Risk factors for intensive care unit admission and mortality in hospitalized COVID-19 patients

Ahmed Ayaz[1],*, Ainan Arshad[2],*, Hajra Malik[1], Haris Ali[1], Erfan Hussain[3], Bushra Jamil[4]

[1]Medical College, Departments of [2]Internal Medicine, [3]Pulmonary and Critical Care, and [4]Infectious Diseases, Aga Khan University, Karachi, Pakistan

Background: This study investigated the clinical features and outcome of hospitalized coronavirus disease 2019 (COVID-19) patients admitted to our quaternary care hospital.
Methods: In this retrospective cohort study, we included all adult patients with COVID-19 infection admitted to a quaternary care hospital in Pakistan from March 1 to April 15, 2020. The extracted variables included demographics, comorbidities, presenting symptoms, laboratory tests and radiological findings during admission. Outcome measures included in-hospital mortality and length of stay.
Results: Sixty-six COVID-19 patients were hospitalized during the study period. Sixty-one percent were male and 39% female; mean age was 50.6±19.1 years. Fever and cough were the most common presenting symptoms. Serial chest X-rays showed bilateral pulmonary opacities in 33 (50%) patients. The overall mortality was 14% and mean length of stay was 8.4±8.9 days. Ten patients (15%) required intensive care unit (ICU) care during admission, of which six (9%) were intubated. Age ≥60 years, diabetes, ischemic heart disease, ICU admission, neutrophil to lymphocyte ratio ≥3.3, and international normalized ratio ≥1.2 were associated with increased risk of mortality.
Conclusions: We found a mortality rate of 14% in hospitalized COVID-19 patients. COVID-19 cases are still increasing exponentially around the world and may overwhelm healthcare systems in many countries soon. Our findings can be used for early identification of patients who may require intensive care and aggressive management in order to improve outcomes.

Key Words: COVID-19; critical illness; outcomes assessment

INTRODUCTION

Despite technological advancements in the field of medicine, humans remain vulnerable to emerging infectious threats. A viral pneumonia of unknown etiology that first surfaced in Wuhan, China has since spread rapidly across the globe. Various mitigation and suppression strategies for disease control have yielded mixed results. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has established itself as a highly adaptable pathogen that is easily transmissible, causing asymptomatic infections in a large majority of people and inflicting great damage when it encounters a vulnerable host [1,2].

As of November 12, 2020, it had killed more than 1.3 million people and led to nearly 52 million confirmed cases around the world [3]. Early studies revealed that the most frequent presenting symptoms of this disease to be fever, cough, fatigue, sore throat and dyspnea [4]. El-

Ayaz A, et al.   Outcomes of hospitalized COVID-19 patients

ACC

derly patients and those with a higher comorbidity burden have a worse prognosis when compared to their younger and healthier counterparts. The former are also at a higher risk of developing acute respiratory distress syndrome (ARDS) and cytokine storm, to devastating effect [5]. To validate these findings, we investigated the clinical features and outcomes of hospitalized coronavirus disease 2019 (COVID-19) patients admitted to our quaternary care center.

MATERIALS AND METHODS

Study Design/Data Source

In this retrospective cohort study, we included all adult patients with laboratory-confirmed COVID-19 infection admitted to Aga Khan University Hospital from March 1 to April 15, 2020. The study was approved by the Institutional Review Board of Aga Khan University (IRB No. 2020-3686-10185). Owing to the retrospective design, the requirement for informed consent was waived.

Patients presenting to COVID-19 screening clinics were initially evaluated by physicians and those who met the World Health Organization (WHO) criteria for suspected infection were admitted into the COVID-19 isolation ward for further evaluation and baseline workup. Specimens collected via nasopharyngeal swab were tested for COVID-19 using an reverse transcription polymerase chain reaction (RT-PCR) assay (Roche, Basel, Switzerland). These patients were managed according to disease severity per WHO guidelines. Patients classified as having severe and critical disease were managed in the intensive care unit (ICU). Patients were discharged after two negative PCRs at least 24 hours apart.

We identified these cases using the presence of an International Classification of Diseases (ICD-9) code for SARS-associated Coronavirus (079.82). COVID-19 PCR results of these patients were then determined by the research team using an electronic medical record system. A confirmed case of COVID-19 was defined by a positive result on RT-PCR assay of a specimen collected via nasopharyngeal swab. Only laboratory-confirmed cases were included and analyzed. Patients who remained in the hospital at the time of data censoring on April 15, 2020 were not included as their outcomes were not known.

Data Collection

Data was collected from the hospital's electronic medical record system by the research team members according to a preapproved proforma. The data was deidentified before anal-

KEY MESSAGES

- Overall mortality in hospitalized coronavirus disease 2019 (COVID-19) patients was 14% and mean length of stay was 8.4±8.9 days.
- Ten patients (15%) required intensive care unit (ICU) care during admission, of which six (9%) were intubated.
- Age ≥60 years, diabetes, ischemic heart disease, ICU admission, neutrophil to lymphocyte ratio ≥3.3 and international normalized ratio ≥1.2 were associated with increased risk of mortality.
- Our findings can be used for early identification of patients who may require intensive care and aggressive management in order to improve outcomes.

ysis. The extracted variables included demographics, comorbid conditions, presenting symptoms, laboratory investigations and radiological findings during the admission. Outcome measures included in-hospital mortality and length of stay.

Statistical Analysis

IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY) was used for data analysis. We used Student t-test or Wilcoxon rank-sum test for continuous variables, and chi-square test or Fisher exact test for categorical variables, based on cell counts to determine associations between those who died and those who survived. We calculated odds ratios for each factor separately after adjusting for potential confounders such as age, sex and comorbid conditions. A P-value ≤0.05 was considered significant.

RESULTS

Sixty-six laboratory-confirmed cases of COVID-19 were admitted to Aga Khan University Hospital during the study period. There were more males (61%) in our cohort; the mean age was 50.6±19.1 years. Nine patients (14%) presented asymptomatically, while fever (60%) was the most common presenting symptom. Mean time from symptom onset to presentation at the hospital and subsequent hospitalization was 3.8±2.3 days. Twelve patients (18%) had a recent travel history with the United Arab Emirates being the most frequent country of stay. Tables 1 and 2 detail the baseline characteristics and hospitalization factors of patients who died compared with those who survived.

Serial chest radiography (CXR) was obtained in all patients and 33 (50%) showed bilateral pulmonary opacities at some point during their stay. The mean length of hospital stay was

Ayaz A, et al.   Outcomes of hospitalized COVID-19 patients

ACC

Table 1. Demographic and clinical characteristics of COVID-19 patients

Characteristics	Overall (n=66)	Expired (n=9)	Survived (n=57)	P-value
Mean age (yr)	50.6±19.1	74.8±9.4	46.8±17.2	<0.001
Sex				0.009
Male	40 (61)	9 (100)	31 (54)	
Female	26 (39)	0	26 (46)	
Comorbid condition				
Diabetes	25 (38)	8 (89)	17 (30)	0.001
Hypertension	30 (46)	8 (89)	22 (39)	0.009
Ischemic heart disease	10 (15)	6 (67)	4 (7)	<0.001
Chronic kidney Disease	3 (5)	3 (33)	0	0.002
Asthma	2 (3)	0	2 (4)	0.999
Malignancy	4 (6)	2 (22)	2 (4)	0.087
Presenting symptom				
Asymptomatic	9 (14)	0	9 (16)	0.341
Fever	40 (60)	4 (44)	36 (63)	0.259
Cough	34 (51)	4 (44)	30 (53)	0.492
Dyspnea	15 (23)	7 (78)	8 (14)	<0.001
Sore throat	9 (14)	0	9 (16)	0.332
Headache	5 (8)	0	5 (14)	0.999
Nausea/vomiting	4 (6)	0	4 (7)	0.999
Hospitalization factor				
ICU admission	10 (15)	4 (44)	6 (11)	0.024
Mechanical ventilation	6 (9)	3 (33)	3 (5)	0.029
Length of stay	8.3±6.7	8.7±6.0	6.5±7.4	0.270
Mean time from symptom onset to hospitalization (day)	3.8±2.3	3.3±2.7	3.9±2.3	0.954
Mean time from symptom onset to death (day)	-	9.1±9.4	-	-
Treatment				
Hydroxychloroquine-azithromycin combination	12 (18)	4 (44)	8 (14)	0.055
Hydroxychloroquine alone	23 (35)	6 (67)	17 (30)	0.055
Azithromycin alone	16 (24)	5 (56)	11 (19)	0.032
Tocilizumab	5 (8)	4 (44)	1 (2)	0.001
Broad spectrum antibiotics	18 (27)	6 (67)	12 (21)	0.010
Systemic glucocorticoids	4 (6)	1 (11)	3 (5)	0.452

Values are presented as mean±standard deviation or number (%).
COVID-19: coronavirus disease 2019; ICU: intensive care unit.

8.4±8.9 days. Twelve (18%) received a hydroxychloroquine-azithromycin combination, 23 patients (35%) received hydroxychloroquine alone and 16 (24%) received azithromycin alone. Hydroxychloroquine was discontinued in one patient due to QT prolongation. Furthermore, five patients (8%) received tocilizumab. Eighteen patients (27%) were started on broad spectrum antibiotics on suspicion of a secondary bacterial infection. Only three of the subsequent blood cultures were positive, showing *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus*, respectively.

Non-ST elevation myocardial infarction during the hospital stay was observed in 5% of cases. Ten patients (15%) developed moderate-to-severe ARDS and were managed in the ICU with prone positioning and noninvasive ventilation. Six of these patients (9%) required mechanical ventilation due to respiratory failure. There were three (50%) and one (25%) deaths in

Ayaz A, et al.   Outcomes of hospitalized COVID-19 patients

ACC

Table 2. Laboratory tests and radiological findings of COVID-19 patients

Characteristics	Overall (n=66)	Expired (n=9)	Survived (n=57)	P-value
Chest X-ray finding				0.002
Normal	33 (50)	0	33 (58)	
Bilateral infiltrates	33 (50)	9 (100)	24 (42)	
Laboratory test				
Hb (g/dl)	13.3±2.1	12.9±2.4	13.5±2.1	0.578
WBC count (×10E9/L)	9.0±7.1	11.6±4.1	8.6±7.4	0.246
Neutrophil to lymphocyte ratio	4.0±3.8	9.5±4.9	3.1±2.8	<0.001
Procalcitonin (ng/ml)	1.1±2.1	0.3±0.1	1.5±2.6	0.221
CRP (mg/L)	86.8±86.7	83.6±80.8	88.1±91.1	0.912
Serum lactate (mmol/L)	1.9±1.5	2.7±2.3	1.5±0.8	0.184
LDH (I.U/L)	803±1,364	569±197	949±1762	0.646
D-dimer (mg/L FEU)	2.9±5.2	3.7±7.1	2.4±3.6	0.652
Ferritin (ng/ml)	791±769	760±934	803±738	0.919
Creatinine (mg/dl)	1.1±1.2	2.4±1.5	0.9±0.8	<0.001
Total bilirubin (mg/dl)	0.7±0.4	0.8±0.4	0.7±0.5	0.820
AST (IU/L)	101±485	444±1,209	35±18	0.019
ALT (IU/L)	100±461	421±1,148	38±29	0.021
PT (sec)	11.3±1.2	12.8±1.9	10.9±0.8	<0.001
PTT (sec)	26.8±7.4	29.3±4.9	25.6±7.7	0.289
INR	1.1±0.1	1.2±0.2	1.0±0.1	<0.001

Values are presented as number (%) or mean±standard deviation.
COVID-19: coronavirus disease 2019; Hb: hemoglobin; WBC: white blood cells; CRP: C-reactive protein; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine transaminase; PT: prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio.
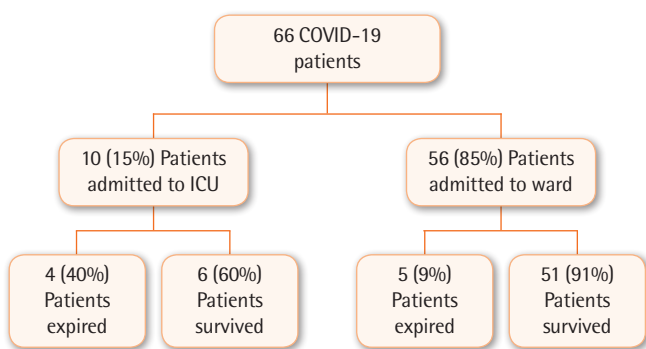

Figure 1. Outcomes of hospitalized coronavirus disease 2019 (COVID-19) patients (n=66). ICU: intensive care unit.

the mechanical ventilation and noninvasive ventilation groups, respectively (Figure 1). The overall mortality rate was 14%. Mortality in the ICU was 40% compared to 9% in the general ward.

Table 3. Adjusted odds of ICU admission in COVID-19 (n=66)

Characteristics	Crude odds	Adjusted odds ratio	95% CI	P-value
Diabetes	5.3	4.9	1.1–21.6	0.029
Hypertension	6.3	6.2	1.2–31.4	0.020
Ischemic heart disease	5.7	5.5	1.2–25.3	0.037
Bilateral infiltrates on chest radiography	14.2	12.3	1.4–101.2	0.006
Neutrophil to lymphocyte ratio ≥3.3	5.6	5.2	1.2–23.1	0.029

ICU: intensive care unit; COVID-19: coronavirus disease 2019; CI: confidence interval.

Table 4. Adjusted odds of mortality in COVID-19 (n=66)

Characteristics	Crude odds	Adjusted odds	95% CI	P-value
Age ≥60 years	22.4	20.5	2.4–177.3	0.001
Diabetes	19.2	18.8	2.2–162.4	0.001
Hypertension	12.9	12.7	1.5–108.8	0.009
Ischemic heart disease	28.6	26.5	4.7–147.8	0.001
ICU admission	15.1	14.6	2.6–80.4	0.001
Mechanical ventilation	12.4	9.0	1.4–54.9	0.029
Bilateral infiltrates on chest radiography	1.5	1.4	1.1–1.7	0.002
Neutrophil to lymphocyte ratio ≥3.3	1.7	1.6	1.1–2.2	0.001
INR ≥1.2	8.5	8.3	1.6–41.2	0.010

COVID-19: coronavirus disease 2019; CI: confidence interval; ICU: intensive care unit; INR, international normalized ratio.

The five ward patients that expired had issued do-not-resuscitate orders.

Factors associated with ICU admission included diabetes, hypertension, ischemic heart disease, neutrophil to lymphocyte ratio ≥3.3 and international normalized ratio (INR) ≥1.2. The odds of ICU admission are presented in Table 3. Factors associated with mortality included age ≥60 years, diabetes, hypertension, ischemic heart disease, ICU admission, neutrophil to lymphocyte ratio ≥3.3 and INR ≥1.2. The odds of mortality are presented in Table 4.

DISCUSSION

In this study, we present clinical characteristics and outcomes of 66 COVID-19 patients admitted to a quaternary care center in Karachi, Pakistan. Younger patients and females of all age groups were less likely to be hospitalized compared to males

Ayaz A, et al.   Outcomes of hospitalized COVID-19 patients

ACC

of older age. This is consistent with results from recent studies conducted in China, Italy and the United States [6-8]. However, whether these differences are due to less exposure to the virus or an innate biological resistance to it remains unclear.

A history of recent travel from the Middle East and the United Kingdom was observed in 19% of our cases. Fever and cough were the most common initial symptoms on admission while 11% of patients presented asymptomatically within another medical or surgical condition and were diagnosed on screening. Only 60% of patients with COVID-19 presented with fever, which is much lower than that in Wuhan (98%) and Shanghai (84%) [9,10]. While body temperature remains the main monitoring tool for surveillance of cases, many afebrile patients in our population would have been missed. Our results corroborate findings from a study conducted by Mao et al. [11], which assessed 50,000 patients presenting to 25 fever clinics in China, and concluded that fever was not a reliable indicator for COVID-19 screening.

Chest computed tomography (CT) reveals typical radiographic features, namely ground-glass opacities and multifocal patchy consolidations, in almost all COVID-19 patients, even when COVID-19 PCR is negative [12-14]. Unfortunately, due to limited resources and financial constraints, chest CT was not performed in any of our patients during the initial weeks of the pandemic; CXR was used as a cheaper and more readily available alternative. Bilateral infiltrates were seen in exactly half of the patients and these findings were also significantly associated with a poor prognosis when compared with those who had normal CXR findings. The utilization of CXR instead of CT in COVID-19 patients' needs to be studied further, especially in resource-restricted settings. Similarly, lung ultrasound is another cost-effective radiological modality that has proven to be extremely useful in triaging patients with suspected CO-VID-19. It can rapidly detect extensive pulmonary involvement in COVID-19 patients, allowing for timely referral to the ICU if needed [15].

Several therapeutic agents have been evaluated for the treatment of COVID-19, but none have been established to be efficacious. The usefulness of hydroxychloroquine in COVID-19 remains inconclusive. Tang et al. [16] performed a randomized control trial assessing 150 patients admitted at 16 hospitals in China and reported no significant improvement in clinical outcomes. Adverse events were more common in hydroxychloroquine recipients than in non-recipients. Our study showed similar results. The use of hydroxychloroquine appeared to be associated with poor outcomes. Remdesivir, an inhibitor of the viral RNA-dependent-RNA polymerase has been identi-

fied as a promising therapeutic candidate for COVID-19 because of its ability to inhibit SARS-CoV-2 *in vitro*. Beigel et al. [17] performed a randomized controlled trial that enrolled 1,063 patients and concluded that Remdesivir was superior to placebo in shortening the time to recovery in hospitalized COVID-19 patients with evidence of respiratory tract infection.

We found a higher mortality rate (14%) in our patients compared to the rates that have been reported in other countries [8,10,18,19]. Many patients who were asymptomatic or had mild symptoms did not present to COVID-19 screening clinics, and hence were not tested. Therefore, realistically, the mortality rate can be presumed to be significantly lower. ICU admission and the need for mechanical ventilation in our cohort were reflective of disease severity; mortality was higher among patients who required invasive ventilation. The mortality rate of 40% in ICU patients is slightly lower than the rate reported among critically ill patients in the United States and China [6, 20,21]. As confirmed by recent studies worldwide, male sex, older age and comorbid conditions were significant also risk factors for ICU admission and mortality in our study [22,23].

Our study has potential limitations. Since this is a single-center study conducted over a limited time period, the sample size was relatively small. Furthermore, the confidence interval for many factors was wide, likely due to the small number of patients in the study. Our results revealed an extremely high mortality rate in COVID-19 patients with moderate-to-severe disease who required hospitalization. COVID-19 cases are still increasing exponentially around the globe and may overwhelm healthcare systems in many countries. Our findings can be used for early identification of patients who may require intensive care and aggressive management in order to improve outcomes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORICID

Ahmed Ayaz   https://orcid.org/0000-0003-3022-7305
Ainan Arshad   https://orcid.org/0000-0002-9013-3899
Hajra Malik   https://orcid.org/0000-0002-1751-8282
Haris Ali   https://orcid.org/0000-0001-9722-0365
Erfan Hussain   https://orcid.org/0000-0003-4817-3800
Bushra Jamil   https://orcid.org/0000-0001-5838-317X

AUTHOR CONTRIBUTIONS

Conceptualization: AA (Ahmed Ayaz), AA (Ainan Arshad), EH, BJ. Data curation: AA (Ainan Arshad), HM, HA. Formal analysis: AA (Ainan Arshad). Methodology: AA (Ahmed Ayaz), AA (Ainan Arshad). Project administration: AA (Ainan Arshad). Writing–original draft: AA (Ainan Arshad), HM, HA. Writing–review & editing: AA (Ainan Arshad), EH, BJ.

REFERENCES

1. Fauci AS, Lane HC, Redfield RR. Covid-19: navigating the uncharted. N Engl J Med 2020;382:1268-9.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382:1199-207.
3. Open COVID-19 Data Curation Group. Novel corona virus (COVID-19)–healthMap [Internet]. Open COVID-19 Data Curation Group; 2020 [cited 2020 Nov 12]. Available from: https://www.healthmap.org/covid-19/.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
5. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
7. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med 2020;382:2372-4.
8. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323:1775-6.
9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
10. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323:1061-9.
11. Mao B, Liu Y, Chai YH, Jin XY, Lu HW, Yang JW, et al. Assessing risk factors for SARS-CoV-2 infection in patients present-

ing with symptoms in Shanghai, China: a multicentre, observational cohort study. Lancet Digit Health 2020;2:e323-30.
12. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020; 296:E32-40.
13. Huang P, Liu T, Huang L, Liu H, Lei M, Xu W, et al. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology 2020; 295:22-3.
14. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology 2020;295:202-7.
15. Volpicelli G, Lamorte A, Villén T. What's new in lung ultrasound during the COVID-19 pandemic. Intensive Care Med 2020;46:1445-8.
16. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020;369:m1849.
17. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19: final report. N Engl J Med 2020;383:1813-26.
18. Mahase E. Coronavirus covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. BMJ 2020;368:m641.
19. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic population. N Engl J Med 2020;382:2302-15.
20. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA 2020;323:1612-4.
21. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region: case series. N Engl J Med 2020;382:2012-22.
22. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91-5.
23. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis 2020;34:101623.