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Original Article

COVID-19 related treatment and outcomes among COVID-19 ICU patients: A retrospective cohort study



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ABSTRACT

Background: The COVID-19 pandemic remains an immediate and present concern, yet as of now there is still no approved therapeutic available for the treatment of COVID-19. This study aimed to investigate and report evidence concerning demographic characteristics and currently-used medications that contribute to the ultimate outcomes of COVID-19 ICU patients.

Methods: A retrospective cohort study was conducted among all COVID-19 patients in the Intensive Care Unit (ICU) of Asir Central Hospital in Saudi Arabia between the 1st and 30th of June 2020. Data extracted from patients' medical records included their demographics, home medications, medications used to treat COVID-19, treatment durations, ICU stay, hospital stay, and ultimate outcome (recovery or death). Descriptive statistics and regression modelling were used to analyze and compare the results. The study was approved by the Institutional Ethics Committees at both Asir Central Hospital and King Khalid University.

Results: A total of 118 patients with median age of 57 years having definite clinical and disease outcomes were included in the study. Male patients accounted for 87% of the study population, and more than 65% experienced at least one comorbidity. The mean hospital and ICU stay was 11.4 and 9.8 days, respectively. The most common drugs used were tocilizumab (31.4%), triple combination therapy (45.8%), favipiravir (56.8%), dexamethasone (86.7%), and enoxaparin (83%). Treatment with enoxaparin significantly reduced the length of ICU stay ($p = 0.04$) and was found to be associated with mortality reduction in patients aged 50–75 ($p = 0.03$), whereas the triple regimen therapy and tocilizumab significantly increased the length of ICU stay in all patients ($p = 0.01$, $p = 0.02$ respectively).

Conclusion: COVID-19 tends to affect males more significantly than females. The use of enoxaparin is an important part of COVID-19 treatment, especially for those above 50 years of age, while the use of triple combination therapy and tocilizumab in COVID-19 protocols should be reevaluated and restricted to patients who have high likelihood of benefit.

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Introduction

Like many other countries, Saudi Arabia has been experiencing an outbreak of novel coronavirus disease 2019 (COVID-19) since the beginning of March [1–3]. COVID-19 rapidly became pandemic and is now considered a global health emergency. While it is most common for people with COVID-19 (40%) to develop only

mild or moderate disease, approximately 15% develop severe disease requiring oxygen support [2,4–6]. As the pandemic evolves, it has been observed that severe cases might develop adverse outcomes quickly, resulting in a persistently increasing death rate [7,8]. Therefore, it is urgent to determine options for prevention and treatment to help identify patients with poor prognosis and to slow the spread of COVID-19. In Saudi Arabia, more than 522,000 COVID-19 cases were identified; and the Ministry of Health (MoH) along with other governmental agencies and organizations have taken all precautions and measurements to control the outbreak.

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MoH has been providing monthly updated treatment protocols and medical approaches on how to manage COVID-19 patients.

Identification of patients who are at higher risk of being infected with COVID-19 is an important preventive approach that allows extra caution to be applied before patients are infected, along with taking early steps and making clinical decisions after infection that slow the rapid progression of the disease and consequently save lives. Several studies have been performed and subsequently reported to describe the clinical characteristics of COVID-19 patients [1,2]. In addition to identifying risk factors to which are attributed an influence on a patient's infection with COVID-19, several currently-used medications have shown promising evidence of relevance.

Given the novelty of this virus and the lack of an existing approved treatment, extensive efforts are underway to test and identify a safe and effective treatment. Most researchers' efforts have been directed toward testing currently-used medications with minimum or even no evidence in COVID-19 management [5,9,10]. It's not known yet whether these medications have any impact on a COVID-19 patient's ultimate outcome. It's possible that these medications might improve patient outcome and reduce time to recovery. Such information would provide important opportunities and hope for patients who are infected while on these medications. Moreover, it might give clinicians the opportunity to use medications associated with positive clinical outcomes in currently-developed COVID-19 management protocols.

The social healthcare system in the Kingdom is considered one of the key contributors towards containing the infection [1]. To meet clinical needs, a multi-disciplinary approach is required, and many COVID-19 management protocols have developed. However, there are limited studies available that have evaluated methods of therapeutic management; as a result, obvious knowledge gaps remain in this area. Our study was conducted to explore the association of risk factors and currently-used drugs for COVID-19 treatment with fatal outcomes and to determine the best available options to treat COVID-19 infection.

Patients and methods

Study design

We conducted a retrospective cohort study among all COVID-19 patients who presented to a tertiary care hospital in Asir Region, Saudi Arabia and were admitted to the Intensive Care Unit (ICU) between the 1st and 30th of June 2020. All patients diagnosed with COVID-19 by next-generation sequencing or real-time RT-PCR methods based on respiratory specimens and who had a definite outcome were included. The study used a single cohort design in light of the fact that the study hospital was the only tertiary care and designated hospital at the recruitment time for transfer of COVID-19 patients from other primary and secondary care regional hospitals. The study was approved by the Institutional Ethics Committee of King Khalid University (KKU-2020-01.01) and by the Ministry of Health Institutional Review Board Committee, Asir Region (REC-02-08-2020).

Data source

Data extracted from patients' medical records included demographics, home medications, medications used to treat COVID-19, treatment duration for each COVID-19-related medication, ICU stay, hospital stay, and ultimate outcome (recovery or death). Patient management protocols, including national and international guidelines adopted by the hospital, were also noted for reference. Data integrity and privacy were ensured by all means:

participants were assigned numeric identifiers, the database was password-protected, and access was restricted to selected investigators with completed confidentiality agreements.

Statistical analysis

Statistical analyses were conducted using SPSS (IBM® SPSS® Statistics 27) [11] and GraphPad Prism (RRID:SCR_002798) [12]. Continuous and categorical variables are presented as means (SD) and n (%), respectively. Descriptive statistics such as absolute numbers and percentages were used to summarize univariate characteristics. A binary logistic regression was conducted to examine whether potentially associated predictor variables had significant effects on the odds of the outcome variable, which was coded as 0 for death (reference category) and 1 for recovery. The significance level was set at 5%. Finally, a regression model was used to investigate the effect of all predictors on each of two variables: hospital stay days and ICU stay days. Variables were included in the analysis if it was associated in at least 30 patients. With respect to COVID-19 treatment medications, a patient was considered treated with a particular agent if they received it for at least 50% of their hospital stay. Since mortality risk from COVID-19 infection might be affected by age, patients were stratified into age-based ranges (<25, 25–49, 50–75, >75) to account for mortality risk differences among different age groups.

Results

Study population and characteristics

From June 1, 2020 to June 30, 2020, 118 patients infected with COVID-19 were admitted and treated in the ICU; data from these patients were included in the final analysis. Patient characteristics are summarized and presented in Table 1. Of the study population, two patients were aged less than 25 years old, 41 between 25–49 years old, 64 between 50–75 years old, and 11 were >75 years old. Male patients accounted for 87% of the study population. Around 68.8% experienced at least one comorbidity, while the remainder had no comorbidity. The mean hospital and intensive care unit (ICU) stay was 11.4 and 9.8 days, respectively.

Treatment for patients infected with COVID-19

The patients received different treatment regimens for COVID-19 based on their respective situations and supporting published evidence during the study period. The predominant medications used to treat COVID-19 among the study population were tocilizumab, triple combination therapy (lopinavir/ritonavir, ribavirin, and interferon beta-1b), favipiravir, and dexamethasone, which were respectively received by 31.4%, 45.8%, 55.1%, 56.8%, and 86.7% of participants. Other medications used for COVID-19 treatment included: acyclovir, lopinavir, oseltamivir, azithromycin, budesonide, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, and hydroxychloroquine, as summarized in Table 1. None of our patients received Remdesivir and Baricitinib due to unavailability. Also, different antibiotics and antifungals were used empirically according to our antibiogram and institutional pneumonia management guidelines. The mean durations of treatment for agents mostly used in treating COVID-19 are illustrated in Fig. 1. With respect to supportive therapy, 83% of patients received enoxaparin for the duration of their hospitalization.

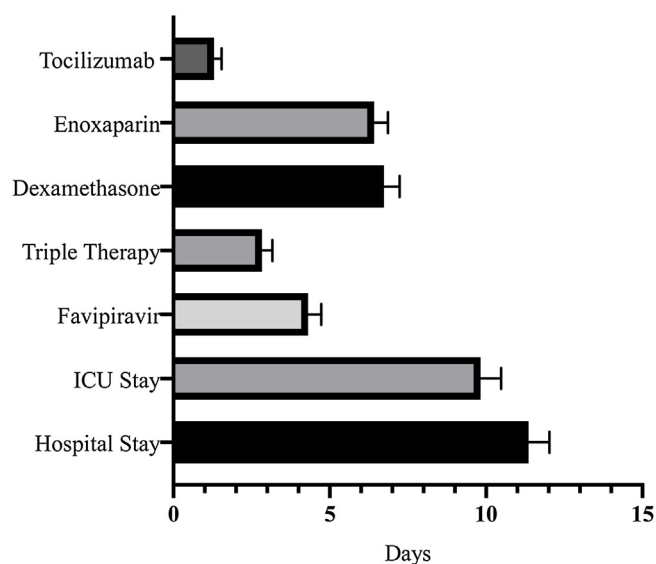
Table 1
Patient demographics.

Characteristic	Total patients (N = 118)	%
Age, mean (SD)	56 (14.9)	
<25	2	1.7
25–49	41	34.7
50–75	64	54.3
>75	11	9.3
Gender		
Male	103	87
Female	15	13
Co-morbidities		
Yes	81	68.6
No	37	31.4
COVID-19-related treatment		
Anti-viral		
Acyclovir	3	2.5
Favipiravir	67	56.8
Lopinavir	3	2.5
Oseltamivir	10	8.5
Triple combination therapy	54	45.8
Antibiotics		
Azithromycin	91	77.1
Corticosteroids		
Budesonide	23	21.4
Dexamethasone	93	86.7
Fludrocortisone	12	11.2
Hydrocortisone	14	13.1
Methylprednisolone	12	11.2
Prednisolone	1	0.9
Other Medication		
Enoxaparin	99	83.9
Hydroxychloroquine	5	4.2
Interferon	65	55.1
Tocilizumab	37	31.4
Intensive Care Unit stay (days), mean (SD)	9.8 (7.2)	
Hospital stay (days), mean (SD)	11.4 (7.2)	

Table 2
Results from evaluation of the effects of patient characteristics and treatments on mortality.

Variable	N (%)	Deaths (%)	OR (95% CI)	p-Value
Age				
<25	2 (1.7)	0	0.56 (0.18, 1.67)	0.30
25–49	41 (34.7)	2 (1.7)		
50–75	64 (54.3)	11 (9.3)		
>75	11 (9.3)	1 (0.8)		
Gender				
Female	15 (12.7)	1 (0.8)	1.51 (0.17, 35.60)	0.74
Male	103 (87.3)	13 (11)		
Comorbidity				
No	45 (38.1)	4 (3.4)	0.89 (0.21, 3.46)	0.87
Yes	73 (61.9)	10 (8.5)		
Cholecalciferol				
No	28 (23.7)	2 (1.7)	0.57 (0.6, 4.22)	0.60
Yes	90 (76.3)	12 (10.2)		
Zinc				
No	58 (49.2)	4 (3.4)	0.52 (0.08, 2.56)	0.44
Yes	60 (50.8)	10 (8.5)		
Favipiravir				
No	51 (43.2)	3 (2.5)	0.53 (0.07, 3.16)	0.50
Yes	67 (56.8)	11 (9.3)		
Triple combination therapy				
No	64 (54.2)	11 (9.3)	2.20 (0.48, 12.22)	0.32
Yes	54 (45.8)	3 (2.5)		
Dexamethasone				
No	24 (20.3)	2 (1.7)	2.13 (0.19, 21.05)	0.51
Yes	94 (79.7)	12 (10.2)		
Enoxaparin ^a				
No	19 (16.1)	5 (4.2)	3.16 (0.70, 14.36)	0.13
Yes	99 (83.9)	9 (7.6)		
Tocilizumab				
No	81 (68.6)	7 (5.9)	0.38 (0.09, 1.40)	0.15
Yes	37 (31.4)	7 (5.9)		
Azithromycin				
No	27 (22.9)	3 (2.5)	0.74 (0.13, 3.35)	0.71
Yes	91 (77.1)	11 (9.3)		

^a Enoxaparin was significantly associated with mortality reduction in patients 50–75 years old with $p = 0.03$ and OR of 7.90 (1.23, 63.85).

Duration of COVID19 related medications**Fig. 1.** Mean duration (days) of COVID-19 related treatments, hospital stay, and ICU stay.

Effect of patient characteristics and COVID-19 treatment on mortality

Several factors were assessed for effects on patient mortality, as reported in Table 2. These factors included age, gender, comorbidities, and treatment with any of: cholecalciferol, zinc, favipiravir, triple combination therapy, dexamethasone, enoxa-

parin, interferon, tocilizumab, and azithromycin. All variables were incorporated in a binary regression model, and none of the assessed variables were found to be significantly associated with patient mortality. A subsequent analysis assessed the influence of these variables on patient mortality in the context of patient age group, as presented in Tables 1 and 2. Interestingly, treatment with enoxaparin was significantly associated with mortality reduction in patients aged 50–75 years old with $p = 0.03$ and odds ratio of 7.90, 95% CI 1.23, 63.85). No other variables were significantly associated with mortality in any age group.

Effect of patient characteristics and COVID-19 treatment on hospital and ICU stay

A multiple regression model was constructed to identify influencing factors and estimate their impacts on the hospital and ICU stays of COVID-19 patients during the study period. Among all variables, only the triple combination therapy significantly increased the length of hospital stay, with p value = 0.02 (3.59, 95% CI 0.70, 6.49), as shown in Table 3. On the other hand, three factors were significantly associated with duration of ICU stay, as reported in Table 4. Enoxaparin use significantly reduced the length of ICU stay, with p value = 0.04 (−3.73 95% CI −7.31, −0.14). Meanwhile, the triple combination therapy and tocilizumab both significantly increased length of ICU stay, with p value = 0.01 (3.9, 95% CI 1.07, 6.72) and p value = 0.02 (3.15, 95% CI 0.4, 5.89), respectively.

Table 3

Results from evaluation of the effects of patient characteristics and treatments on hospital stay length.

Variable	N (%)	Estimate	p-Value
Age, mean (SD)	56 (14.9)	0.33 (−1.77, 2.44)	0.75
Gender			
Female	15 (12.7)	−2.28 (−6.15, 1.6)	0.25
Male	103 (87.3)		
Comorbidity	73 (61.9)	1.98 (−0.67, 4.62)	0.14
Cholecalciferol	90 (76.3)	2.26 (−1.66, 6.17)	0.26
Zinc	60 (50.8)	2.34 (−0.61, 5.3)	0.12
Favipiravir	67 (56.8)	0.34 (−2.85, 3.53)	0.84
Triple combination therapy	54 (45.8)	3.59 (0.7, 6.49)	0.02
Dexamethasone	94 (79.7)	0.74 (−3.23, 4.72)	0.71
Enoxaparin	99 (83.9)	−2.03 (−5.71, 1.64)	0.28
Tocilizumab	37 (31.4)	2.34 (−0.47, 5.15)	0.1
Azithromycin	91 (77.1)	−0.14 (−3.26, 2.98)	0.93

Table 4

Results from evaluation of the effects of patient characteristics and treatments on Intensive Care Unit stay length.

Variable	N (%)	Estimate	p-Value
Age, mean (SD)	56 (14.9)	0.47 (−1.59, 2.52)	0.65
Gender			
Female	15 (12.7)	−0.74 (−4.52, 3.04)	0.7
Male	103 (87.3)		
Comorbidity	73 (61.9)	1.77 (−0.81, 4.35)	0.18
Cholecalciferol	90 (76.3)	1.41 (−2.42, 5.23)	0.47
Zinc	60 (50.8)	2.62 (−0.26, 5.51)	0.07
Favipiravir	67 (56.8)	1.77 (−1.35, 4.88)	0.26
Triple combination therapy	54 (45.8)	3.9 (1.07, 6.72)	0.01
Dexamethasone	94 (79.7)	0.17 (−3.71, 4.06)	0.93
Enoxaparin	99 (83.9)	−3.73 (−7.31, −0.14)	0.04
Tocilizumab	37 (31.4)	3.15 (0.4, 5.89)	0.02
Azithromycin	91 (77.1)	−0.43 (−3.48, 2.61)	0.78

Discussion

COVID continues to devastate and cripple countries across the world, with the magnitude of this devastation varying between countries. Evidence suggests that variation in the severity of the disease between populations can be attributed to differences in their demographic features, comorbidities, and immunological responses. In this retrospective cohort study, we investigated the contribution of clinical variables and COVID-19 treatment agents to the ultimate outcomes of ICU-admitted COVID-19 patients, specifically in the southern region of Saudi Arabia.

Our study population had a median age of 57 with the majority being 50–75 years of age. Male patients accounted for around 87% of participants, which is significantly higher than the proportion of females. Globally, trends in age distribution among COVID-19 patients have fluctuated as the pandemic progresses [13,14]. In March 2020, the U.S. Centers for Disease Control and Prevention reported that about half of COVID-19 patients were 55 or older, whereas in May 2020 nearly 70% of people who tested positive were younger than 60, with a median age of 48 [15]. Meanwhile, a national retrospective study conducted by Yousef et al. in Saudi Arabia reported a median age of 36 years, with only 4.8% being age 14 or less and 5.9% being 66 or above [2]. However, the sex ratio of COVID-19 patients has been fairly consistent across diverse countries [2,4,6,7,15–18]. The higher infection rate prevalent among males in this study could be attributed to greater levels of exposure, as males are relatively more exposed to external environments than females. Additionally, more than 65% of the study population experienced at least one comorbidity. Finally, the mean hospital and ICU stay was around 11 and 10 days, respectively.

Numerous studies, including ours, have evaluated the association of mortality in COVID-19 with demographic and clinical variables like age, gender, and comorbidities. COVID-19 shows

extremely strong risk stratification across age, socioeconomic factors, and clinical factors [2,4,6,16,18]. Increasing age, male sex, and acute illness severity are reported as associated with increased mortality risk [19]. In contrast with this trend, our results showed no significant association with patient mortality. This could be possibly due to early datasets like ours having limited sample size and assessments, wherein the association of mortality with these variables has yet to be completely established.

In terms of therapeutic management, the drugs most commonly used to treat participants in this study were tocilizumab, triple combination therapy, favipiravir, and dexamethasone. Globally, the most-commonly used medication varies from country to country according to each nation's approved treatment protocol. A systematic review on therapeutic management of COVID-19 patients conducted by Tobaiqy et al. found corticosteroids and antivirals like lopinavir and oseltamivir to be most common agents used for COVID-19 treatment [10]. In this study, around 83% of participants received enoxaparin as a supportive therapy during their hospitalization, which practice has been adopted in light of several studies demonstrating high incidence of venous thromboembolic vents (VTE) and arterial thromboembolism in COVID-19 patients due to a hypercoagulable state. Interestingly, we found enoxaparin use to be significantly associated with mortality reduction in patients aged 50–75 years old, which is congruent with multiple studies conducted around the world [5,20,21]. Additionally, enoxaparin use significantly reduced length of ICU stay in all patients, and subsequent analysis revealed this effect to be predominant in patients aged 50–75 years old. The age-group specificity of this effect could be explained by the limited sample numbers in other age groups. On the other hand, the risk of VTE and arterial thromboembolism increases with patient age; therefore, it is reasonable to find enoxaparin reduces risk significantly in this age group.

Tocilizumab (TCZ) has emerged as an alternative treatment for COVID-19 patients with cytokine storm, but there is insufficient evidence regarding its clinical efficacy and safety [22]. One meta-analysis of case series reports showed the use of tocilizumab in COVID-19 patients to be associated with a mortality rate of 21% [23]. Some interim recommendations consider tocilizumab to be an experimental medicine that should only be considered in severe cases [24]. In our study, around 31.4% of participants completed tocilizumab doses during their hospitalization. However, the use of tocilizumab significantly increased ICU stay and had no benefit in terms of mortality reduction. In light of the short study duration and limited evidence regarding the clinical safety and efficacy of tocilizumab in COVID-19 patients, the association between increased length of ICU stay and tocilizumab use is concerning. Therefore, this finding suggests that tocilizumab use should be restricted and limited until more research has generated evidence concerning its safety and efficacy in COVID-19 patients and the corresponding impact on hospital stay duration. Lastly, even though several studies had shown promising results from the use of triple combination therapy [25], our findings indicate that this treatment is associated with lengthening hospital and ICU stay. In the study conducted by Hung et al., patients who were randomized to the triple combination therapy did not receive interferon-beta as part of the regimen, which could explain the conflict between their findings and this study.

This study was undertaken during the ongoing pandemic, therefore faced limitations on direct and real-time access to patients that made prospective data collection difficult. It was also a single cohort study conducted in a limited population for a limited duration that studied retrospective data with limited demographic and clinical variables and measured definite outcomes. In light of the results and limitations of this study, a more inclusive and well-designed study is warranted that can generate conclusive evidence regard-

ing the various demographic and clinical variables that affect the management of COVID-19 patients in clinical practice.

In conclusion, the results of this study suggest that use of anti-coagulants in treating COVID-19 reduces mortality in those 50 years and older and shortens length of ICU stay in all age groups. Additionally, the use of triple combination therapy or tocilizumab in COVID-19 treatment should be restricted to patients who could potentially benefit while experiencing minimum complications. Future studies with larger sample sizes are warranted to thoroughly evaluate the medications currently used for COVID-19 treatment and determine the best available treatment options for each patient.

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Competing interests

None declared.

Ethical approval

Not required.

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