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

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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-
elderly 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 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 de-identified before analysis. 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
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 Table 1.

### 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.
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1.1–21.6
11.6
33 (50)
2.2–162.4
0.006
0.919
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0.578
29.3
1.2
12.7
19.2
2.4–177.3
8.3
<0.001
25.6
26.8
1.2–31.4
4.7–147.8
9.5
<0.001
0.001
444
P-value
0.001
0.7
8.5
949
8.6
0.019
2.9
0.7
-0.009
28.6
4.9
2.4
0.3
1.4–101.2
0.029
Crude
0.001
0.001
5.5
0.9
Crude
760
38
0.010
101
0.912
3.7
9.0
1.5
6.3
0.021
803
100
0.221
0.002
95% CI
0.652
0.029
1.6–41.2
0.020
0.029
2.6–80.4
1.2–25.3
0.037

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                  |                |              |                |         |
| Normal                               | 33 (50)        | 0            | 33 (58)        | 0.002   |
| 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 (×10^9/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 (IU/L)                           | 803±1,364      | 569±197      | 949±1,762      | 0.646   |
| D-dimer (mg/L FEU)                   | 2.9±5.2        | 3.7±7.1      | 2.4±3.6        | 0.652   |
| Ferritin (mg/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  |
| 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; PT: 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 ratio | 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.
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 asymptptomatically 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 COVID-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 identified 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 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.

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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.

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