International Journal of Infectious Diseases 105 (2021) 180–187

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Clinical features and outcomes of critically ill patients with coronavirus disease 2019 (COVID-19): A multicenter cohort study

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ARTICLE INFO

Article history:
Received 5 January 2021
Received in revised form 27 January 2021
Accepted 7 February 2021

Keywords:
COVID19
Clinical features
Critically ill
Intensive care units (ICUs)
30-day ICU mortality

ABSTRACT

Background: 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 COVID-19 in Saudi Arabia.

Method: This was a multicenter, non-interventional cohort study for all critically ill patients aged 18 years or older, admitted to intensive care units (ICUs) between March 1 to August 31, 2020, with an objectively confirmed diagnosis of COVID-19. The diagnosis of COVID-19 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. An extensive list of clinical features was associated with higher 30-day ICU mortality rates, such as requiring mechanical ventilation (MV) or developing acute kidney injury within 24 hours of ICU admission, higher body temperature, white blood cells, blood glucose level, serum creatinine, fibrinogen, procalcitonin, creatine phosphokinase, aspartate aminotransferase, and total iron-binding capacity. During ICU stay, the most common complication was respiratory failure that required MV (71.4%), followed by acute kidney injury (AKI) and thrombosis with a proportion of 46.8% and 11.4%, respectively.

Conclusion: Among patients with COVID-19 who were admitted to the ICU, several variables were associated with an increased risk of ICU mortality at 30 days. Respiratory failure that required MV, AKI, and thrombosis were the most common complications during ICU stay.

Abbreviations: ICUs, intensive care units; COVID-19, coronavirus disease; MV, mechanical ventilation; MOH, Ministry of Health; WHO, World Health Organization; KSA, Kingdom of Saudi Arabia.

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https://doi.org/10.1016/j.ijid.2021.02.037

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 (Guan et al., 2020). 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 (Ouassou et al., 2020). COVID-19 is manifested by a broad spectrum of symptoms, ranging from asymptomatic manifestations to severe illness and death. To relieve these symptoms, COVID-19 is currently managed by certain antiviral medications, and in critical cases, supportive treatments, including supplemental oxygen and mechanical ventilation (Kirksey et al., 2020).

On March 2, 2020, the first confirmed case of COVID-19 was announced in Saudi Arabia, and by October 28, 2020, the ministry of health (MOH) had reported a total of 345,631 confirmed cases with a case fatality rate of 0.86% (Al-Khani et al., 2020). Owing to the implementation of successful healthcare policies, the epidemiological COVID-19 curve in the 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 (Alyami et al., 2020).

The in-depth clinical and laboratory characteristics of COVID-19 have 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 hospitals in Saudi Arabia. They found that 70% were mild cases (Ibrahim et al., 2020).

Although it is a limited number of cases, it highlights that reporting and assessing patients' characteristics 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, considering the comorbidities, severity of the disease, and immune system responses (Alsofayan et al., 2020).

The Saudi MOH has been driving the national COVID-19 management protocols and living guidance, which was developed according to the latest scientific, evidence-based COVID-19 studies. Each institution either adopted the same protocol or modified it following their internal expert committees (Ministry of Health, 2020).

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

Methods

Study design

This research was designed as a multicenter, non-interventional cohort study of critically ill patients admitted to intensive care units (ICUs) with a confirmed diagnosis of COVID-19 in KSA. The diagnosis of COVID-19 was confirmed objectively by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) on nasopharyngeal and/or throat swabs. The retrospective component included de-identified data of COVID-19 PCR positive patients admitted before the date of IRB approval (March–April 2020). The prospective component was conducted between May 1 and August 31, 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 less than 1 day or more than 60 days, and/or labeled as "Do-Not-Resuscitate" status within the first 24 h of ICU admission were excluded as those patients were deemed to be not eligible to receive resuscitative measures.

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 was 81% and 19% in KAMC-CR and KAUH, respectively. The primary site for this multicenter, prospective cohort study was King Abdulaziz Medical City (Riyadh).

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, comorbidities, pre-hospital (Home) medications, vital signs, laboratory tests and radiological finding within 24 hours of ICU admission, ICU support measures needed during the ICU stay, off-label use of medications for COVID-19, and the COVID-19 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 to describe in detail the clinical and laboratory characteristics of critically ill patients with COVID-19 admitted to Intensive Care Units (ICUs) in Saudi Arabia. The secondary endpoints were to determine the mean ICU LOS duration, mechanical ventilation duration, ICU mortality, and risk factors for poor prognosis in Saudi Arabia.

Data management and statistical analysis

We report the values of variables as percentages, mean with 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, 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 determine 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 determine 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. We did not make the multiplicity adjustment.

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 patients' average age 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 through ER (48.8%) followed by critical care response team (CCRT) activation from wards/floor (44.3%) with a median of three days before ICU admission.

Before 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 a proportion of 16.3%, 15.7%, 12.9%, and 12.9% respectively (Additional file 1).

Overall outcomes

Overall survival was 52.6% (295 patients). Whereas the overall ICU mortality within 30 days was 42.3% (237 patients). The median ICU LOS, hospital LOS and mechanical ventilation duration were 10 days (interquartile range (IQR): 6.0–17.5), 17 days (IQR: 11.0–25.0), and 9 days (IQR: 3.0–17.0 days), respectively. The rate of ICU readmission within three months for survival was 9.15% (Table 1).

Baseline findings within 24 h of ICU admission and risk of 30 days mortality

Clinical and laboratory findings on admission are shown in Additional file 2. 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+ in the proportions 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).

Table 1
Overall outcomes.

Overall outcomes	All patients
Overall survival, 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 (9.15)

^ Denominator of the percentage is the total number of patients; # Denominator of the percentage is patients who survived.

Among 560 patients, 370 (66.1%) required mechanical ventilation during the first 24 h. Requiring mechanical ventilationon 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 h of ICU admission. Among patients who had ICU mortality within 30 days, metabolic acidosis was the most frequent condition (P = <0.0001). Higher alveolar-arterial gradient with a median of 430.7 mmHg (IQR: 292.7–582.8 mmHg), (P < 0.0001), and lower base excess with a 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-day ICU mortality. On the other hand, platelet 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 h of ICU admission were associated with higher ICU mortality within 30 days (P-value <0.0001). Besides, positive cumulative fluid balance within 24 h of ICU admission was associated with higher ICU mortality but was not statistically significant (Additional file 2).

On ICU admission, bilateral patchy shadowing followed by 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 a 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-day ICU mortality (P-value 0.0001) (Additional file 2).

Off-label use medications during ICU

Among the COVID-19 off-label use medications during ICU stay, systemic corticosteroids were the most common (84.5%), followed by tocilizumab, anticoagulation treatment dose, oseltamivir, azithromycin, and ascorbic Acid, with proportions of 38.9%, 28.1%, 30.2%, 28.9%, 24.8 and 21.6%, respectively (Table 2).

COVID19 testing and risk of 30 days mortality

Approximately 53.4% of the patients had a positive COVID-19 RT-PCR prior to ICU admission, with a mean of four days from the first positive sample. The median time to reach the viral load peak is seven days from the first positive COVID-19 RT-PCR. While the median time for COVID19 viral load to be undetected is thirteen days.

Table 2
Summary of common off-label use medications during ICU.

Off-label use of medications during ICU	All patients (N = 560)
Systemic corticosteroids, n (%)	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.

Table 3
COVID19 testing-ICU mortality within 30 days.

Variables	All patients (N = 560)	ICU mortality within 30 days		P-value	OR (95%CI)/estimates(95%CI)	P-value
		Yes (N = 237)	No (N = 323)			
Positive COVID-19 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-19 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 COVID-19 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 COVID-19 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 COVID-19 clearance, n (%)	208 (37.1)	194 (81.9)	14 (4.3)	<0.0001**	88.9 (44.22–178.71)	<0.0001$

Among all admitted patients, 208 (37.1%) of patients continued to have persistent positive COVID-19 PCR testing, which was significantly associated with ICU mortality within 30 days (P < 0.0001) (Table 3).

ICU complications and risk of 30 days mortality

During ICU stay, the most common complication was respiratory failure that required MV (71.4%), followed by acute kidney injury, thrombosis, and liver injury with proportions of 46.8%, 11.4%, and 7.1%, respectively. Acute kidney injury was significantly high among patients with ICU mortality within 30 days as compared to survivors during ICU stay (74.7% vs. 26.2%) (P < 0.0001), and it was a 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 higher 30-day ICU mortality (aOR 2.2, 95% CI 1.02–4.81, P-value 0.0435) as well as patients 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 a 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).

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).

Patients who developed disseminated intravascular coagulation were associated with higher thrombosis rates during ICU stay after adjusting for their severity scores (aOR 27.1 CI 5.10–144.3, P-value 0.0001) (Additional file 3).

Discussion

In this multicenter prospective study, the majority of the included patients were male (74.5%), and 40% of the patients were ≥65 years, which was consistent with previously published studies (Yang et al., 2020; Huang et al., 2020; Chen et al., 2020a,b,c; Grasselli et al., 2020). 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 (Cummings et al., 2020; Wang et al., 2020a,b; Jamous et al., 2020; Zhou et al., 2020a,b; Chen et al., 2020a,b,c). 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 due to urbanization and adopting a sedentary lifestyle compared to other countries (International Diabetes Federation – Home, 2020).

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%, and 67% (Xie et al., 2020; Arentz et al., 2020). This variation in mortality rate might be attributed to 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 patients who were admitted to hospitals with lower ICU bed capacity had a higher risk of death (Gupta et al., 2020). In a previous multicenter cohort study that included 2215 critically ill adults with confirmed COVID-19

Table 4
ICU support measures during ICU stay.

ICU support measures needed	All patients (N = 560)	ICU mortality within 30 gays				
		Yes (N = 237)	No (N = 323)	P-value	OR (95%CI)	P-value
Mechanical ventilation, n (%)	400 (71.4)	220 (92.8)	180 (55.7)	<0.0001^^	6.1 (3.32–11.05)	<0.0001
Extracorporeal membrane oxygenation (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)	<0.0001**	1.7 (1.01–2.94)	0.0454
Conventional dialysis, n (%)	88 (15.7)	60 (25.3)	28 (8.7)	<0.0001**	1.6 (0.89–2.79)	0.1203
Inhaled nitric oxide, n (%)	47 (8.4)	34 (14.3)	13 (4.0)	<0.0001**	5.7 (2.60–12.37)	<0.0001
Vasopressors/inotropes, n (%)	306 (54.6)	201 (84.8)	105 (32.5)	<0.0001**	7.3 (4.49–11.89)	<0.0001
Plasmapheresis, n (%)	6 (1.1)	4 (1.7)	2 (0.6)	0.2477**	0.9 (0.14–5.79)	0.9106

Table 5
Thrombosis during ICU stay.

Variables	All patients (N = 560)	Thrombosis during ICU				
		Yes (N = 64)	No (N = 496)	P-value	OR (95%CI)	P-value[$]
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/m^2)						
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
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.

from the USA, the reported median ICU LOS was nine days (IQR, 5–14 days), and the median hospital LOS was 16 days (IQR, 11–22 days), which was comparable to our data (Gupta et al., 2020).

The median APACHE II score on admission to ICU was ten. In comparison, this score was ten in a study in Singapore (Chew et al., 2020), fourteen in the Intensive Care National Audit and Research Centre (ICNARC) report for the United Kingdom (ICNAC report, 2020), fifteen in the Scottish Intensive Care Society Audit Group (SICSAG) report (Scottish Intensive Care Society Audit Group report, 2020), seventeen in a study in Wuhan (Chen et al., 2020a,b,c). The median NUTRIC and SOFA score were three and five, respectively. Shock, acute kidney injury, and mixed acid-base disorders were experienced by around a quarter of the patients. Two-thirds of the patients received mechanical ventilation, and this population had the most benefit from corticosteroids (Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report, 2020). The severity of ARDs in our patients seems higher than in other studies. The median PaO2/FiO2 ratio was 98.3, while it was 118.5 in the ICNARC report (ICNAC report, 2020), 132 in the Atlanta study (Auld et al., 2020), 160 in a study in Lombardy (Leisman et al., 2020), and 194 in the Singaporean study (Chew et al., 2020). Several inflammatory biomarkers were elevated in our study, such as ferritin, CRP, D-dimer, CPK, and fibrinogen, which are critical biomarkers in ARDs and the cytokine release syndrome associated with COVID-19 (Leisman et al., 2020).

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 respiratory support in the dexamethasone arm compared to the standard of care arm (Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report, 2020). Despite the current controversial efficacy of tocilizumab, its adverse reactions, and its expensive price, it was used in more than a third of patients (Information on COVID-19 Treatment, Prevention, and Research, 2020; COVID-19 Guideline, Part 1: Treatment and Management, 2020). Although a treatment dose of heparin is not currently recommended, around a third of our patients received this dose (Information on COVID-19 Treatment, Prevention, and Research, 2020). Oseltamivir is recommended as an empiric anti-influenza treatment in hospitalized patients while awaiting influenza testing results (Information on COVID-19 Treatment, Prevention, and Research, 2020). 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 (Information on COVID-19 Treatment, Prevention, and Research, 2020; COVID-19 Guideline, Part 1: Treatment and Management, 2020). Vitamin C and thiamine were used in around 20% of patients; however, there are insufficient data on these supplements (Information on COVID-19 Treatment, Prevention, and Research, 2020). Hydroxychloroquine was rarely used in our study as it is no longer recommended in hospitalized COVID-19 patients (Information on COVID-19 Treatment, Prevention, and Research, 2020; COVID-19 Guideline, Part 1: Treatment and Management, 2020).

Our study of critically ill COVID-19 patients found that the median time for the viral load to be undetected was thirteen days. The median time to viral clearance ranged from seven to twelve days and up to 28 days in some reports (Nicola et al., 2020). A previous study conducted in Hunan took 17 days for patients to test negative (Cao et al., 2020). Our report of a median of thirteen days for viral clearance aligns with the reported duration of an average of two weeks. We expected critically ill patients to have prolonged virus release. Data from a large cohort of COVID-19 patients from a single University Hospital in Milano (Italy) reported a viral clearance rate within fourteen and 28 days were 32% and 54%, respectively (Nicola et al., 2020).

We also observed a significant association between patients with persistently 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 patients reported that neither the viral clearance rate at fourteen and 28 days nor the time to negative viral RNA load was predictive of mortality rate (Nicola et al., 2020). Our observation is different from this report; our result is also relevant for daily clinical practice, and it could be potentially used to guide patient care. A 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 (Magleby et al., 2020). The persistent viral load hypothesis 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 surprising to report a higher respiratory failure percentage. Several mechanisms have been proposed in the literature as the cause for substantial respiratory failure seen in COVID-19 patients. These include diffuse alveolar damage, which accounts for ARDs, pulmonary edema, and vascular occlusion; ventilation and perfusion mismatch are other possible mechanisms for hypoxemic respiratory failure (Li and Ma, 2020). Our results of a high respiratory failure rate and a high percentage requiring MV are in line with Wang et al., who concluded that hypoxemic respiratory failure requiring MV is the most concerning complication in COVID-19 patients (Wang et al., 2020a,b). We reported a higher mortality rate among our patients requiring MV, compared to the 35.7% death rate of mechanically ventilated COVID-19 patients reported in an earlier study (Auld et al., 2020).

According to our result, AKI was the second most common complication encountered in our group, at 46.8%. The relationship between COVID-19 and AKI remains unclear. Numerous mechanisms have been addressed in the literature about the 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 of the COVID-19 virus. Additionally, viral infection can stimulate inflammatory mediators and a cytokine storm, which results in microvascular injury and causes AKI (Gabarre et al., 2020). The rate of AKI among our group was higher than the reported rate by Wang et al., who found that only twelve (10.8%) experienced a slight increase in serum creatinine or urea nitrogen within the first 48 h of hospital stay; however, this report was in non-critically ill COVID-19 patients (Wang et al., 2020a,b). Previous studies have identified older age and comorbidities, and severe ARDS as risk factors for AKI in hospitalized and critically ill viral infection patients (Sang et al., 2020). 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., who reported higher mortality in COVID-19 AKI patients. They concluded that 30-day mortality was significantly higher in the stage three AKI group than in other groups (Cheng et al., 2020). The risk of AKI in critically ill COVID-19 patients should be considered, and close monitoring of renal function is recommended. More than 30% of our population required renal replacement therapy, 18.9% in the form of CRRT; this finding is in line with previously reported results from several studies where 25% of patients in ICU required RRT (Rubin et al., 2020; Mahase, 2020). 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 noticed an 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 concluding that iNO is associated with limited improvement in oxygenation in patients with ALI or ARDS but confers no mortality benefit and may cause harm (Adhikari et al., 2007). Several clinical trials are ongoing to assess its efficacy and safety in critically ill COVID-19 patients (Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19 – Full-Text View – ClinicalTrials.gov, 2020).

COVID-19 may predispose both venous and arterial thromboembolic disease due to excessive inflammation, hypoxia, immobilization, and DIC (Chen et al., 2020a,b,c; Guan et al., 2020; Zhou et al., 2020a,b). We have evidence of a high thrombosis rate of 11.4% in critically ill COVID-19 patients despite prophylactic anticoagulation, which is in line with 16% reported in an earlier prospective cohort study (Helms et al., 2020). Another study conducted in three Dutch hospitals found a remarkably higher rate of composite thrombosis outcomes in ICU COVID-19 patients (31%), which is higher than our reported rate (Klok et al., 2020). 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 the thrombosis risk in critically ill COVID-19 patients and strongly suggests 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. An extensive 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 (Latz et al., 2020). 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 plan 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 (Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report, 2020), efforts are 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.

Our study's uniqueness 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; due to the nature of our study, it was difficult to control for these changes. The data was collected for critically ill patients with COVID-19, so our study's results cannot be generalized to mild or moderate COVID-19 patients. The noninterventional nature of our study allowing for treatment decisions based on the treating physicians' bias toward using one treatment regimen versus another 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. Requiring mechanical ventilation or devolving acute kidney injury within 24 h of ICU admission, higher body temperature, white blood cells, blood glucose level, serum creatinine, fibrinogen, procalcitonin, creatine phosphokinase, aspartate aminotransferase, and total iron-binding capacity were associated with higher 30-day ICU mortality.

Author contributions

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

Funding

None.

Availability of data and material

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

Ethics approval and consent to participate

The study was approved on April 29, 2020, by King Abdullah International Medical Research Center (KAIMRC) - Institutional Review Board, Riyadh, Saudi Arabia (Reference No: RC20/192/R), and was also approved by King Abdulaziz 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 an 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 governmental and local research center's policy.

Consent for publication

Not applicable.

Competing interests

No author has a conflict of interest in this study.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.02.037.

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