The Daily COVID-19 Literature Surveillance Summary

August 14, 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

- In this study, investigators from Canada compared mean change in driving from baseline (using Apple Mobility Trends) and COVID-19 mortality rate as of April 30th, 2020 in 36 countries with the highest number of COVID-19 cases globally, excluding those for which driving distance data was not available. They found decreased driving to be associated with lower COVID-19 mortality ($p<0.001$), highlighting the importance of social distancing measures to curb the spread and mortality associated with COVID-19.

Epidemiology

- Newborns of COVID-19 mothers: short-term outcomes of colocating and breastfeeding from the pandemic's epicenter: A retrospective cross-sectional study conducted at Elmhurst Hospital Center, New York between March 19 and April 22, 2020 by researchers from Icahn School of Medicine at Mount Sinai found 73.3% of newborns of SARS-CoV-2 positive mothers were roomed-in together (94% also breastfed) and 6.7% overall tested positive for COVID-19, but none required NICU admission for SARS-CoV-2 related illness. Authors suggest that rooming-in and breastfeeding newborns of mothers with COVID-19 may be low risk and could provide educational opportunities regarding isolation, PPE use, and safe breastfeeding to equip mothers to better care for their newborns at home.

- A retrospective cohort study of 3,248 adults with COVID-19 (confirmed via RT-PCR) conducted at 5 hospitals within Mount Sinai Health System, New York between March 1 and May 1, 2020 found patients with a history of stroke had a statistically significantly higher risk of in-hospital death (adjusted odds ratio 1.28 [95% CI 1.01-1.68], adjusted for medical comorbidities). They suggest stroke may be an independent risk factor for in-hospital death and that this warrants further research to confirm the association and explore underlying pathophysiologic mechanisms.

- Severe vitamin D deficiency may be a marker for poor prognosis in COVID-19 patients with acute respiratory failure and advocate for further research. A retrospective study conducted at the Respiratory Intermediate Care Unit (RICU) of the Hospital Policlinic in Bari, Italy from March 11 to April 30, 2020 found 81% of COVID-19 patients with acute respiratory failure had vitamin D deficiency. Additionally, the subset of patients with severe vitamin D deficiency (<10 ng/mL, n=10, 24%) had increased mortality risk (50% chance of dying after 10 days of hospitalization) compared to those with vitamin D ≥ 10 ng/mL who had a 5% mortality risk ($p = 0.019$).

Understanding the Pathology

- A literature review by interdisciplinary researchers in Iran examined bacterial co-infection and secondary infection in patients with COVID-19 and discuss numerous possible microbiologic mechanisms including elevated bacterial adhesion, impaired mucociliary clearance or chemotaxis, reduction of surfactant levels, and enhanced susceptibility via immune cell dysfunction. The authors hope these findings will promote understanding of pathophysiological mechanisms, which can assist in developing novel management and control strategies in COVID-19 patients with bacterial co-infection.

Transmission & Prevention

- Among these 29 seropositive individuals (59% of whom did not self-isolate), 15 had anosmia, which was the only positive predictor for seropositivity (OR 18.2, $p<0.001$), while 10/29 were completely asymptomatic, indicating the need for frequent testing for staff in maternity units (and beyond) to minimize risk of transmission. A cross-sectional study of 200 healthcare professionals conducted in the UK from 2 tertiary-level maternity units from May 11, 2020 - June 5, 2020 investigated prevalence of IgG anti-SARS-CoV-2 immune seroconversion among the healthcare professionals. They found that 5/40 anesthetists, 7/52 obstetricians, and 17/108 midwives were seropositive (total 29/200, 14.5%).

Management

- A cross sectional study conducted in Wuhan, China from January 1 to February 8, 2020 by Zhongnan Hospital of Wuhan University followed 108 patients with mild COVID-19 treated with oseltamivir and found that the majority self-reported nearly full adherence to a 14-day home isolation protocol, though fewer patients maintained separate toilets and daily exercise (22.2% and 47.2% vs. 70% for other measures). Nearly half (45.37% [n=49]) of patients had negative SARS-CoV-2 PCR at 14 days, and authors suggest that home isolation along with regular contact between patients and doctors could be an effective strategy for saving medical and social resources.

R&D: Diagnosis & Treatments

- Early administration of lopinavir/ritonavir plus hydroxychloroquine does not alter the clinical course of SARS-CoV-2 infection: a retrospective cohort study: A retrospective study conducted at Luigi Sacco Hospital in Milan, Italy from

February 21 to March 20, 2020 found patients with COVID-19 in early (≤5 days from symptom onset) versus late (>5 days from symptom onset) treatment with hydroxychloroquine (HCQ) 200 mg twice daily and lopinavir/ritanovir (LPV/r) 400/100 mg twice daily (minimum 5-day course) had no significant difference in clinical outcomes (p=0.213) or 30 day mortality (adjusted odds ratio 1.45; 95% CI: 0.50-4.19). However; age, obesity, and mechanical ventilation were all independently associated with increased probability of death. Authors suggest timing of treatment with LPV/r plus HCQ may not affect clinical outcomes, calling into question the benefits of this regimen in treatment of COVID-19.

TABLE OF CONTENTS

CLIMATE

GLOBAL

MOBILITY AND MORTALITY DURING THE COVID-19 PANDEMIC

Zipursky JS, Redelmeier DA.. J Gen Intern Med. 2020 Aug 10. doi: 10.1007/s11606-020-05943-7. Online ahead of print.
Level of Evidence: Other - Modeling

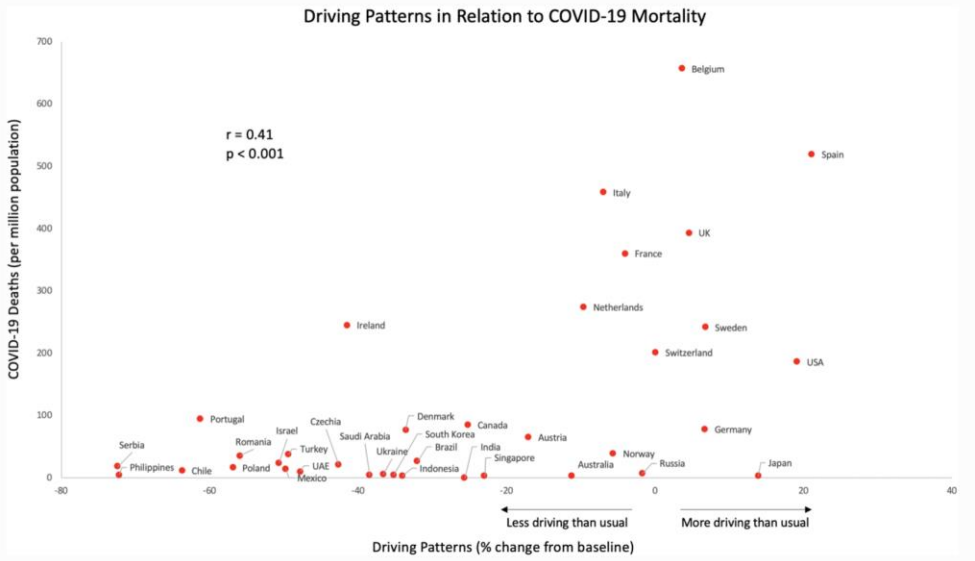
BLUF

In this study, investigators from Canada compared mean change in driving from baseline (using Apple Mobility Trends) and COVID-19 mortality rate as of April 30th, 2020 in 36 countries with the highest number of COVID-19 cases globally, excluding those for which driving distance data was not available (n=9). They found decreased driving to be associated with lower COVID-19 mortality (Figure 1, p<0.001), highlighting the importance of social distancing measures to curb the spread and mortality associated with COVID-19.

FIGURES

Figure 1

From: Mobility and Mortality During the COVID-19 Pandemic



Association between driving patterns and COVID-19 mortality in the 36 countries with the highest number of COVID-19 cases. Countries to the right of zero exhibited increased driving, and countries to the left exhibited decreased driving. Countries low on the vertical axis experienced a relatively small mortality rate, and countries high on the vertical axis experienced a relatively large mortality rate. Overall data show a significant positive association between reduced driving and decreased mortality.

EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

ERRORS AND BIASES IN META-ANALYSIS OF THE PREVALENCE OF OLFACTORY DYSFUNCTION IN PATIENTS WITH COVID-19

Santamaría-Gadea A, de Los Santos G, Alobid I, Mullol J, Mariño-Sánchez F.. Otolaryngol Head Neck Surg. 2020 Aug 11:194599820951133. doi: 10.1177/0194599820951133. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

This letter to the editor criticizes a recent meta-analysis reporting the prevalence of olfactory dysfunction (OD) in patients with COVID-19 as 86%. The meta-analysis looked at 10 articles, in which emphasis was placed on three studies that used "well-validated instruments." However, a closer look at these studies revealed subjective methods, use of unfamiliar or unrecognizable smells as assessment instruments, and questionnaires given in participants' non-native languages, suggesting the studies over-represent OD in the setting of COVID-19.

ADULTS

HISTORY OF STROKE IS INDEPENDENTLY ASSOCIATED WITH IN-HOSPITAL DEATH IN PATIENTS WITH COVID-19

Kummer BR, Klang E, Stein LK, Dhamoon MS, Jetté N.. Stroke. 2020 Aug 10:STROKEAHA120030685. doi: 10.1161/STROKEAHA.120.030685. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cohort study of 3,248 adults with COVID-19 (confirmed via RT-PCR) conducted at 5 hospitals within Mount Sinai Health System, New York between March 1 and May 1, 2020 found patients with a history of stroke (n=387, 11.9%) had a statistically significantly higher risk of in-hospital death (adjusted odds ratio 1.28 [95% CI 1.01-1.68], adjusted for medical comorbidities; Table 1). They suggest stroke may be an independent risk factor for in-hospital death and that this warrants further research to confirm the association and explore underlying pathophysiologic mechanisms.

ABSTRACT

BACKGROUND AND PURPOSE: In December 2019, an outbreak of severe acute respiratory syndrome coronavirus causing coronavirus disease 2019 (COVID-19) occurred in China, and evolved into a worldwide pandemic. It remains unclear whether the history of cerebrovascular disease is associated with in-hospital death in patients with COVID-19. METHODS: We conducted a retrospective, multicenter cohort study at Mount Sinai Health System in New York City. Using our institutional data warehouse, we identified all adult patients who were admitted to the hospital between March 1, 2020 and May 1, 2020 and had a positive nasopharyngeal swab polymerase chain reaction test for severe acute respiratory syndrome coronavirus in the emergency department. Using our institutional electronic health record, we extracted clinical characteristics of the cohort, including age, sex, and comorbidities. Using multivariable logistic regression to control for medical comorbidities, we modeled the relationship between history of stroke and all-cause, in-hospital death. RESULTS: We identified 3248 patients, of whom 387 (11.9%) had a history of stroke. Compared with patients without history of stroke, patients with a history of stroke were significantly older, and were significantly more likely to have a history of all medical comorbidities except for obesity, which was more prevalent in patients without a history of stroke. Compared with patients without history of stroke, patients with a history of stroke had higher in-hospital death rates during the study period (48.6% versus 31.7%, P<0.001). In the multivariable analysis, history of stroke (adjusted odds ratio, 1.28 [95% CI, 1.01-1.63]) was significantly associated with in-hospital death. CONCLUSIONS: We found that history of stroke was associated with in-hospital death among hospitalized patients with COVID-19. Further studies should confirm these results.

FIGURES

Characteristic	History of Stroke (N=387)	No History of Stroke (N=2861)	*P* Value
Age, median (IQR), y	75.0 (65.0–83.0)	66.0 (55.0–77.0)	<0.001
Male sex	219 (56.6)	1671 (58.4)	0.53
Comorbidities			
Hypertension	329 (85.0)	1828 (63.9)	<0.001
Coronary artery disease	152 (39.3)	558 (19.5)	<0.001
Diabetes mellitus	231 (59.7)	1283 (44.8)	<0.001
Dyslipidemia	191 (49.4)	958 (33.5)	<0.001
Congestive heart failure	107 (27.6)	357 (12.5)	<0.001
Atrial fibrillation	69 (17.8)	253 (8.8)	<0.001
Chronic kidney disease	127 (32.8)	491 (17.2)	<0.001
Obesity	110 (28.4)	1031 (36.0)	0.004
COPD	55 (14.2)	237 (8.3)	<0.001
Asthma	55 (14.2)	371 (13.0)	0.55
Active smoking	124 (32.0)	604 (21.1)	<0.001
Malignancy	77 (19.9)	447 (15.6)	0.038
Died during hospitalization	188 (48.6)	908 (31.7)	<0.001

Figures are reported as N (%), unless otherwise noted. COPD indicates chronic obstructive pulmonary disease; and IQR, interquartile range.

Table 1. Patient Characteristics, Stratified by Presence of Stroke History.

VITAMIN D DEFICIENCY AS A PREDICTOR OF POOR PROGNOSIS IN PATIENTS WITH ACUTE RESPIRATORY FAILURE DUE TO COVID-19

Carpagnano GE, Di Lecce V, Quaranta VN, Zito A, Buonamico E, Capozza E, Palumbo A, Di Gioia G, Valerio VN, Resta O.. J Endocrinol Invest. 2020 Aug 9. doi: 10.1007/s40618-020-01370-x. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

This retrospective study conducted at the Respiratory Intermediate Care Unit (RICU) of the Hospital Policlinic in Bari, Italy from March 11 to April 30, 2020 found 81% of COVID-19 patients with acute respiratory failure had vitamin D deficiency (defined as <30 ng/mL, n=34, Table 1). Additionally, the subset of patients with severe vitamin D deficiency (<10 ng/mL, n=10, 24%) had increased mortality risk (50% chance of dying after 10 days of hospitalization, Figure 1) compared to those with vitamin D ≥ 10 ng/mL who had a 5% mortality risk (p = 0.019). The authors suggest severe vitamin D deficiency may be a marker for poor prognosis in COVID-19 patients with acute respiratory failure and advocate for further research. Of note, findings are somewhat limited by the small population studied.

ABSTRACT

PURPOSE: Hypovitaminosis D is a highly spread condition correlated with increased risk of respiratory tract infections. Nowadays, the world is in the grip of the Coronavirus disease 19 (COVID 19) pandemic. In these patients, cytokine storm is associated with disease severity. In consideration of the role of vitamin D in the immune system, aim of this study was to analyse vitamin D levels in patients with acute respiratory failure due to COVID-19 and to assess any correlations with disease severity and prognosis. METHODS: In this retrospective, observational study, we analysed demographic, clinical and laboratory data of 42 patients with acute respiratory failure due to COVID-19, treated in Respiratory Intermediate Care Unit (RICU) of the Policlinic of Bari from March, 11 to April 30, 2020. RESULTS: Eighty one percent of patients had hypovitaminosis D. Based on vitamin D levels, the population was stratified into four groups: no hypovitaminosis D, insufficiency, moderate deficiency, and severe deficiency. No differences regarding demographic and clinical characteristics were found. A survival analysis highlighted that, after 10 days of hospitalization, severe vitamin D deficiency patients had a 50% mortality probability, while those with vitamin D >= 10 ng/mL had a 5% mortality risk (p = 0.019). CONCLUSIONS: High prevalence of hypovitaminosis D was found in COVID-19 patients with acute respiratory failure, treated in a RICU. Patients with severe vitamin D deficiency had a significantly higher mortality risk. Severe vitamin D deficiency may be a marker of poor prognosis in these patients, suggesting that adjunctive treatment might improve disease outcomes.

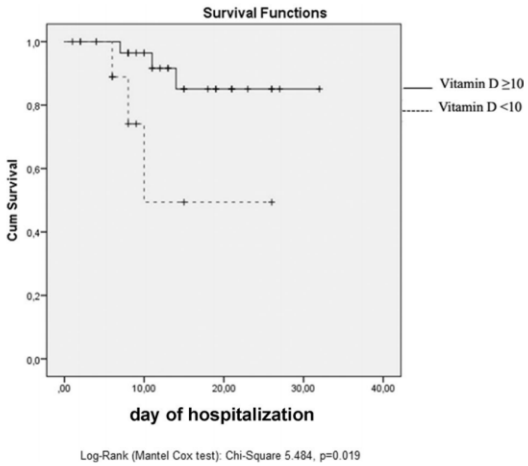


Figure 1. Survival analysis in patients with vitamin D<10 ng/mL vs patients with vitamin D≥10 ng/mL.

Patients (*n*)	42
Sex (M/F, *n*, %)	30/12 (71/29)
Age (years, mean, SD)	65 ± 13
BMI (mean, SD)	28,5 ± 5
ARDS (P/F < 300) (*n*, %)	37 (88)
Mild (300 < P/F ≤ 200) (*n*, %)	16 (38)
Moderate (200 < P/F ≤ 100) (*n*, %)	16 (38)
Severe (P/F < 100) (*n*, %)	5 (12)
SOFA score (mean, SD)	3 ± 1.4
Smoking habit (*n*, %)	
Smokers	2 (5)
Ex-smokers	18 (43)
Never smokers	22 (52)
Patients with comorbidity (*n*, %)	36 (86)
Hypertension	26
Cardiovascular disease	16
Chronic kidney disease	16
Diabetes type II	11
Cerebrovascular disease	5
Psycosis, depression, anxiety	10
Malignancy	5
COPD	5
Asthma	2
Vit. D serum level (ng/mL, mean, SD)	20.46 ± 11.6
Non Hypovitaminosis D (vit. D ≥ 30 ng/mL) (*n*, %)	8 (19%)
Hypovitaminosis D (vit. D < 30 ng/mL) (*n*, %)	34 (81%)

BMI body mass index, *ARDS* acute respiratory distress syndrome, *SOFA* sequential organ failure assessment, *COPD* chronic obstructive pulmonary disease, *Vit* vitamin

Table 1. Demographic and clinical characteristics of patients.

PEDIATRICS

NEWBORNS OF COVID-19 MOTHERS: SHORT-TERM OUTCOMES OF COLOCATING AND BREASTFEEDING FROM THE PANDEMIC'S EPICENTER

Patil UP, Maru S, Krishnan P, Carroll-Bennett R, Sanchez J, Noble L, Wasserman R.. J Perinatol. 2020 Aug 10. doi: 10.1038/s41372-020-0765-3. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cross-sectional study conducted at Elmhurst Hospital Center, New York between March 19 and April 22, 2020 by researchers from Icahn School of Medicine at Mount Sinai found 73.3% (n=33) of newborns of SARS-CoV-2 positive mothers were roomed-in together (94% also breastfed) and 6.7% overall (n=3) tested positive for COVID-19, but none required NICU admission for SARS-CoV-2 related illness (Figure 1, Table 1). Authors suggest that rooming-in and breastfeeding newborns of mothers with COVID-19 may be low risk and could provide educational opportunities regarding isolation, PPE use, and safe breastfeeding to equip mothers to better care for their newborns at home.

FIGURES

Fig. 1 SARS-CoV-2 test results and clinical characteristics of the newborns and their mothers.

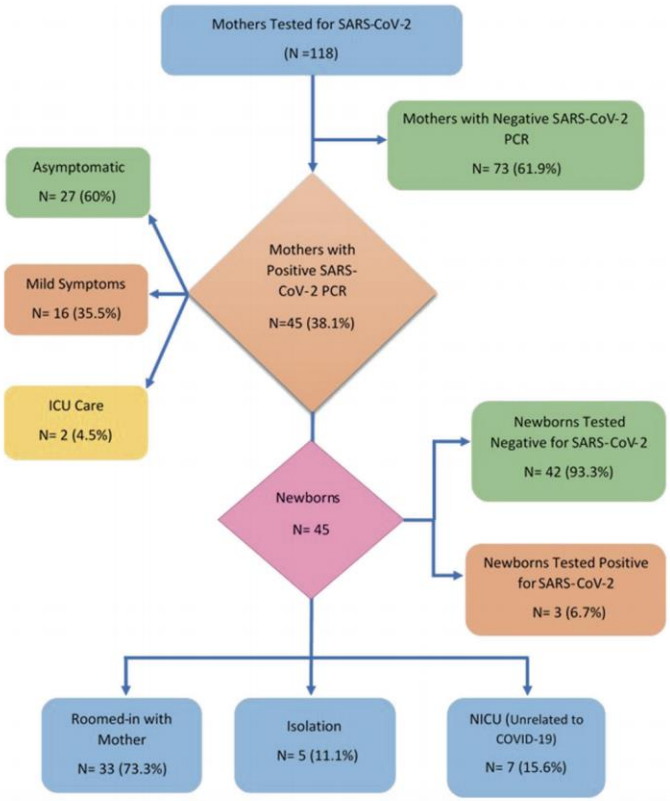


Table 1 Demographic and clinical characteristics of newborns of SARS-CoV-2 positive mothers.

Characteristics	Patients/Value ($N = 45$)
Maternal characteristics	
Age, median (IQR), years	30 (27.5–35.5)
Vaginal delivery, no. (%)	30 (66.7)
Cesarean section, no. (%)	15 (33.3)
Length of stay, median (IQR), days	3 (2–3)
Asymptomatic, no. (%)	27 (60)
Symptomatic, no. (%)	18 (40)
Symptoms, no. (%)	
Fever	15 (33.3)
Cough	16 (35.6)
Sore throat	4 (8.9)
Shortness of breath	6 (13.3)
Intensive care unit admission, no. (%)	2 (4.4)
Mothers needing intubation, no.	0
Treatment with medications for COVID-19, no. (%)	
Hydroxychloroquine	6 (13.3)
Azithromycin	5 (11.1)
Tocilizumab	1 (2.2)
Newborn characteristics	
Birth weight, mean (±SD), g	3133 (±556)
Sex, no. (%)	
Female	19 (42.2)
Male	26 (47.8)
Gestational age, mean (range), weeks	34 (30 5/7–41)
Term (≥37 weeks), no. (%)	41 (91.1)
Preterm (<37 weeks), no (%)	4 (8.9)
APGAR at 1 min, median	9
APGAR at 5 min, median	9
NICU admission, no. (%)	7 (15.6)
Prematurity	3/7 (42.8)
Suspected sepsis	4/7 (57.2)
Isolation during initial practice, no. (%)	5 (11.1)
Breastfeeding and colocation, no. (%)	
Roomed-in	33 (73.3)
Breastfeeding	31/33 (94)
Received any breastmilk	40 (88.9)
Nasopharyngeal PCR positive for SARS-CoV-2, no. (%)	3 (6.7)
Newborn with symptoms of COVID-19, no.	0
Discharge disposition, no. (%)	
Discharge to the same household	40/43 (93.0)
Discharge to different household	3 (7.0)
Adherence to in-person newborn visit, no. (%)	39/43 (90.6)
Symptomatic on in-person newborn visit, no.	0
Adherence to televisit, no. (%)	43/43 (100)
Symptomatic on televisit, no.	0

ADVANCED AGE

HILAR LYMPHADENOPATHY, A NOVEL FINDING IN THE SETTING OF CORONAVIRUS DISEASE (COVID-19): A CASE REPORT

Mughal MS, Rehman R, Osman R, Kan N, Mirza H, Eng MH.. J Med Case Rep. 2020 Aug 9;14(1):124. doi: 10.1186/s13256-020-02452-3.

Level of Evidence: 5 - Case report

BLUF

Researchers from Long Branch, New Jersey present a case report of a 73-year-old woman with severe COVID-19 who recovered after receiving hydroxychloroquine and azithromycin (Figure 1). The authors highlight a computed tomography (CT) finding of atypical bilateral hilar lymphadenopathy (Figure 2), which has not been previously reported as a COVID-19

manifestation. The authors urge clinicians to report atypical imaging findings so such findings' associations with disease severity and outcomes can be investigated.

ABSTRACT

BACKGROUND: As the outbreak of coronavirus disease 2019 (COVID-19) has progressed, computed tomography has emerged as an integral part of the diagnosis alongside reverse transcriptase-polymerase chain reaction assays. Frequently encountered imaging findings include peripheral airspace consolidations; bilateral ground-glass opacities; and, less commonly, cavitation. Hilar lymphadenopathy is a rarely reported finding in the setting of COVID-19. CASE PRESENTATION: A 73-year-old Caucasian woman presented to our hospital with fever and fatigue. She had a maximum body temperature of 102.3 F with lymphopenia and thrombocytopenia. She was diagnosed with severe acute respiratory syndrome coronavirus 2 infection on the basis of a positive result from a reverse transcriptase-polymerase chain reaction of a nasopharyngeal swab sample. Contrast-enhanced chest computed tomography revealed multifocal, subpleural ground-glass opacities with nodular consolidations bilaterally. Computed tomography also demonstrated atypical bilateral hilar lymphadenopathy, a rarely reported imaging feature of COVID-19. Chest computed tomography 1 month before the presentation did not show focal consolidations or lymphadenopathy. This indicated that the findings were due to the patient's severe acute respiratory syndrome coronavirus 2 infection. She received 5 days of oral hydroxychloroquine and experienced resolution of her symptoms. CONCLUSION: Chest computed tomography has been used extensively to diagnose and characterize the distinguishing radiological findings associated with viral pneumonia. It has emerged as an integral part of the diagnosis of COVID-19 alongside reverse transcriptase-polymerase chain reaction assays. Clinicians must be aware of uncommon clinical and radiological findings in order to diagnose this entity. Hilar lymphadenopathy is commonly seen with fungal infections, mycobacterial infections, and sarcoidosis. An extensive literature review found that bilateral hilar lymphadenopathy has not been reported in the setting of COVID-19. More data are needed to establish the clinical impact of this novel finding.

FIGURES

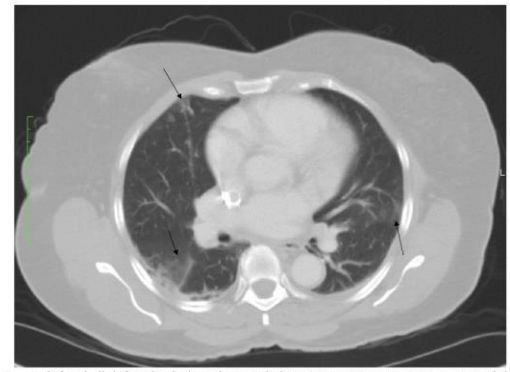


Figure 1. Contrast-enhanced chest computed tomography reveals multifocal, subpleural ground-glass attenuation opacities (arrow) (a) with nodular consolidations bilaterally (arrow) (b).

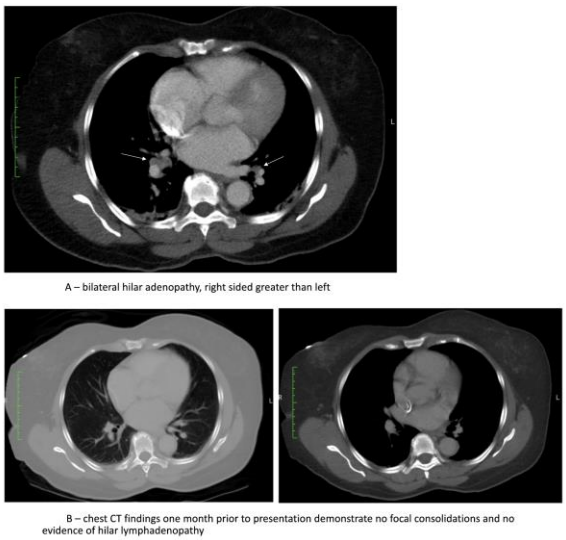


Figure 2. (a) Atypical bilateral hilar lymphadenopathy (arrow), a novel finding of coronavirus disease 2019. (b) Chest computed tomography 1 month before presentation demonstrates no focal consolidations and no lymphadenopathy.

BACTERIAL CO-INFECTIONS WITH SARS-COV-2

Mirzaei R, Goodarzi P, Asadi M, Soltani A, Aljanabi HAA, Jeda AS, Dashtbin S, Jalalifar S, Mohammadzadeh R, Teimoori A, Tari K, Salari M, Ghiasvand S, Kazemi S, Yousefimashouf R, Keyvani H, Karampoor S.. IUBMB Life. 2020 Aug 8. doi: 10.1002/iub.2356. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A literature review by interdisciplinary researchers in Iran examined bacterial co-infection and secondary infection in patients with COVID-19 (Table 3) and discuss numerous possible microbiologic mechanisms including elevated bacterial adhesion, impaired mucociliary clearance or chemotaxis, reduction of surfactant levels, and enhanced susceptibility via immune cell dysfunction (Table 2). The authors hope these findings will promote understanding of pathophysiological mechanisms, which can assist in developing novel management and control strategies in COVID-19 patients with bacterial co-infection (Table 4).

ABSTRACT

The pandemic coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has affected millions of people worldwide. To date, there are no proven effective therapies for this virus. Efforts made to develop antiviral strategies for the treatment of COVID-19 are underway. Respiratory viral infections, such as influenza, predispose patients to co-infections and these lead to increased disease severity and mortality. Numerous types of antibiotics such as azithromycin have been employed for the prevention and treatment of bacterial co-infection and secondary bacterial infections in patients with a viral respiratory infection (e.g., SARS-CoV-2). Although antibiotics do not directly affect SARS-CoV-2, viral respiratory infections often result in bacterial pneumonia. It is possible that some patients die from bacterial co-infection rather than virus itself. To date, a considerable number of bacterial strains have been resistant to various antibiotics such as azithromycin, and the overuse could render those or other antibiotics even less effective. Therefore, bacterial co-infection and secondary bacterial infection are considered critical risk factors for the severity and mortality rates of COVID-19. Also, the antibiotic-resistant as a result of overusing must be considered. In this review, we will summarize the bacterial co-infection and secondary bacterial infection in some featured respiratory viral infections, especially COVID-19.

FIGURES

TABLE 3 List of bacterial co-infection with COVID-19

Bacterium	Infection	References
Staphylococcus aureus	Necrotizing pneumonia	152
Mycoplasma pneumoniae	Exacerbate clinical symptoms, increase morbidity and prolonged intensive care unit stay	153
Legionella pneumophila	Pneumonia	154
Enterobacter cloacae	Pneumonia	155
Acinetobacter baumannii	Pneumonia	146,155
Klebsiella pneumoniae	Pneumonia	146
Mycoplasma pneumoniae	Interstitial pneumonia	149
Mycoplasma pneumoniae	Not reported	151
Legionella pneumophila	Not reported	151
Streptococcus pneumoniae	Not reported	151
Prevotella	Not reported	156–158
Haemophilus	Not reported	158,159
Lautropia	Not reported	159
Cutibacterium	Not reported	159

TABLE 4 Several functional suggestions for management and control of bacterial co-infection with COVID-19

Suggestion	Description
Using a broad-spectrum diagnostic panel	Improves diagnosis, evaluation, and clinical management of patients with other respiratory viral infection concurrent with COVID-19
Developing novel treatment and prevention strategies	Increases our knowledge about the underlying molecular mechanisms accounting for viral-bacterial co-infection to promote novel therapeutic and prevention approaches
Performing antibacterial susceptibility tests and potential therapy	Prevents reduced antimicrobial susceptibility and treatment failure due to co-infections[174]
Considering the biofilm-associated bacterial infections	Facilitates treatment management as biofilm formation on artificial devices has been observed previously, thereby affecting infection outcomes, especially in COVID-19 patients under mechanical ventilation[175]
Classifying mechanisms of pathogen interactions	Increases the ability of infection control as the extension of chemotherapy-resistant pathogens is a severe global obstacle[174]

TABLE 2 Summary of the potential mechanisms responsible for the bacterial coinfection with viral respiratory infections

Mechanism	Description	References
Elevation in bacterial adherence due to viral infection	Virus can modulate surface membrane receptors, thereby enhancing bacterial adhesion	16,96–98
Cell destruction by viral enzymes	Viral enzymes destroy mucosal glycoproteins, mainly those inhibiting bacterial attachment	98,99
Reduction of mucociliary clearance	Virus can reduce mucociliary clearance leading to the decreased production of bactericidal materials	100
Reduction in chemotaxis	Virus can decrease the chemotactic factors, leading to the reduced cell response to attacking organisms	101
Direct effect on phagocytic and induction of post phagocytic alveolar macrophage functions	Virus hinders or modifies a number of immune functions, such as phagosome-lysosome fusion and intracellular killing	102,103
Induction of immature phagocytes	Virus can disrupt macrophages and probably replace them with immature phagocytes	98,104,105
Reduction of surfactant levels	Virus impairs the function of alveolar type-2 pneumocyte	98,106,107
Induction of dysbiosis in lower respiratory tract microbiome	Microbiome dysbiosis can affect the immune response against respiratory viral infection	108
Dysregulation of the innate and adaptive immune responses	Virus decreases the number of alveolar macrophages through the development of apoptosis	42,88,90,91
Modulation of apoptosis and inflammation	Autophagy and apoptosis facilitates secondary bacterial pneumonia after viral infection	109
Reduction of antibacterial immune function at the respiratory epithelium	Respiratory viral infection leads to the predisposition to secondary bacterial infection via the deviation of the respiratory tract immune status	110–115
Dysregulation of nutritional immunity	Some viruses can subvert nutritional protection to promote bacterial infection	116–118
Immunosuppression	Immunosuppression is induced by several viruses such as HIV	119–121
Synergism during viral/bacterial co-infections	Both viruses and bacteria play a role in the immunopathogenicity of co-infection	8,122,123
Release of planktonic bacteria from biofilms	Viruses can manipulate many factors such as chemokines and hydrogen peroxide, thereby leading to the disruption of biofilm structure	42,124–126

Abbreviation: HIV, human immunodeficiency viruses.

A CROSS-SECTIONAL STUDY OF IMMUNE SEROCONVERSION TO SARS-COV-2 IN FRONTLINE MATERNITY HEALTH PROFESSIONALS

Bampoe S, Lucas DN, Neall G, Sceales P, Aggarwal R, Caulfield K, Siassakos D, Odor PM.. Anaesthesia. 2020 Aug 10. doi: 10.1111/anae.15229. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A cross-sectional study of 200 healthcare professionals (Table 1) conducted in the UK from 2 tertiary-level maternity units from May 11, 2020 - June 5, 2020 investigated prevalence of IgG anti-SARS-CoV-2 immune seroconversion among the healthcare professionals. They found that 5/40 anesthetists, 7/52 obstetricians, and 17/108 midwives were seropositive (total 29/200, 14.5%). Among these 29 seropositive individuals (59% of whom did not self-isolate), 15 had anosmia, which was the only positive predictor for seropositivity (OR 18.2, p<0.001), while 10/29 were completely asymptomatic, indicating the need for frequent testing for staff in maternity units (and beyond) to minimize risk of transmission (Tables 2, 3).

ABSTRACT

COVID-19, the respiratory disease caused by SARS-CoV-2, is thought to cause a milder illness in pregnancy with a greater proportion of asymptomatic carriers. This has important implications for the risk of patient-to-staff, staff-to-staff and staff-to-patient transmission among health professionals in maternity units. The aim of this study was to investigate the prevalence of previously undiagnosed SARS-CoV-2 infection in health professionals from two tertiary-level maternity units in London, UK, and to determine associations between healthcare workers' characteristics, reported symptoms and serological evidence of prior SARS-CoV-2 infection. In total, 200 anaesthetists, midwives and obstetricians, with no previously confirmed diagnosis of COVID-19, were tested for immune seroconversion using laboratory IgG assays. Comprehensive symptom and medical histories were also collected. Five out of 40 (12.5%; 95%CI 4.2-26.8%) anaesthetists, 7/52 (13.5%; 95%CI 5.6-25.8%) obstetricians and 17/108 (15.7%; 95%CI 9.5-24.0%) midwives were seropositive, with an overall total of 29/200 (14.5%; 95%CI 9.9-20.1%) of maternity healthcare workers testing positive for IgG antibodies against SARS-CoV-2. Of those who had seroconverted, 10/29 (35.5%) were completely asymptomatic. Fever or cough were only present in 6/29 (21%) and 10/29 (35%) respectively. Anosmia was the most common symptom occurring in 15/29 (52%) seropositive participants and was the only symptom that was predictive of positive seroconversion (OR 18; 95%CI 6-55). Of those who were seropositive, 59% had not self-isolated at any point and continued to provide patient care in the hospital setting. This is the largest study of baseline immune seroconversion in maternity healthcare workers conducted to date and reveals that one out of six were seropositive, of whom one out of three were asymptomatic. This has significant implications for the risk of occupational transmission of SARS-CoV-2 for both staff and patients in maternity units. Regular testing of staff, including asymptomatic staff should be considered to reduce transmission risk.

FIGURES

	Participants (n = 200)
Age; years	37 (30–37 [21–66])
Weight; kg	70 (60–80 [44–118])
BMI; kg m^{-2}	24.2 (21.8–27.7 [16.7–40.2])
Female	167 (84%)
Occupation	
Anaesthetist	40 (20%)
Midwife	108 (54%)
Obstetrician	52 (26%)
Ethnicity	
Caucasian	139 (70%)
BAME total	61 (31%)
Asian or Asian British	25 (13%)
Black or Black British	25 (13%)
Mixed	9 (5%)
Other	2 (1%)
Smoke	
Never smoked	141 (71%)
Former smoker	36 (18%)
Smoker	13 (7%)
Unknown	10 (5%)
Comorbidities	
Immunosuppressed/ receiving steroids	0
Cardiac disease	0
Hypertension	10 (5%)
Chronic obstructive pulmonary disorder	0
Diabetes	1 (0.5%)
Diabetes with end organ complications	0
Asthma	21 (11%)
Chronic kidney disease	0
Moderate/severe hepatic disease	1 (0.5%)

Table 1. Participant baseline, occupational and comorbid characteristics. Values are median (IQR [range]) or number (proportion).

Symptoms	Seroconverted n = 29	No antibodies detected n = 171	p value
Asymptomatic	10 (35%)	59 (35%)	0.998
Dry cough or fever or anosmia	16 (55%)	53 (31%)	0.113
Dry cough	10 (35%)	41 (24%)	0.230
Fever	6 (21%)	15 (9%)	0.053
Anosmia	15 (52%)	9 (5%)	<0.001
Headache	14 (48%)	61 (36%)	0.195
Myalgia	12 (41%)	42 (25%)	0.593
Nasal congestion	6 (21%)	25 (15%)	0.404
Sore throat	6 (21%)	52 (30%)	0.286
Shortness of breath	5 (17%)	24 (14%)	0.650
Diarrhoea	4 (14%)	24 (14%)	0.972
Nausea or vomiting	3 (10%)	14 (8%)	0.700
Photophobia	2 (7%)	0	0.020
Productive cough	1 (3%)	9 (5%)	0.678
Abdominal pain	1 (3%)	12 (7%)	0.471

Table 2. Reported symptoms and SARS-CoV-2 detection by serology, values are number (proportion).

Characteristic	OR (95%CI)	p value
Age; years		
18–30		
31–50	1.1 (0.3–4.0)	0.921
51–70	1.1 (0.2–5.4)	0.872
BMI > 30	0.6 (0.1–2.6)	0.494
Sex		
Female	1.0 (ref)	
Male	1.1 (0.2–5.5)	0.883
Ethnicity		
Caucasian	1.0 (ref)	
BAME	1.6 (0.6–4.5)	0.362
Fever	1.5 (0.3–7.7)	0.611
Anosmia	18.2 (6.0–55.2)	< 0.001
Headache	1.1 (0.4–3.4)	0.858
Self-isolated	0.4 (0.1–1.9)	0.281
Dry cough	1.0 (0.3–3.4)	0.864

Table 3. Factors associated with the detection of antibodies to SARS-CoV-2 in maternity-health care workers. Values are OR (95%CI).

INVESTIGATION AND ANALYSIS OF 108 CASES OF HOME ISOLATED PATIENTS WITH MILD COVID-19

Li H, Peng YY, Lu JP.. Disaster Med Public Health Prep. 2020 Aug 12:1-13. doi: 10.1017/dmp.2020.296. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

A cross sectional study conducted in Wuhan, China from January 1 to February 8, 2020 by Zhongnan Hospital of Wuhan University followed 108 patients with mild COVID-19 treated with oseltamivir and found that the majority self-reported nearly full adherence to a 14-day home isolation protocol (Table 1), though fewer patients maintained separate toilets and daily exercise (22.2% and 47.2% vs. 70% for other measures)(Table 2, Summary). Nearly half (45.37% [n=49]) of patients had negative SARS-CoV-2 PCR at 14 days, and authors suggest that home isolation along with regular contact between patients and doctors could be an effective strategy for saving medical and social resources.

SUMMARY

Additional findings of the study include:
- Median age of participants was 49 years (range 20-82)
- 100% of participants returned questionnaires and were return visited for follow up
- All 108 patients were able to monitor body temperature, take prescribed medications, regularly contact their physicians, and not go out in public (Table 2)
- Patients were least likely to follow guidelines recommending using a separate bathroom from other household members (24/108 [22.2%]) and maintaining moderate exercise (51/108, [47.2%]
-After 2 weeks of isolation, 49 patients tested negative via SARS-CoV-2 PCR (45.37%) and 49 patients tested positive but had improved symptoms (45.37%)
-3 patients (2.78%) with worsening symptoms were hospitalized during isolation.
-No patients died during the study.
-7 additional family members became infected during the study period; authors did not report from how many households nor the total number of family members followed.

ABSTRACT

BACKGROUND: COVID-19 began to spread across Wuhan, China by the end of 2019 and patients were unable to be hospitalized since medical resources were limited. METHODS: A questionnaire survey was conducted among 108 participants with mild COVID-19 who have isolated at home under the guidance of doctors. The results of the questionnaire and outpatient data were integrated to evaluate participants' compliance with various epidemic prevention measures. RESULTS: During isolation, most participants were able to follow epidemic prevention measures under the guidance of doctors. After 14 days from the start of isolation, 45.37% of the participants recovered. About half of the participants were relieved of symptoms, and most of them were transferred to mobile cabin hospitals to continue isolation. 3 participants with worsening symptoms were transferred to the designated hospitals. There were no deaths of the participants, but there were 7 family members that were infected. CONCLUSION: During a period of home isolation under the guidance of a doctor, individuals can comply with epidemic prevention measures and symptoms can be improved. Scientific home isolation may be an effective way to relieve the strain of medical and social resources during the epidemic of COVID-19.

FIGURES

Table 1. Anti-epidemics measures in home isolation

Variable	Measures
Isolation Environment	1. All participants should live in a well-ventilated single room or public area and avoid living in the same room with family members. In addition, participants should wear surgical masks or N95 masks in their daily lives
	2. Open the window for ventilation at least twice a day and 30 minutes each time to maintain the air flow in the bedroom, use 75% alcohol or 1000mg/L chlorine-containing disinfectant to clean and wipe furniture in bedroom every day;
	3. Daily household items and toilet should be completely separated from other family members to avoid cross infection, tableware used by our participants should be cleaned and disinfected separately;
	4. A regular caregiver is needed to take care of daily life of each participant (A caregiver should wear a disposable surgical mask or N95 mask when entering the isolation room);
Condition self-monitoring	1. Check body temperature frequently. The normal body temperature is below 37.3 ℃. If possible, use the blood oxygen clip to monitor the finger pulse oxygen, the normal blood oxygen saturation should be higher than 94%.
	2. If the body temperature exceeds 38 ℃ for 2 consecutive days, and symptoms of dyspnea such as shortness of breath, breathlessness, and continuous decrease in blood oxygen saturation occur, it is necessary to visit the designated hospital in time.
	3. Caregivers monitor body temperature daily and seek medical attention if symptoms such as fever, cough, and diarrhea occur within 14 days of the last contact with the isolators.
Diet and drug guidance	1. According to the severity of symptoms (evaluated by doctor), the participants were asked to take Lianhua Qingwen granules (1 pack of tid) for 5-10 days; Oseltamivir Phosphate Capsules (75mg bid) for 5 days; Moxifloxacin Hydrochloride Tablets (0.4g qd) for 6-12 days; Some participants with obvious symptoms add Arbidol Tablets (0.2g tid) for7-10 days as appropriate. When the body temperature returns to normal for 3 days and the cough symptoms are relieved, the drug can be stopped.
	2. Participants should increase the amount of drinking water, about 2000ml per day. For participants with fever, if the body temperature is lower than 38 ℃, physical cooling should be given; if the body temperature ⩾ 38.5 ℃, take 1 tablet of Paracetamol (325mg).
	3. Ensure adequate energy intake, reasonable mix of fruits, vegetables and meat, eat more high-quality protein foods to ensure adequate protein and vitamin intake.
Psychological counseling	1. During the isolation period, caregivers should create a good living environment to ensure normal circadian rhythm and eating habits
	2. While providing care, family members should also actively encourage participants, and help them to build their confidence in overcoming the disease.
	3. Prepare books or electronic products to distract them and relieve anxiety.
	4. Medical staff maintain regular online communication to understand the situation in time, carry out epidemic knowledge propaganda, and inform the importance of home isolation.

Table 1. Anti-epidemics measures in home isolation, continued

Table 2. Implementation of epidemic prevention measures

Investigation content	Fully complied		Partially complied		Not complied	
	Number	%	Number	%	Number	%
Separate room living	102	94.44	6	5.56	0	0.00
Ventilation Daily	104	96.30	4	3.70	0	0.00
Separate toilet, disinfected after use	24	22.22	10	9.26	74	68.52
Cover nose and mouth with tissue when coughing or sneezing	71	65.74	18	16.67	19	17.59
Disinfect hands after contacting respiratory secretion	81	75.00	15	13.89	12	11.11
Daily home disinfection	79	73.15	26	24.07	3	2.78
Monitoring body temperature	108	100.00	0	0.00	0	0.00
Wear masks during activities in public areas of the family	101	93.52	5	4.63	2	1.85
A constant caregiver	77	71.30	25	23.15	6	5.56
Take medicine according to the doctor's instruction	108	100.00	0	0.00	0	0.00
Maintain moderate daily exercise	51	47.22	41	37.96	16	14.81
Regular contact with doctors	108	100.00	0	0.00	0	0.00
Prohibition of going out during quarantine	108	100.00		0.00		0.00

EARLY ADMINISTRATION OF LOPINAVIR/RITONAVIR PLUS HYDROXYCHLOROQUINE DOES NOT ALTER THE CLINICAL COURSE OF SARS-COV-2 INFECTION: A RETROSPECTIVE COHORT STUDY

Giacomelli A, Pagani G, Ridolfo AL, Bit LO, Conti F, Pezzati L, Bradanini L, Casalini G, Bassoli C, Morena V, Passerini S, Rizzardini G, Cogliati C, Ceriani E, Colombo R, Rusconi S, Gervasoni C, Cattaneo D, Antinori S, Galli M.. J Med Virol. 2020 Aug 10. doi: 10.1002/jmv.26407. Online ahead of print.

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

BLUF

A retrospective study conducted at Luigi Sacco Hospital in Milan, Italy from February 21 to March 20, 2020 found patients with COVID-19 (n=172; Table 1) in early (≤5 days from symptom onset) versus late (>5 days from symptom onset) treatment with hydroxychloroquine (HCQ) 200 mg twice daily and lopinavir/ritanovir (LPV/r) 400/100 mg twice daily (minimum 5-day course) had no significant difference in clinical outcomes (p=0.213; Figure 2) or 30 day mortality (adjusted odds ratio 1.45; 95% CI: 0.50-4.19). However; age, obesity, and mechanical ventilation were all independently associated with increased probability of death (Figure 3). Authors suggest timing of treatment with LPV/r plus HCQ may not affect clinical outcomes, calling into question the benefits of this regimen in treatment of COVID-19.

ABSTRACT

BACKGROUND: As it has been shown that lopinavir (LPV) and hydroxychloroquine (HCQ) have in vitro activity against coronaviruses, they were used to treat COVID-19 during the first wave of the epidemic in Lombardy, Italy. METHODS: To compare the rate of clinical improvement between those who started LPV/ritonavir (LPV/r)+HCQ within five days of symptom onset (early treatment, ET) and those who started later (delayed treatment, DT). This was a retrospective intent-to-treat analysis of the hospitalized patients who started LPV/r+HCQ between 21 February and 20 March 2020. The association between the timing of treatment and the probability of 30-day mortality was assessed using uni- and multivariable logistic models. RESULTS: The study involved 172 patients: 43 (25%) in the ET and 129 (75%) in the DT group. The rate of clinical improvement increased over time to 73.3% on day 30, without any significant difference between the two groups (Gray's test P=0.213). After adjusting for potentially relevant clinical variables, there was no significant association between the timing of the start of treatment and the probability of 30-day mortality (adjusted odds ratio [aOR] ET vs DT=1.45, 95% confidence interval 0.50-4.19). Eight percent of the patients discontinued the treatment because of severe gastrointestinal disorders attributable to LPV/r. CONCLUSION: The timing of the start of LPV/r+HCQ treatment does not seem to affect the clinical course of hospitalised patients with COVID-19. Together with the severe adverse events attributable to LPV/r, this raises concerns about the benefit of using this combination to treat COVID-19. This article is protected by copyright. All rights reserved.

FIGURES

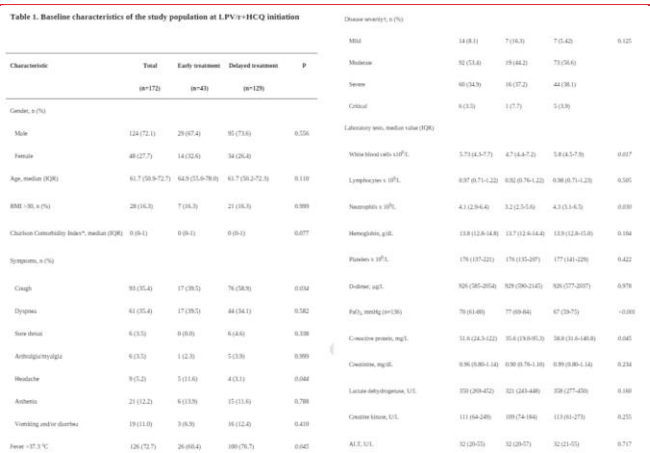


Table 1. Baseline characteristics of the study population at LPV/r+HCQ initiation

Characteristic	Total (n=172)	Early treatment (n=43)	Delayed treatment (n=129)	P
Gender, n (%)				
Male	124 (72.1)	29 (67.4)	95 (73.6)	0.356
Female	48 (27.7)	14 (32.6)	34 (26.4)	
Age, median (IQR)	61.7 (50.9-72.7)	64.9 (55.6-78.0)	61.7 (50.2-72.3)	0.110
BMI >30, n (%)	28 (16.3)	7 (16.3)	21 (16.3)	0.999
Charlson Comorbidity Index*, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.077
Symptoms, n (%)				
Cough	93 (35.4)	17 (39.5)	76 (58.9)	0.034
Dyspnea	61 (35.4)	17 (39.5)	44 (34.1)	0.582
Sore throat	6 (3.5)	0 (0.0)	6 (4.6)	0.338
Arthralgia/myalgia	6 (3.5)	1 (2.3)	5 (3.9)	0.999
Headache	9 (5.2)	5 (11.6)	4 (3.1)	0.044
Asthenia	21 (12.2)	6 (13.9)	15 (11.6)	0.788
Vomiting and/or diarrhea	19 (11.0)	3 (6.9)	16 (12.4)	0.410
Fever >37.5 °C	126 (72.7)	26 (60.4)	100 (76.7)	0.045
Disease severity†, n (%)				
Mild	14 (8.1)	7 (16.3)	7 (5.42)	0.125
Moderate	92 (53.4)	19 (44.2)	73 (56.6)	
Severe	60 (34.9)	16 (37.2)	44 (38.1)	
Critical	6 (3.5)	1 (7.7)	5 (3.9)	
Laboratory tests, median value (IQR)				
White blood cells x10^9/L	5.73 (4.3-7.7)	4.7 (4.4-7.2)	5.8 (4.5-7.9)	0.017
Lymphocytes x 10^9/L	0.97 (0.71-1.22)	0.92 (0.76-1.22)	0.98 (0.71-1.23)	0.505
Neutrophils x 10^9/L	4.1 (2.9-6.4)	3.2 (2.5-5.6)	4.3 (3.1-6.5)	0.030
Hemoglobin, g/dL	13.8 (12.8-14.8)	13.7 (12.6-14.4)	13.9 (12.8-15.0)	0.164
Platelets x 10^9/L	176 (137-221)	176 (135-207)	177 (141-229)	0.422
D-dimer, µg/L	926 (585-2054)	929 (590-2145)	926 (577-2037)	0.978
PaO_2, mmHg (n=136)	70 (61-80)	77 (69-84)	67 (59-75)	<0.001
C-reactive protein, mg/L	51.6 (24.3-122)	35.6 (19.0-95.3)	58.0 (31.6-140.8)	0.045
Creatinine, mg/dL	0.96 (0.80-1.14)	0.90 (0.76-1.10)	0.99 (0.80-1.14)	0.234
Lactate dehydrogenase, U/L	350 (269-452)	321 (243-440)	358 (277-450)	0.160
Creatine kinase, U/L	111 (64-249)	109 (74-184)	113 (61-273)	0.255
ALT, U/L	32 (20-53)	32 (20-57)	32 (21-53)	0.717

Figure 2 Cumulative incidence of improvement in the ET group (dashed line) vs DT group (solid line).

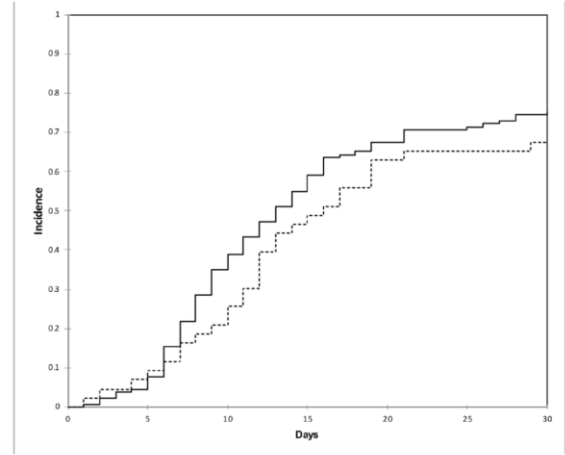
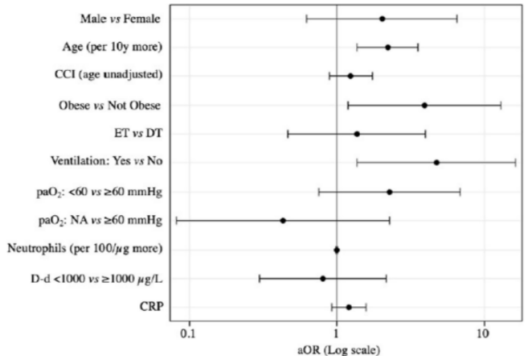


Figure 3 Multivariable model results (adjusted odds ratios).

CCI: Charlson Comorbidity Index; ET: early treatment group; DT: delayed treatment group; paO_2: partial oxygen pressure; D-d: D-dimer; NA: not assigned; CRP: C-reactive protein; aOR: adjusted odds ratio; Log: logarithmic.



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