Clinical Features and Outcomes of Critically Ill Patients with Coronavirus Disease 2019 (COVID19): A Multicenter Cohort Study

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Abstract

Background

A novel coronavirus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causing coronavirus disease-19 (COVID-19) manifested by a broad spectrum of symptoms, ranging from asymptomatic manifestations to severe illness and death. The purpose of the study was to extensively describe the clinical features and outcomes in critically ill patients with COVID19 in Saudi Arabia.

Method

A multi-center, non-interventional, observational study for all critically ill patients aged 18 years or older who are admitted to intensive care units (ICUs) between March 1st to August 31st, 2020 with an objectively confirmed diagnosis of COVID19. The diagnosis of COVID19 was confirmed by Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR) on nasopharyngeal and/or throat swabs. Multivariate logistic regression and generalized linear regression were used. We considered a P value of < 0.05 statistically significant.

Results

A total of 560 patients met the inclusion criteria. The overall survival rate was 52.6 % (295 patients). Moreover, the overall ICU mortality rate within 30 days was 42.3 % (237 patients). The median ICU length of stay (LOS), hospital LOS, and mechanical ventilation duration were of 10 days (IQR 6.00-17.50), 17 days (IQR 11-25), and 9 days (IQR 3-17 days), respectively. The rate of ICU readmission for survival within three months was 9.7 %. An extensive list of clinical features was associated with ICU mortality rate within 30 days.

Conclusion

In the most comprehensive report to date from Saudi Arabia, among patients with COVID19 who were admitted to the ICU, several variables were associated with increasing the risk of ICU death at 30 days, and the incidence of ICU mortality rate within 30 days 42.3%.

Introduction

A novel coronavirus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causing coronavirus disease-19 (COVID-19) emerged in China, in late 2019 1. Shortly afterward, and due to the virus's extensive spread to nearly all countries, the WHO announced the COVID-19 outbreak as a pandemic on March 11, 2020 2. COVID-19 is manifested by a broad spectrum of symptoms, ranging from asymptomatic manifestations to severe illness and death. In order to relieve these symptoms, COVID-19 is currently managed by certain antiviral medications, and in extreme cases, supportive treatments, including supplemental oxygen and mechanical ventilation 3.
On March 2, 2020, the first confirmed case of COVID-19 was announced in Saudi Arabia, and by 28 October 2020, the MOH had reported a total of 345,631 confirmed cases with a case fatality rate of 0.86% \(^4\). Owing to the implementation of successful healthcare policies, the epidemiological COVID19 curve in Kingdom of Saudi Arabia (KSA) reached a steady level two months from the beginning of the pandemic. Moreover, the rates of critical cases and mortality in KSA are low due to the younger population in Saudi Arabia compared to European, North American, and Asian countries and the government’s efficient precautionary measures \(^5\).

The in-depth clinical and laboratory characteristics of COVID-19 has been reported among COVID-19 Saudi Arabia patients; however, it is limited to case series and small sample size studies. Recently a total of 150 case series has been reported the clinical and therapeutic characteristics of hospitalized patients with confirmed COVID-19 in specialized hospital in Saudi Arabia. They found that 70% were mild cases \(^6\).

Although it is a limited number of cases, it highlights that reporting and assessing the characteristics of patients with confirmed COVID-19 are important to plan and implement policy interventions. There are limited reports demonstrating the variability in features of the disease between populations, taking into consideration the comorbidities, severity of the disease and immune system responses \(^7\).

The Saudi MOH has been driving the national COVID19 management protocols and living guidance, which had been developed in accordance with the latest scientific, evidence-based COVID-19 studies. Specific institution either adopted the same protocol or modified it in accordance with their internal expert committees \(^8\).

To the best of our knowledge, there is a lack of multicenter studies that examined the clinical course for patients with COVID-19 admitted to the ICU in Saudi Arabia. We therefore conducted this study to extensively examine the clinical characteristics, outcomes, and off label use of medications in critically ill patients with COVID19 in Saudi Arabia.

**Methods**

**Study design**

A multi-center, non-interventional, observational study of critically ill patients admitted to intensive care units (ICUs) with confirmed diagnosis of COVID19 in KSA. The diagnosis of COVID19 was confirmed objectively by Reverse Transcriptase – Polymerase Chain Reaction (RT-PCR) on nasopharyngeal and/or throat swabs. Retrospective part included de-identified data of COVID-19 PCR positive patients admitted prior to the date of IRB approval (March-April 2020). The prospective part was conducted between May 1\(^{st}\) and August 31\(^{st}\),2020. Patients were followed daily during ICU Length of stay (LOS) until in-hospital death or discharge whichever occurred first.

**Eligibility criteria**
Patients 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. Patients with ICU LOS \( \leq \) 1 day or \( \geq \) 60 days, and/or labeled as “Do-Not-Resuscitate” status within the first 24 hours of ICU admission were excluded.

Setting

This study was conducted in two large, tertiary governmental hospitals. The first hospital was King Abdulaziz Medical city – Central Region (KAMC-CR) located in Riyadh and the second was King Abdulaziz University Hospital (KAUH) located in Jeddah. The distribution of total enrolled patients were 81 %, and 19 % in KAMC-CR and KAUH respectively. The primary site for this multicenter, prospective cohort study was King Abdulaziz Medical city (Riyadh).

King Abdulaziz Medical City is a tertiary-care academic referral hospital in Riyadh, Saudi Arabia. The ICUs admits medical, surgical, trauma, burn and transplant patients, and operates as a closed unit with 24/7 onsite coverage by critical care board-certified intensivists. King Abdulaziz University Hospital is a tertiary care academic hospital located in Jeddah, Saudi Arabia. The hospital has a bed capacity of 1067 beds and ICUs admit medical, surgical and cardiac patients, and operates as a closed unit with 24/7 onsite coverage by critical care intensivists.

Data collection

We collected the following information, demographic data, Acute Physiology And Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) and Nutrition Risk in Critically ill (NUTRIC) scores, co-morbidities, pre-hospital (Home) medications, vital signs, laboratory tests and radiological finding within 24 hours of ICU admission, ICU support measures needed during ICU stay, off label use of medications for COVID19, COVID19 viral load. In addition, D-Dimer, Fibrinogen Level, D-dimer/fibrinogen ratio, thrombosis during ICU stay, procalcitonin, iron study, radiological studies, and complication (s) during ICU stay were prospectively collected and followed.

Outcomes

The primary endpoint was extensively to describe the clinical and laboratory characteristics of critically ill patients with COVID 19 admitted to Intensive Care Units (ICUs) in Saudi Arabia. The secondary endpoints to determine the mean ICU LOS duration, mean MV duration, ICU mortality and risk factors for poor prognosis in Saudi Arabia.

Data management and Statistical analysis

We summarized categorical variables as number (percentage) and numerical variables (continuous variables) as mean and standard deviation (SD). The normality assumptions were assessed for all numerical variables using statistical test (i.e. Shapiro–Wilk test) and also using graphical representation (i.e. histograms and Q-Q plots). We compared categorical variables using the chi square or Fisher exact test, 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 with ICU mortality within 30 days and Thrombosis during ICU stay.

Multivariate logistic regression and generalized linear regression were used to find out the relationship between ICU mortality within 30 days, thrombosis during ICU stay and the different outcomes considered in this study, adjusting for the patient’s baseline severity scores (namely, APACHE II, NUTRIC and SOFA scores).

We assessed model fit using the Hosmer-Lemeshow goodness-of-fit test. Generalized linear regression was also used to find out the relationship between study outcome and the different study parameters considered in this study, adjusting for baseline severity scores. The odds ratios (OR) and estimates with the 95% confidence intervals (CI) were reported for the associations. 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 used SAS version 9.4 for all statistical analyses. The multiplicity adjustment was not done.

Results

Demographic and Clinical Characteristics

A total of 560 critically ill patients with COVID-19 who had been admitted in ICUs at the two governmental hospitals, clinical characteristics, laboratory tests and off label use medications were obtained. The average age of the patients was 60 years (SD 14.58); 224 (40%) of the patients were ≥ 65 years old. A total of 417 (74.5%) were male. Among the 560 patients, diabetes mellitus (57.7%) was the most common coexisting illness followed by hypertension (53.6%) and dyslipidemia (22.7%). On the other hand, 17.3% of the patients had no coexisting comorbid condition. The most common admission source was direct ICU admission (48.8%) followed by critical care response team (CCRT) activation from wards/floor (44.3%) with a median of 3 days before ICU admission.

Prior to ICU admission, 25% of the patients were on statins, followed by Calcium channel blockers, Antiplatelets, Angiotensin II receptor blockers (ARBs) and Angiotensin-converting enzyme inhibitors (ACEIs) with proportion of 16.3%, 15.7%, 12.9% and 12.9% respectively. (Additional file 1).

Overall Outcomes

Overall survival rate was 52.6% (295 patients). Whereas, the overall ICU mortality rate within 30 days was 42.3% (237 patients). The median ICU LOS, hospital LOS and Mechanical ventilation duration were 10 days (Interquartile range (IQR): 6.00 to 17.50), 17 days (IQR: 11 days to 25 days) and 9 days (IQR:3 days to 17 days) respectively. The rate of ICU readmission for survival within 3 months was 9.7% (Table 1).
### Table 1
**Overall outcomes**

| Overall outcomes                                      | All Patients               |
|-------------------------------------------------------|----------------------------|
| Overall survival rate, n (%)                          | 295 (52.67)                |
| Overall ICU mortality within 30 days, n (%)           | 237 (42.32)                |
| Duration of Mechanical Ventilation, Median (IQR)     | 9.0 (3.00, 17.00)          |
| ICU Length of Stay Days, Median (IQR)                 | 10.0 (6.00, 17.50)         |
| Hospital LOS (Days), Median (IQR)                     | 17.0 (11.00, 25.00)        |
| ICU readmission within 3 months, n (%)                | 27 (9.74)                  |
| -Denominator of the percentage is the total number of patients |

- Denominator of the percentage is the total number of patients

## Baseline Findings within 24 hours of ICU admission and Risk of 30 Days Mortality

(Additional file 2) shows the clinical and laboratory findings on admission. Higher baseline severity scores (APACHE II & SOFA score) and nutritional risk (NUTRIC score) were associated with higher 30 days ICU mortality (P < 0.0001). The most common blood group types were O+, A+ and B+ with proportion of 22.5%, 18.2% and 14.3% respectively (Additional file 1). Among common blood group types, A+ was associated with higher 30 days-ICU mortality (57.8%) (P = 0.0361) as well as thrombosis during ICU stay (P = 0.0113) (Table 5).

Among 560 patients, 370 (66.1%) require mechanical ventilation (MV) during the first 24 hours. Requiring MV on ICU admission was associated with higher ICU mortality within 30 days (P = < 0.0001). Mixed Acid-Base Disorder was the most frequent acid-base disorder (21.61%) within 24 hours of ICU admission. Among patients who had ICU mortality within 30 days, metabolic acidosis was the most frequent (P = < 0.0001). Higher alveolar-arterial gradient with median of 430.7 mmHg (IQR: 292.7-582.8 mmHg), (P < .0001), and lower base excess with median of -1.9 (IQR: -3.95 to 0.45) were associated with higher rates of 30 days ICU mortality.

Within 24 hours of ICU admission, higher body temperature, white blood cells (WBCs), blood glucose level (BGL), serum creatinine, fibrinogen, procalcitonin, creatine phosphokinase (CPK), aspartate aminotransferase (AST) and Total iron-binding capacity (TIBC) were associated with higher 30-days ICU mortality. On the other hand, platelets count, serum iron, lymphocytes, Glasgow Coma Scale (GCS) and mean arterial pressure (MAP) were higher among the survivors within 30 days of ICU admission.

Patients who developed Acute kidney injury (AKI) within 24 hours of ICU admission, were associated with higher ICU mortality within 30 days (p-value < .0001). In addition, positive cumulative fluids balance within 24 hours of ICU admission was associated with higher ICU mortality but not was statistically significant (Additional file 2).
On ICU admission, Bilateral Patchy Shadowing followed with Local Patchy Shadowing with a proportion of 60.8% and 7.32 respectively were the most common radiological finding on chest X-ray. Patients with radiological finding of Bilateral Interstitial Abnormalities were associated with higher 30 days-ICU mortality. No radiographic abnormality was found in 37 patients (6.61%), and was associated with lower 30-days ICU mortality (p-value 0.0001) (Additional file 2).

**Off label use medications during ICU**

Among the COVID19 off label use medications during ICU stay, systemic corticosteroids were the most common (84.5%), followed by Tocilizumab, anticoagulation treatment dose, Oseltamivir, Azithromycin, Ascorbic Acid, with proportion of 38.9%, 28.1%, 30.2%, 28.9%, 24.8 and 21.6% respectively (Table 2).

| Off label use of medications during ICU | All patients (N = 560) |
|----------------------------------------|------------------------|
| Systemic Corticosteroids during ICU    | 473 (84.5)             |
| Tocilizumab, n(%)                      | 218 (38.9)             |
| Anticoagulation treatment dose, n(%)   | 169 (30.2)             |
| Oseltamivir, n(%)                      | 162 (28.9)             |
| Azithromycin, n(%)                     | 139 (24.8)             |
| Ascorbic acid, n(%)                    | 121 (21.6)             |
| Statins, n(%)                          | 107 (19.1)             |
| Zinc, n(%)                             | 103 (18.4)             |
| Aspirin, n(%)                          | 81 (14.5)              |
| Thiamine, n(%)                         | 58 (10.4)              |
| Hydroxychloroquine, n(%)              | 42 (7.5)               |
| Lopinavir & Ritonavir, n(%)            | 34 (6.1)               |
| Favipiravir, n(%)                      | 11 (2.0)               |

-Denominator of the percentage is the total number of patients

**COVID19 Testing and Risk of 30 days Mortality**

53.4% of the patients have a positive COVID19 RT-PCR with a mean of 4 days prior to ICU admission. The median time to reach the viral load peak is 7 day from the first positive sample. While, the median time for COVID19 viral load to be undetected is 13 days.
Among all admitted patients, 208 (37.1%) of patients have persistent positive COVID19 PCR testing, that was significantly associated with ICU mortality within 30 days (P < 0.0001) (Table 3).

Table 3
COVID19 Testing- ICU mortality within 30 Days

| Variables                                                                 | All patients | ICU mortality within 30 Days | P-value | OR (95%CI)/Estimates(95%CI) | P-value |
|--------------------------------------------------------------------------|--------------|------------------------------|---------|-----------------------------|---------|
|                                                                           | (N = 560)    | Yes (N = 237)                | No (N = 323) |                              |         |
| Positive COVID testing prior ICU admission, n (%)                        |              | 299 (53.4)                  | 129 (54.4) | 170 (52.6)                  |         |
|                                                                           |              | 0.6733^\^                   | 0.8 (0.56–1.30) |                          | 0.4505 |
|                                                                           |              | Days prior to ICU admission from positive COVID testing, Mean (SD) | | | |
|                                                                           |              | 4.20 (4.11)                 | 4.45 (4.58) | 4.01 (3.71)                  |         |
|                                                                           |              | 0.6454^\^                   | 0.85 (-0.51,2.22) |                          | 0.2194 |
|                                                                           |              | Time for COVID19 Viral load to reach peak (days), Median (IQR) | | | |
|                                                                           |              | 7.0 (5.00,11.00)            | 6.0 (5.00,9.00) | 7.0 (5.00,11.00)            |         |
|                                                                           |              | 0.3392^\^                   | -0.20 (-3.35,2.94) |                          | 0.8986 |
|                                                                           |              | Time for COVID19 Viral load undetectable, Median (IQR) | | | |
|                                                                           |              | 13.0 (8.00,26.50)           | 19.5 (11.00,25.00) | 13.0 (5.00,27.00)           |         |
|                                                                           |              | 0.0900^\^                   | -2.43 (-11.36,6.51) |                          | 0.5947 |
|                                                                           |              | Death before COVID19 Clearance, n (%) | | | |
|                                                                           |              | 208 (37.1)                  | 194 (81.9) | 14 (4.3)                    | <.0001** |
|                                                                           |              | 88.9 (44.22-178.71)         |            |                             | <.0001$ |

ICU Complications and Risk of 30 Days Mortality
The most common complication during ICU stay was respiratory failure that required MV (71.4%), followed by acute kidney injury (AKI), thrombosis and liver injury with a proportion of 46.8%, 11.4% and 7.1% respectively. AKI was significantly high among patient with ICU mortality within 30 days as compared survivors during ICU stay (74.7% Vs. 26.2%) (P < 0.0001) and it was significant risk factor after adjusting for their baseline disease severity scores (aOR 4.3, 95% CI 2.77–6.64, p-value 0.0001) (Additional file 3).
Patients who developed liver injury during ICU stay had a higher ICU mortality (aOR 2.2, 95% CI 1.02–4.81, p-value 0.0435) as well as patient who developed Disseminated Intravascular Coagulation (DIC) (p-value 0.0010) (Additional file 3).

**ICU Support Measures and Risk of 30 Days Mortality**

The most common ICU support measures needed during ICU stay were MV (71.4%), followed by vasopressors/Inotropes, continuous renal replacement therapy (CRRT), conventional dialysis and using Inhaled Nitric Oxide (iNO) with a proportion of 54.6%, 18.9%, 15.7% and 8.4% (Table 4). Using iNO as support measure during ICU stay, was associated with higher ICU mortality within 30 days (aOR 5.7, 2.61–19.19, p-value 0.0001) (Table 5).

### Table 4

| ICU Support Measures Needed | All patients (N = 560) | ICU mortality within 30 Days | P-value | OR (95%CI) | P-value |
|-----------------------------|------------------------|-----------------------------|---------|------------|---------|
|                             | Yes (N = 237) | No (N = 323) | P-value |          |         |
| Mechanical Ventilation n (%) | 400 (71.4) | 220 (92.8) | 180 (55.7) | < .0001^^ | 6.1 (3.32–11.05) | < .0001 |
| ECMO, n(%)                  | 10 (1.8) | 8 (3.4) | 2 (0.6) | 0.0207 ** | 4.8 (0.89–25.86) | 0.0673 |
| CRRT, n (%)                 | 106 (18.9) | 73 (30.8) | 33 (10.2) | < .0001** | 1.7 (1.01–2.94) | 0.0454 |
| Conventional Dialysis, n (%) | 88 (15.7) | 60 (25.3) | 28 (8.7) | < .0001** | 1.6 (0.89–2.79) | 0.1203 |
| Inhaled Nitric Oxide, n (%)  | 47 (8.4) | 34 (14.3) | 13 (4.0) | < .0001** | 5.7 (2.60–12.37) | < .0001 |
| Vasopressors Inotropes, n(%) | 306 (54.6) | 201 (84.8) | 105 (32.5) | < .0001** | 7.3 (4.49–11.89) | < .0001 |
| Plasmapheresis, n (%)       | 6 (1.1) | 4 (1.7) | 2 (0.6) | 0.2477** | 0.9 (0.14–5.79) | 0.9106 |
| Variables            | All patients (N = 560) | Thrombosis During ICU | P-value | OR (95%CI) | P-value$ |
|----------------------|------------------------|-----------------------|---------|------------|---------|
|                      | Yes (N = 64)           | No (N = 496)          |         |            |         |
| APACHE II score      | 12.0 (7.00, 25.00)     | 20.0 (12.00, 30.00)   | 12.0 (7.00, 23.00) | 0.0002$ | 1.0 (0.99–1.04) | 0.2083 |
| SOFA score           | 5.0 (3.00, 8.00)       | 7.0 (4.50, 9.00)      | 4.0 (3.00, 8.00)   | 0.0015$ | 0.8 (0.76–0.94) | 0.0532 |
| BMI (kg/m2)          |                        |                       |         |            |         |
| Under Weight         | 10 (1.8)               | 2 (3.1)               | 8 (1.6)  | 0.5215^^   | 1       | -       |
| Normal               | 98 (17.5)              | 16 (25.0)             | 82 (16.5) | 0.3 (0.04–1.96) | 0.6656 |
| Pre-Obese            | 189 (33.8)             | 21 (32.8)             | 168 (33.9) | 0.1 (0.02–0.92) | 0.2070 |
| Obese-Class I        | 137 (24.5)             | 12 (18.8)             | 125 (25.2) | 0.1 (0.02–0.81) | 0.1048 |
| Obese-Class II       | 66 (11.8)              | 7 (10.9)              | 59 (11.9)  | 0.2 (0.02–1.10) | 0.4351 |
| Obese-Class III      | 60 (10.7)              | 6 (9.4)               | 54 (10.9)  | 0.1 (0.01–0.91) | 0.1826 |
| ABO (blood group), n (%) |                   |                       |         |            |         |
| O+                   | 126 (22.5)             | 14 (24.1)             | 112 (25.8) | 0.0047**  | 0.3 (0.07–1.14) | 0.0013 |

-Denominator of the percentage is the total number of patients

^ Wilcoxon rank sum test is used to calculate the P-value.

**Fisher Exact /^^Chi-square test is used to calculate the P-value.

$ Multivariate logistic regression is used to calculate odds ratio and p-value after adjusting for patients baseline APACHE II, NUTRIC and SOFA scores.
## Variables

| Variables          | All patients (N = 560) | Thrombosis During ICU | P-value | OR (95%CI) | P-value$ |
|--------------------|------------------------|-----------------------|---------|------------|----------|
|                    | (N = 64) (N = 496)     |                       |         |            |          |
| A+                 | 102 (18.2)             | 14 (24.1)             | 88 (20.2) | 0.3(0.09–1.39) | 0.0113   |
| B+                 | 80 (14.3)              | 17 (29.3)             | 63 (14.5) | 0.7(0.17–2.65) | 0.6382   |
| Ab+                | 15 (2.7)               | 2 (3.5)               | 13 (3.0)  | 0.9(0.15–5.08) | 0.8458   |
| O-                 | 12 (2.1)               | 2 (3.5)               | 10 (2.3)  | 1           | -        |
| B-                 | 9 (1.6)                | 3 (5.2)               | 6 (1.4)   | 4.4(0.59–32.22) | 0.0129   |
| A-                 | 8 (1.4)                | 0                     | 8 (1.8)   | 0.7(0.08–5.21) | 0.8285   |

-Denominator of the percentage is the total number of patients

^ Wilcoxon rank sum test is used to calculate the P-value.

**Fisher Exact /^^Chi-square test is used to calculate the P-value.

$ Multivariate logistic regression is used to calculate odds ratio and p-value after adjusting for patients baseline APACHE II, NUTRIC and SOFA scores.

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## Thrombosis During ICU stay

Among 64 patients (11.4%) who developed thrombosis during ICU stay, A+ and B- were the most common blood group types with a proportion of 24.1% (p-value:0.0113) and 5.2% (p-value:0.0129) respectively after adjusting for patient’s severity scores and obesity (Table 5).

Patient who developed DIC were associated with higher thrombosis rate during ICU stay after adjusting for patient’s severity scores (aOR 27.1 CI 5.10-144.3, p-value 0.0001) (Additional file 3).

## Discussion

In this multicenter prospective study, majority of the included patients were male (74.5%), and 40% of the patients were ≥ 65 years, which was consistent with previously published studies⁹,¹⁰,¹¹,¹². Diabetes
mellitus was the most prevalent comorbid condition in our cohort affecting more than half of the patients admitted to the ICU (57.7%), followed by hypertension (53.6%) respectively, while in most reports hypertension was the most prevalent comorbid condition. This observation can be explained by the high number of diabetes mellitus cases in our region as the prevalence of Diabetes in adults is 18.3% in Saudi Arabia as a result of the state of urbanization and adopting sedentary lifestyle compared to other countries.

This study demonstrated an overall 30-day mortality of 42.3% in critically ill patients with COVID-19 infection. Previous reports from China, Italy, and United States (US) have described different mortality rates among critically ill patients ranging from 16%, to 38%, 42.1%, 53.8% (19), and 67% (20). This variation in mortality rate might be attributed different factors such as baseline patient characteristics, different duration of follow up among studies, and different ICU bed availability among different hospitals as a study reported that patient who were admitted to hospitals with lower ICU bed capacity had a higher risk of death. In a previous multicenter cohort study that included 2215 critically ill adults with confirmed COVID-19 from US, the reported median ICU LOS was 9 days (IQR, 5–14 days) and the median hospital LOS was 16 days (IQR, 11–22 days) which was comparable to our data.

The median APACHE II score on admission to ICU was 12. In comparison, this score was 10 in a study in Singapore, 14 in the Intensive Care National Audit and Research Centre (ICNARC) report for the United Kingdom, 15 in the Scottish Intensive Care Society Audit Group (SICSAG) report, 17 in a study in Wuhan. The median NUTRIC score and SOFA score were 3 and 5, respectively. Shock, AKI, and mixed acid-base disorders were experienced by around a quarter of patients. Two-thirds of patients received mechanical ventilation, and these population had the greatest benefit of corticosteroids. The severity of ARDs in our patients seems less than other studies. The median PaO2/FiO2 ratio was 98.3, while it was 118.5 in the ICNARC report, 132 in Atlanta study, 160 in a study in Lombardy, and 194 in the Singaporean study. Several inflammatory biomarkers were elevated in our study such as ferritin, CRP, D-dimer, CPK, and fibrinogen, which are key biomarkers in ARDs and cytokine release syndrome associated with COVID-19.

For the off label use of medications, as expected systemic corticosteroids were used in the majority of patients since a randomized controlled trial (Recovery trial) found a significant mortality benefit in COVID-19 patients who received a respiratory support in the dexamethasone arm compared to the standard of care arm. Despite the current controversial efficacy of tocilizumab, its adverse reactions and expensive price, it was used in more than a third of patients. Although treatment dose of heparin is not currently recommended, around a third of our patients received this dose. For oseltamivir, it is recommended as empiric anti-influenza treatment in hospitalized patients while awaiting influenza testing results. In our study it was used in around a third of included patients. Azithromycin was used in a quarter of patients. It is unclear whether it was used for community-acquired pneumonia or the prescribers believed in its efficacy in COVID-19, which is not currently supported. Vitamin C and
thiamine were used in around 20% of patients but there are insufficient data on these supplements \(^4^9\). Hydroxychloroquine was rarely used in our study as it is no longer recommended in hospitalized COVID-19 patients \(^4^9,^5^0\).

In our study of critically ill COVID-19 patients we found that the median time for viral load to be undetected was 13 days. Median time to viral clearance was ranging from 7 to 12 days and up to 28 days in some reports\(^2^2\). In a previous study conducted in the capital of Hunan, it took 17 days for patients to test negative\(^2^3\). Our report of median 13 days for viral clearance is in alignment with reported duration of average two weeks, we expect that critically ill patients to have prolonged virus release. Data from a large cohort of COVID-19 patient from a single University Hospital in Milano (Italy), reported a viral clearance rate within 14 and 28 days were 32% and 54%, respectively\(^2^2\).

We also observed a significant association between patients with persistence positive COVID-19 PCR and ICU mortality within 30 days, to date little is known about the association between timing of clearance and disease severity or mortality. One large cohort study of COVID-19 patient reported that neither viral clearance rate at 14 and 28 days nor time to negative viral RNA load were predictor of mortality rate\(^2^2\). Our observation is different than this report, also our result is important in daily clinical practice, and it could be potentially used to guide patient care. Similar association was reported in an earlier retrospective cohort study, they concluded that SARS-CoV-2 viral load among hospitalized patients with COVID-19 independently correlates with the risk of intubation and in-hospital mortality\(^2^4\). The hypothesis of persistence viral load and its relationship with disease severity and risk of mortality warrant further investigation.

The most common complication during ICU stay was respiratory failure followed by acute kidney injury and thrombosis. Since our COVID-19 patients are all critically ill patients, it is not surprisingly to report higher respiratory failure percentage. Several mechanisms have been proposed in literatures as the cause for substantial respiratory failure seen in COVID-19 patients. These include diffuse alveolar damage which account for ARDs, pulmonary edema, vascular occlusion and ventilation and perfusion mismatch are other possible mechanism for hypoxic respiratory failure\(^2^5\). Our results of high respiratory failure rate and high percentage of requiring MV are in line with Wang D et al, which concluded that hypoxemic respiratory failure requiring MV is the most concerning complication in COVID-19 patients\(^2^6\). We reported a higher mortality rate among our patients requiring MV in comparison with 35.7% death rate of mechanically ventilated COVID-19 patients that was reported in an earlier study\(^2^7\).

According to our result, the AKI was the second common complication encountered in our group with 46.8%. The relationship between COVID-19 and AKI remains unclear. Numerous possible mechanisms have been addressed in literatures about possible cause of COVID-19 related AKI. These include direct renal infection of the virus, angiotensin converting enzyme 2 (ACE2) which is abundant in the kidney has been identified as the main target for COVID-19 virus. Additionally, viral infection can stimulate inflammatory mediators and cytokine storm, this results in microvascular injury and cause AKI\(^2^8\). The rate
of AKI among our group was higher than the reported rate by Wang L et al, which have found that only 12 (10.8%) experienced a small increase in serum creatinine or urea nitrogen within the first 48 hours of hospital stay, however this report were in non-critically ill COVID-19 patients. Previous studies have identified older age and comorbidities and severe ARDS as risk factors for AKI in hospitalized and critically ill viral infection patients. After adjusting our population baseline disease severity, we found that AKI is a significant risk factor for ICU mortality in critically ill COVID-19 patients. This association is in line with the results of Cheng et al, reported higher mortality in COVID-19 AKI patients. They concluded that 30-day mortality was significantly higher in the stage 3 AKI group compared with other groups. The risk of AKI in critically ill COVID-19 patients should be considered and close monitoring to renal function is recommended. More than 30% of our population required renal replacement therapy, 18.9% in form of CRRT, this finding is line with previous reported results from several studies were 25% of patients in ICU required RRT. To date there is no definitive treatment for COVID-19 associated AKI, standard practice and medical care for sepsis related AKI could be utilized in AKI related to COVID-19.

We have noticed increased mortality in COVID-19 patients requiring inhaled Nitric Oxide (iNO), there is limited data regarding the efficacy and safety of iNO in COVID-19 patients. There is no specific recommendation regarding the use of iNO in COVID-19 with ARDS and limited published data about its efficacy and safety with COVID-19 patients. One META analysis published in 2007 evaluated the Effect of iNO on oxygenation and mortality in acute lung injury concluded that iNO is associated with limited improvement in oxygenation in patients with ALI or ARDS but confers no mortality benefit and may cause harm. Several clinical trials are ongoing to assess its efficacy and safety in critically ill COVID-19 patients.

COVID-19 may predispose both venous and arterial thromboembolic disease due to excessive inflammation, hypoxia, immobilization and DIC. We have evidence of high thrombosis rate of 11.4% in critically ill COVID-19 patients despite the use of prophylactic anticoagulation, which is in line with 16% reported in an earlier prospective cohort study. Another study conducted in three Dutch hospitals found a remarkable higher rate of composite thrombosis outcomes in ICU COVID-19 patients (31%) which is higher than our reported rate. Nonetheless, most experts agree that the signal for increased thrombotic risk is enough to recommend pharmacologic venous thromboembolism (VTE) prophylaxis in all hospitalized COVID-19 patients as long as there is no contraindication. Our finding reinforces thrombosis risk in critically ill COVID-19 patients and strongly suggest using pharmacological VTE prophylaxis in all COVID-19 patients admitted to the ICU.

Interestingly, among our population who developed thrombosis during ICU, blood group A+ and B- were the most significant group types to develop thrombosis. A large retrospective review showed no significant connection between blood type and worsening of the disease, between blood type and the need for hospitalization, positioning requirements for patients during intubation, or any inflammatory markers. However, they did not assess the association between blood group type and thrombosis risk, this finding needs to be further evaluated. After controlling for the confounding factors, we are planning
to conduct a further research study to assess the ICU mortality in relation to the pharmacotherapeutic regimen(s) received during the patient’s hospital stay.

While dexamethasone has shown some promising results in severe COVID-19 patients, efforts still ongoing to find effective treatments for COVID-19 and several clinical trials are taking place to test the efficacy and safety of various drugs in critically ill patients. Finally, there is no strong evidence of significant clinical outcomes improvement in critically ill COVID-19 patients.

The uniqueness of our study is the extensive list of variables and outcomes we were able to capture throughout the study period. These variables and outcomes could be used for benchmarking between different countries and healthcare settings. Our study may have been affected by several limitations. During the study period, there were several changes in the national treatment protocols for COVID-19 and due to the nature of our study it was very hard to control for these changes. The data was collected for critically ill patients with COVID-19 so the results of our study cannot be generalized to mild or moderate COVID-19 patients. The nonintervention nature of the study allows for treatment decision based on the treating physicians bias toward using one treatment regimen versus other cannot be ruled out. We encountered many confounding factors which could affect the external validity and the interpretation of the mortality outcome. However, we conducted several analyses to control for these variables.

**Conclusion**

Several variables were associated with increasing the risk of ICU death at 30 days, and the incidence of ICU mortality rate within 30 days 42.3%. The median ICU LOS, hospital LOS, and mechanical ventilation (MV) duration were of 10 days, 17 days, and 9 days respectively.

**Abbreviation**

Intensive care units (ICUs), Coronavirus disease (COVID-19), Mechanical ventilation (MV), Ministry of Health (MOH), World Health Organization (WHO), Kingdom of Saudi Arabia (KSA)

**Declarations**

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Not applicable.

**Author contributions**

All authors contributed to data collections, analysis, drafted, revised, and approved the final version of the manuscript.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved in April 29th, 2020 by King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Reference No: RC20/192/R). Also been approved by King Abdualziz University, faculty of medicine, unit of biomedical ethics research committee, Jeddah, Saudi Arabia (Reference No: 231-20). Participants’ confidentiality was strictly observed throughout the study by using anonymous unique serial number for each subject and restricting data only to the investigators. Informed consent was not required due to the research's method as per the policy of the governmental and local research center.

Consent for publication

Not applicable.

Competing interests

No author has a conflict of interest in this study.

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