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Research paper

Clinical characteristics and outcomes of patients with heart failure admitted to the intensive care unit with coronavirus disease 2019 (COVID-19): A multicenter cohort study

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ABSTRACT

Background: Patients with underlying heart failure (HF) in the setting of COVID-19 who require admission to the intensive care unit (ICU) might present with a unique set of challenges. This study aims to extensively describe the characteristics and outcomes of patients with HF who were admitted to ICU with COVID-19.

Methods: We conducted a multicenter retrospective analysis for all adult patients with HF and an objectively confirmed diagnosis of COVID-19 who were admitted to ICUs between March 1 and August 31, 2020, in Saudi Arabia.

Results: A total of 723 critically ill patients with COVID-19 were admitted into ICUs during the study period: 59 patients with HF and 664 patients with no HF before admission to ICU. Patients with HF had statistically significant more comorbidities, including diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, and acute coronary syndrome. Moreover, higher baseline severity scores (APACHE II & SOFA score) and nutritional risk (NUTRIC score) were observed in HF patients. Overall, patients with HF had more in-hospital and ICU deaths in comparison to patients without HF: (64.3% vs. 44.6%, P-value <0.01) and (54.5% vs. 39%, P-value = 0.02), respectively. Patients with HF had a similar incidence of thrombosis, ICU length of stay, duration of mechanical ventilation, and hospital length of stay compared to patients with no HF.

Conclusion: In this study, patients with HF had more in-hospital and ICU deaths than patients with no HF. Thus, history of HF could be used to help direct case management during hospitalization and possibly dictate proactive COVID-19 care.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an emerging pandemic that is known to cause severe acute respiratory syndrome. In December 2019, it was first identified in Wuhan, China. The World Health Organization declared the outbreak a public health emergency of international concern in January and a pandemic in March 2020 [1]. Saudi Arabia was among the countries that had been negatively impacted by COVID-19 [2]. Patients with underlying cardiovascular disease (CVD) are prone to more severe disease manifestations and worse outcomes [3,4]. This was reported in a study that was conducted by Linschoten et al., which evaluated the cardiac complications resulting from COVID-19 infection.

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They reported that the presence of any preexisting cardiac disease was significantly higher in patients who experienced cardiac complications resulting from COVID-19 infection (29.8% vs. 42.2%, \( p < 0.001 \)) [5]. Heart Failure (HF), in particular, was also significantly higher in patients with cardiac complications compared to patients without cardiac complications (10.3% vs. 4.7%, \( p < 0.001 \)) [5]. Meanwhile, in another study conducted by Bhatt et al., it was found that HF patients diagnosed with COVID-19 had a 24.2% in-hospital mortality rate [6]. Their findings also revealed that compared to those hospitalized with acute HF or for other causes, patients with HF hospitalized with COVID-19 had substantially greater use of in-hospital resources. The use of resources included numerous increased rates of intensive care unit (ICU) treatment (29% vs. 15%) [6].

In Saudi Arabia, there are multiple studies reporting the clinical characteristics of critically ill COVID-19 patients [7,8]. However, none were specific to patients with pre-existing HF who were admitted to the ICU with COVID-19. Thus, this study aims to describe the clinical characteristics and outcomes in HF patients admitted to the ICU as a result of COVID-19 infection in Saudi Arabia.

2. Methods

2.1. Study design and setting

We conducted a multicenter, non-interventional, retrospective study of HF patients admitted to ICUs with a confirmed diagnosis of COVID-19 in Saudi Arabia between March 1 and August 31, 2020. The diagnosis of COVID-19 was confirmed objectively by reverse transcriptase-polymerase chain reaction (RT-PCR). In addition, we identified patients with pre-existing HF using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes. This study was conducted in two large tertiary governmental hospitals, including King Abdulaziz Medical City, Riyadh City, and King Abdulaziz University Hospital, Jeddah City. The Institution’s Review Board approved the study protocol.

2.2. Eligibility criteria

Patients with HF were enrolled in the study if they were critically ill, aged 18 years or older, and admitted to ICU with a positive PCR COVID-19. We excluded patients with ICU length of stay (LOS) of less than one day. We also excluded patients labeled as ‘no code’ status within the first 24 h of ICU admission.

2.3. Data collection and outcomes

We collected the following information: demographic data, comorbidities, home medications, severity scores (such as Acute Physiology and Chronic Health Evaluation II [APACHE II], Sequential Organ Failure Assessment [SOFA], and Nutrition Risk in Critically Ill [NUTRIC]), vital signs, and laboratory tests within 24 h of ICU admission. In addition, D-dimer, fibrinogen level, and procalcitonin were collected. We reported the following outcomes and the clinical and laboratory characteristics of critically ill patients with COVID-19 and HF admitted to ICUs in Saudi Arabia. We also reported the ICU and hospital LOS, mechanical ventilation (MV) duration, and ICU and hospital mortality. We also reported the following ICU complications: acute kidney injury, liver injury, respiratory failure requiring MV, and thrombosis during an ICU stay.

2.4. Statistical analysis

We reported categorical variables as numbers and percentages and continuous variables as a mean with a standard deviation (SD), or median with interquartile range (IQR), as appropriate. The normality assumptions were assessed for all numerical variables using statistical tests (i.e., Shapiro–Wilk test) and graphical representation (i.e., histograms and Q–Q plots). We compared categorical variables using the chi-square or Fisher exact test. We compared normally distributed numerical variables with the t-test, and other quantitative variables with the Mann–Whitney U test. Baseline characteristics, baseline severity, and outcome variables were compared between patients who had underlying HF versus those who didn’t have HF. No imputation was made for missing data as the cohort of patients in our study was not derived from random selection. We considered a \( P \) value of <0.05 statistically significant, and we used SAS version 9.4 for all statistical analyses.

3. Results

3.1. Demographic and clinical characteristics

During the study period, a total of 723 critically ill patients with COVID-19 had been admitted to the ICUs. Of those, 59 patients had underlying HF disease, and 664 patients had no HF disease prior to ICU admission. The average duration of HF was nine years. Patients with HF were older than patients with no HF. Moreover, higher baseline severity scores (APACHE II & SOFA score) and nutritional risk (NUTRIC Score) were observed in HF patients. Also, baseline estimated glomerular filtration rate (eGFR) and platelet counts were significantly lower in the HF group (Table 1). Patients with HF had significantly more comorbidities such as diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, and acute coronary syndrome (Table 2). Significantly more patients in the HF group were on angiotensin-converting enzyme inhibitors, anticoagulants, antiplatelets, b-blockers, and statins prior to admission to the hospital (Table 2).

3.2. Study outcomes

As shown in (Table 3), critically ill COVID-19 patients with HF had similar ICU LOS, MV duration, and hospital LOS compared to patients with no HF. However, patients with HF had more in-hospital and ICU deaths in comparison to the non-HF group (64.3% vs. 44.6%, \( P \)-value <0.01, and 54.5% vs. 39%, \( P \)-value = 0.02, respectively).

As shown in (Table 4), patients with HF had a similar incidence of thrombosis and respiratory failure requiring MV, compared to patients with no HF (14% vs. 10%, \( P \)-value = 0.33, and 79.3% vs. 68.8%, \( P \)-value = 0.09, respectively). However, HF patients had a significantly higher rate of acute kidney injury, compared to patients with no HF (50.8% vs. 26.8%, \( P \)-value <0.01) and liver injury (24.1% vs. 6.9%, \( P \)-value <0.01).

4. Discussion

In this retrospective, multicenter observational study, we described the clinical features and outcomes of critically ill COVID-19 patients with an underlying HF disease in Saudi Arabia. In our cohort, patients with COVID-19 and an underlying HF disease had higher rates of in-hospital and ICU mortality than patients without underlying HF disease (64.3% vs. 44.6%, \( P \)-value <0.01, and 54.5% vs. 39%, \( P \)-value = 0.02, respectively). On the other hand, our study didn’t observe a significant difference in ICU and hospital LOS among patients with HF versus patients without HF.

This contrasts with a previous study that showed that COVID-19 patients with HF had a longer hospital stay than patients without HF [9]. Additionally, there was no significant difference in our population in terms of the duration of mechanical ventilation. However, the previous study showed that COVID-19 patients with HF were twice likely to require mechanical ventilation. The inflammatory response, which occurs in COVID-19 as an elevated immune response, might explain the increase in mortality in patients with COVID-19 accompanied by HF [10].

As mentioned previously, we observed a significant difference in in-hospital and ICU mortality between patients with and without HF. The risk of mortality in critically ill HF patients with COVID-19 is higher
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than for the previously reported overall mortality rate of 23% [11]. Preexisting cardiovascular disease, including HF, is a risk factor for poor prognosis with different types of pneumonia [12]. The systematic inflammatory response, which is extensive among patients with COVID-19, can lead to AKI and impaired sodium and water balance. This also

Moreover, a previous study reported a higher mortality rate in patients with HF who suffered from COVID-19 compared to the influenza virus [14]. The higher rate of mortality could be justified by the severity of

Table 1
Baseline characteristics.

| Variable at baseline | Overall (723) | With HF (N = 59) | Without HF (N = 664) | P-value |
|----------------------|--------------|------------------|----------------------|--------|
| Age (years), mean (SD) | 60.7 (14.83) | 68.7 (11.56) | 60.0 (14.89) | <0.01 |
| Male, n (%) | 531 (72.0) | 66 (11.0) | 484 (72.9) | 0.05 |
| Body mass index (kg/m²), mean (SD) | 30.3 (7.29) | 31.2 (8.30) | 30.3 (7.20) | 0.55 |
| APACHE II score, median (IQR) | 13.0 (8.00, 22.00) | 16.0 (11.00, 25.00) | 12.0 (7.00, 21.00) | <0.01 |
| SOFA score, median (IQR) | 5.0 (3.00, 8.00) | 7.0 (4.00, 9.00) | 5.0 (3.00, 8.00) | 0.01 |
| NUTRIC score, median (IQR) | 3.0 (2.00, 6.00) | 5.0 (4.00, 7.00) | 3.0 (2.00, 5.00) | <0.01 |
| GCS at baseline, median (IQR) | 15.0 | 15.0 (8.00, 15.0) | 15.0 | 0.01 |
| Tocilizumab use during ICU admission, n (%) | 218 (39.1) | 10 (26.3) | 207 (40.9) | 0.08 |
| Systemic corticosteroids use during ICU admission, n (%) | 639 (87.9) | 48 (82.8) | 583 (88.5) | 0.20 |
| Estimated glomerular filtration rate (ml/min), median (IQR) | 74.0 | 38.5 | 77.0 | <0.01 |
| Lactic acid (mg/dl), median (IQR) | 1.8 (1.30, 2.48) | 1.7 (1.20, 2.44) | 1.8 (1.31, 2.48) | 0.55 |
| Platelet’s count (10^9/L), median (IQR) | 251.0 | 219.0 | 253.5 | 0.01 |
| White blood cells (10^9/L), median (IQR) | 10.0 (6.99, 14.00) | 10.7 (8.43, 13.95) | 10.0 (6.90, 13.95) | 0.39 |
| Bilirubin (μmol/L), median (IQR) | 10.0 (7.00, 14.00) | 10.3 (7.20, 14.60) | 10.0 (7.00, 13.40) | 0.83 |
| Alanine aminotransferase (IU/L), median (IQR) | 38.0 | 35.0 | 39.0 | 0.12 |
| Aspartate transaminase (IU/L), median (IQR) | 55.0 | 54.5 | 55.0 | 0.74 |
| C-reactive protein (mg/l), median (IQR) | 156.0 | 139.0 | 158.0 | 0.16 |
| Procalcitonin (ng/ml), median (IQR) | 0.4 (0.15, 1.36) | 0.8 (0.23, 1.96) | 0.3 (0.15, 1.35) | 0.12 |
| Ferritin (ng/ml), median (IQR) | 869.0 | 675.0 | 902.4 | 0.07 |
| Fibrinogen level (g/ml), median (IQR) | 6.8 (4.94, 346.50) | 8.7 (3.89, 399.00) | 6.7 (4.95, 332.00) | 0.99 |
| D-dimer (mg/ml), median (IQR) | 3.4 (1.18, 9.59) | 5.7 (2.28, 15.96) | 3.2 (1.14, 8.54) | 0.01 |
| Potassium (mmol/L), median (IQR) | 4.2 (3.75, 4.75) | 4.1 (3.70, 4.80) | 4.2 (3.80, 4.75) | 0.72 |
| Sodium (mmol/L), median (IQR) | 137.0 | 137.0 | 137.0 | 0.53 |
| Hematocrit, median (IQR) | 0.4 (0.35, 0.47) | 0.4 (0.37, 0.47) | 0.4 (0.35, 0.47) | 0.25 |

| Table 2
Comorbid conditions and home medications.

| Variable at baseline | Overall (723) | With HF (N = 59) | Without HF (N = 664) | P-value |
|----------------------|--------------|------------------|----------------------|--------|
| Comorbid conditions, n (%) | 168 (23.2) | 27 (45.8) | 139 (20.9) | <0.01 |
| Diabetes mellitus | 442 (61.0) | 49 (79.3) | 391 (58.9) | <0.01 |
| Hypertension | 412 (56.8) | 52 (88.1) | 359 (54.1) | <0.01 |
| Acute coronary syndrome | 12 (1.7) | 8 (13.6) | 4 (0.6) | <0.01 |
| Coronary artery bypass grafting | 21 (2.9) | 8 (13.6) | 13 (2.0) | <0.01 |
| Ischemic heart disease | 63 (8.7) | 15 (25.4) | 48 (7.3) | <0.01 |
| Asthma | 62 (8.6) | 7 (11.9) | 54 (8.1) | <0.01 |
| Atrial fibrillation | 20 (2.8) | 7 (11.9) | 13 (2.0) | <0.01 |
| Chronic obstructive pulmonary disease | 23 (3.5) | 8 (13.6) | 15 (2.1) | <0.01 |
| Chronic kidney disease | 25 (3.5) | 8 (13.6) | 17 (2.6) | <0.01 |
| Complications during ICU stay.

| Table 3
Clinical outcomes.

| Outcomes | Number of outcomes/total no. of patients | P-value |
|----------|----------------------------------------|--------|
| With HF (N = 59) | None-HF (N = 664) |
| In-hospital mortality, n (%) | 36 (64.3) | 286 (44.6) | <0.01 |
| ICU mortality within 30 days, n (%) | 30 (54.5) | 242 (39.0) | 0.02 |
| MV duration during ICU stay (days), median (IQR) | 7.5 (3.00, 15.00) | 8.0 (3.00, 16.00) | 0.84 |
| ICU Length of Stay (days), median (IQR) | 10.0 (7.00, 16.00) | 10.0 (6.00, 18.00) | 0.93 |
| Hospital Length of Stay (days), median (IQR) | 18.0 (9.00, 25.00) | 17.0 (11.00, 25.00) | 0.63 |

ICU = intensive care unit; IQR = interquartile range.

| Table 4
Complications during ICU stay.

| Complications during ICU stay | Number of outcomes/Total no. of patients | P-value |
|-----------------------------|----------------------------------------|--------|
| With HF (N = 59) | Without HF (N = 664) |
| Acute kidney injury, n (%) | 30 (50.8) | 14 (24.1) | <0.01 |
| Liver injury, n (%) | 46 (79.3) | 65 (10.0) | 0.33 |

NUTRIC = Nutrition Risk in Critically ill; SOFA = Sequential Organ Failure Assessment; SD = standard deviation.

APACHE II = Acute Physiologic Assessment and Chronic Health Evaluation II; GCS = Glasgow Coma Scale; ICU = intensive care unit; IQR = interquartile range; NUTRIC = Nutrition Risk in Critically ill; SOFA = Sequential Organ Failure Assessment; SD = standard deviation.
of COVID-19 infection course in patients with HF and the significance of hemodynamic compromise, which often requires cardiopulmonary support.

In comparison to the previously published studies in this patient population, we examined the incidence of ICU complications, which constitute another essential factor that can increase mortality and prolong an ICU or hospital stay. CVD patients are at a higher risk for adverse effects [15,16]. In our study, the incidence of thrombosis and respiratory failure requiring MV were similar among patients with HF and patients without HF (14% vs. 10%; P-value = 0.33) and (79.3% vs. 68.8%; P-value = 0.09), respectively. It is noteworthy to mention that at baseline, HF patients in our study had more comorbid cardiovascular conditions such as hypertension (88.1% vs. 54.1%), dyslipidemia (45.8% vs. 20.9%), and acute coronary syndrome (8% vs. 4%). The ACE/ACE2 ratio is increased in such patients within organs. Thus, it is postulated that those patients are at a higher risk for disease severity, thrombotic complications, and inflammatory response. Thus, complications tend to be more severe [17].

On the contrary, a significant difference was observed in the incidence of acute kidney and liver injury among patients with HF and those without (50.8% vs. 26.8%, P-value<0.01) and (24.1% vs. 6.9%, P-value <0.01), respectively. The incidence of AKI reported in critically ill COVID-19 patients was up to 29% [18]. A similar incidence rate was observed in our population without HF (26.8%). However, a higher incidence was reported in patients with HF. Several factors can potentially explain such findings. First, our HF population had more frequent comorbidities such as hypertension (88.1% vs. 54.1%) and diabetes mellitus (83.1% vs. 58.9%). These are well-known factors related to renal vulnerability [19-21]. Secondly, the virus’s direct effect on the myocardium, the inflammatory response associated with disease course, and the disturbance of oxygen supply and demand can all predispose to the acute exacerbation of the HF condition [18]. As a result, a worsening renal function can, in situ, lead to a cardiorenal syndrome (type 1). A decline in the glomerular filtration rate is seen as a result of both the activation of the renin-angiotensin-aldosterone system and renal congestion [22]. The median estimated glomerular filtration rate reported in our patients with HF group was 38.5 ml/min as opposed to patients without HF 77.0 ml/min. Moreover, liver injury in patients without HF was lower than the reported literature (14–53%) [23]. Generally, the prevalence of hepatic dysfunction in acute HF is 20% to 30% [18]. The proposed mechanism behind liver injury in acute HF patients is liver hypoperfusion and congestion. To date, no study reported data on the volume status of HF medications at the time of hospital admission in critically ill patients, so we can only assume these probable explanations lead to much higher incidence of AKI and liver injury.

The present study had some limitations. First, it was conducted in retrospective fashion for which we might have certain reporting and documentation bias. There is also a possibility for incomplete capturing of eligible patients. Also, we were not able to extract the brain natriuretic peptide and troponin levels as they were not obtained at baseline nor during patients’ hospitalization. Furthermore, we faced a frequent change in the management of patients with COVID-19 as evidence continued to emerge over time. That said, this study adds to the pool of evidence that critically ill patients presenting with COVID-19 and underlying HF diseases are more prone to worse clinical outcomes. To the best of our knowledge, this is the largest study to date to assess the clinical outcome in this patient population in Saudi Arabia. The major public health implication of this study is to expedite the prevention process. Institutionally, the results of this study could be used to direct case management during hospitalization and possibly dictate proactive COVID-19 care in patients with HF [24].

5. Conclusion

In this retrospective analysis, patients with COVID-19 and underlying HF had similar ICU and hospital LOS, duration of MV, and thrombosis rate compared to patients with no HF. However, patients with HF had more in-hospital and ICU deaths compared to those with no HF. For this reason, a history of HF could be used to help direct case management during hospitalization and possibly dictate proactive COVID-19 care.

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CRediT authorship contribution statement

Bin Saleh: Conceptualization, Methodology, Investigation, Resources, Writing (original draft); Hafiz: Conceptualization, Methodology, Investigation, Resources, Writing (original draft); Alsuaimain: Conceptualization, Methodology, Investigation, Resources, Writing (original draft), Data Curation; Aljuhani: Conceptualization, Methodology, Investigation, Resources, Writing (original draft), Data Curation; Alharbi Writing (Review and editing), Supervision; Alharbi: Conceptualization, Methodology, Investigation, Resources, Supervision; Vishwakarma: Software, formal analysis, Writing (Review and editing); Albeikary: Writing (Review and editing), Supervision; Alkathiri: Writing (Review and editing), Supervision; Alnazi: Conceptualization, Methodology, Investigation, Resources, Writing (original draft); Almujarri: Conceptualization, Methodology, Investigation, Resources, Writing (original draft); Alobathani: Writing (Review and editing); Alharbi: Writing (Review and editing); Zowawi: Writing (Review and editing), Supervision; Badredlin: Conceptualization, Methodology, Investigation, Resources, Writing (original draft), Writing (Review and editing), Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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