog	Mixed breed	9	Female	Negative	Negative	Mild	41
covid22	Dog	Great dane	11	Female	Negative	Negative		
covid23	Dog	Spanish water dog	3	Female	Negative	Negative	Mild	26

†Two confirmed human cases in the same household. Mild: upperway respiratory clinic without radiological data from pulmonary involvement; Moderate: respiratory involvement with radiological alteration without th need for oxygen; Severe: respiratory involvement with radiological alteration and need of oxygen.

Table 1 (continued)

EVALUATION OF THE EFFICACY OF SOFOSBUVIR PLUS DACLATASVIR IN COMBINATION WITH RIBAVIRIN FOR HOSPITALIZED COVID-19 PATIENTS WITH MODERATE DISEASE COMPARED WITH STANDARD CARE: A SINGLE-CENTRE, RANDOMIZED CONTROLLED TRIAL

Abbaspour Kasgari H, Moradi S, Shabani AM, Babamahmoodi F, Davoudi Badabi AR, Davoudi L, Alikhani A, Hedayatizadeh Omran A, Saeedi M, Merat S, Wentzel H, Garratt A, Levi J, Simmons B, Hill A, Tirgar Fakheri H.. J Antimicrob Chemother. 2020 Aug 19:dkaa332. doi: 10.1093/jac/dkaa332. Online ahead of print.

Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

A single-center RCT study investigated efficacy of combination therapy with 400 mg sofosbuvir, 60 mg daclatasvir, and 1200 mg ribavirin among 48 patients (24 in intervention group, 24 controls) with moderate COVID-19 infection admitted between March 20, 2020 and April 8, 2020 to Ghaem Shahr Razi hospital in Mazandaran Province, Iran (Figure 1). This study found a shorter time to recovery in the intervention group (p=0.033) but no significant difference in ICU admission rates, number of deaths, or median duration of hospital stay (Table 2 and Figure 2), suggesting the need for larger population studies to provide a more definitive evaluation of the efficacy of the proposed sofosbuvir/daclatasvir/ribavirin regimen.

ABSTRACT

BACKGROUND: New therapeutic options are urgently needed to tackle the novel coronavirus disease 2019 (COVID-19). Repurposing existing pharmaceuticals provides an immediate treatment opportunity. We assessed the efficacy of sofosbuvir and daclatasvir with ribavirin for treating patients with COVID-19. METHODS: This was a single-centre, randomized controlled trial in adults with moderate COVID-19 admitted to the Ghaem Shahr Razi Hospital in Mazandaran Province, Iran. Patients were randomly assigned to 400 mg sofosbuvir, 60 mg daclatasvir and 1200 mg ribavirin (intervention group) or to standard care (control group). The primary endpoint of this study was length of hospital stay. This study is registered by IRCT.ir under the ID: IRCT20200328046886N1. RESULTS: Between 20 March 2020 and 8 April 2020, 48 patients were recruited; 24 patients were randomly assigned to the intervention group and 24 to the control group. The median duration of hospital stay was 6 days in both groups (P = 0.398). The number of ICU admissions in the sofosbuvir/daclatasvir/ribavirin group was not significantly lower than the control group (0 versus 4, P = 0.109). There was no difference in the number of deaths between the groups (0 versus 3, P = 0.234). The cumulative incidence of recovery was higher in the sofosbuvir/daclatasvir/ribavirin arm (Gray's P = 0.033). CONCLUSIONS: This randomized trial was too small to make definitive conclusions. There were trends in favour of the sofosbuvir/daclatasvir/ribavirin arm for recovery and lower death rates. However, there was an imbalance in the baseline characteristics between the arms. Larger randomized trials should be conducted to investigate this treatment further.

FIGURES

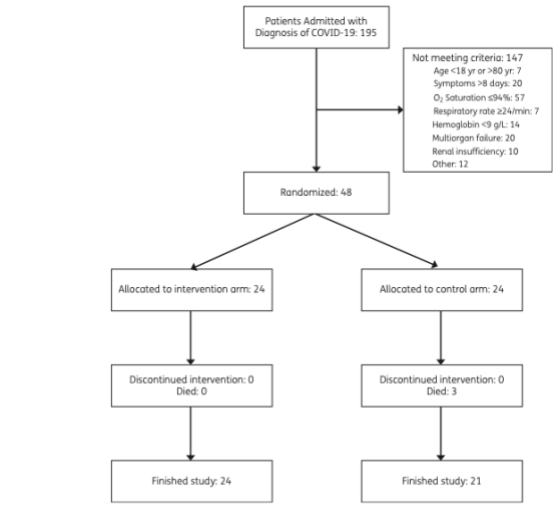

Figure 1. Trial profile.

Figure 1: Trial profile.

Table 2. Clinical outcomes comparison between the two groups

	SOF/DCV/RBV ($n = 24$)	Control ($n = 24$)	*P* value
Duration of hospitalization (days), median (IQR)	6 (5–7)	6 (5.5–7.5)	0.398
Final outcome, *n* (%)			
recovery	24 (100)	21 (88)	0.234
death	0 (0)	3 (13)	
Time to recovery (days), median (IQR)[a]	6 (5–7)	6 (6–8)	0.033
Other outcomes			
ICU admission, *n* (%)	0 (0)	4 (17)	0.109
duration (days), median (IQR)	—	2.5 (1.5–7)	
invasive mechanical ventilation, *n* (%)	0 (0)	4 (17)	0.109
duration (days), median (IQR)	—	2.5 (1.5–7)	

SOF/DCV/RBV, sofosbuvir/daclatasvir/ribavirin.
P values are calculated using Fisher's exact test for categorical outcomes and Mann–Whitney *U*-test for continuous outcomes.
[a]Estimated from the CIF, accounting for death as a competing risk; *P* value is for Gray's test for the equality of CIFs.

Table 2: Clinical outcomes comparison between the two groups.

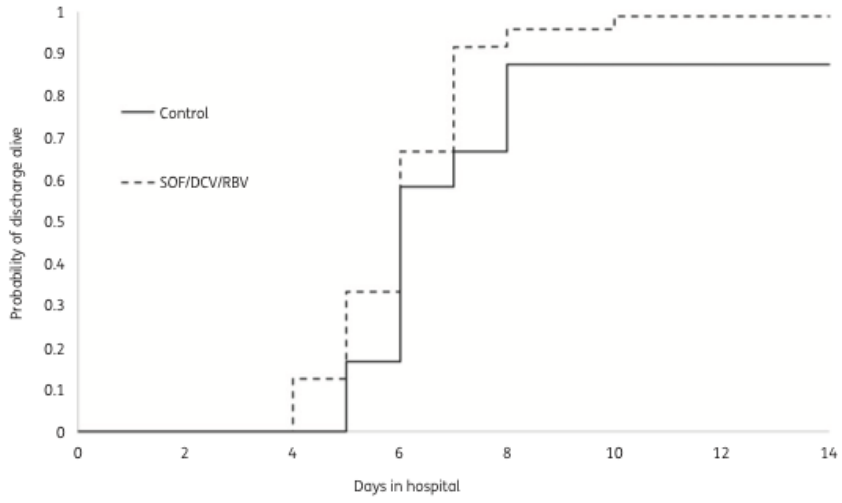

Figure 2. Cumulative incidence of recovery by treatment arm. SOF/DCV/RBV, sofosbuvir/daclatasvir/ribavirin.

Figure 2: Cumulative incidence of recovery by treatment arm. SOF/DCV/RBV, Sofosbuvir/daclatasvir/ribavirin.

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