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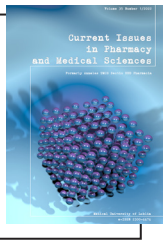

Pharmacotherapy prescribing pattern and outcome for hospitalized patients with severe and critical COVID-19

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ABSTRACT

There are many treatment modalities for COVID-19 – with varied outcome. Therefore, authors designed this study to assess prescribing patterns and the clinical outcome for hospitalized patients with severe and critical COVID-19 so as to determine the most effective approach.

Authors conducted a retrospective observational study on 346 adult patients with either severe or critical COVID-19, who were admitted to public hospitals in Al-Najaf city, Iraq from June to September 2020. Patients' information, medications and outcomes were collected from their medical records in the registered office of the hospital.

A total of 346 patients were enrolled, with a majority of patients being adults above 35 years old and male (70.2%). Most patients (81%) received corticosteroid as dexamethasone, and about 45% of all patients were given convalescent plasma therapy, while a few patients were prescribed antiviral favipiravir (23%) and lopinavir/ritonavir (19%). As supportive care medications, anticoagulant such as enoxaparin was administered to most of the patients (93%) and more than half of all patients received the broad-spectrum antibiotic, meropenem.

The majority of the patients recovered and were discharged alive (66%), however, the in-hospital mortality rate was 26%. Interestingly, patients treated with enoxaparin alone or in combination with hydroxychloroquine were associated with better outcome.

The prescribing pattern of COVID-19 specific medications and supportive care is aligned with guideline recommendations and associated with a beneficial therapeutic outcome.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a pandemic disease originating in late 2019 in the People's Republic of China that spread rapidly worldwide [1]. The first reported case in the Najaf governorate, Iraq, was confirmed on February 24, 2020 [2]. As of early June 2021, the global reported cases of COVID-19 have exceeded 170 million with over 3 million deaths [3].

The clinical spectrum of this illness ranges from asymptomatic infection, to acute respiratory distress syndrome (ARDS), circulatory shock, multiorgan failure, and ultimately death [4]. The death rate related to COVID-19 is relatively high – ranging from 5% to 35%, especially in elderly patients and those who have comorbidities [5]. Although different treatment strategies have been explored and used based on emergency approval and evidence-based medicine, there is no definitive and effective treatment to ensure improvement and cure [6]. The preferred management strategy is supportive care for patients with mild disease [7]. For moderate to severe disease, treatments with different pharmacological classes have been used. Many antiviral agents have been tried to suppress viral replication (among others, α-interferon, favipiravir, oseltamivir and remdesivir) [6,8]. Steroid therapy also has been recommended to suppress inflammatory responses associated with severe COVID-19 [9,10]. Additionally, many other pharmacotherapy (among others, administration of antibiotic drugs, anticoagulants, immunomodulatory agents [11], antipyretics and tonics) approaches have been widely applied, based on different disease stages and manifestations [6,9].

At the beginning of the outbreak, all COVID-19 patients were treated with hydroxychloroquine 400 mg every 12 hours on day one of admission, followed by 200 mg twice daily on day 5 and azithromycin 500 mg once daily for 3 days, unless contraindication. As well, oseltamivir therapy

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was initiated, with a dose of 150 mg twice daily for five days. This regimen was stopped and another was begun utilizing antiviral drugs such as favipiravir, remdesivir, and kaltera in July 2020. The clinical guidelines included adjunctive immunomodulatory therapy with corticosteroids and tocilizumab and other medications, including antibiotics, low molecular heparin and tonics – according to the Iraqi Ministry of Health (MOH) approved guidelines [12]. We designed this study to evaluate the employed pharmacotherapy utilization patterns and outcomes for the hospitalized patients with COVID-19.

METHODS

Study Design and patients

A retrospective observational study was carried using the medical records of the adult patients diagnosed with COVID-19 who were admitted to public hospitals in AL Najaf, Iraq, within the period of June to September 2020. We included all adult patients with confirmed COVID-19 and who were hospitalized with the severe or critical stage of the disease. We excluded patients with incomplete or missing data in their medical records. A total of 346 patients fulfilled eligibility criteria and were included in our analysis. The study was approved by the scientific research committee of the Al-Najaf health Institute, and by the ethics and scientific committee of the college of pharmacy/Kufa University.

Data Sources and patients' variables

The medical records of patients were categorized chronologically in the registered offices of the province's public hospitals. The selection of these medical records was based on the date of admission, and was reviewed retrospectively. A chart extraction sheet was used to collect information from the patients' medical records and was optimized by a pilot study on 50 of these. The collected information took in patients` demographics (age, gender, employment), associated comorbidities (systemic hypertension, diabetes, coronary heart disease, asthma or chronic obstructive pulmonary disease, and others), admission and discharge date, clinical manifestation, oxygen-support categories (which were defined according to an ordinal scale of 1 – ambient air; 2 – low-flow oxygen; 3 – high-flow oxygen; and 4 – mechanical ventilation) [11], vital signs on admission, laboratory values, medications, and outcomes which included mortality rate during hospitalization or recovery and discharged alive from hospital.

Statistical Analysis

Descriptive statistics were applied to represent the data as mean ±SD for normally distributed continuous variables, and for non-normally distributed continuous variables – median and interquartile range (IQR) (25% to 75% percentile range) values. The Mann-Whitney U test was employed to compare nonparametric variables. Categorical variables were shown as frequencies and percentages, and the Chi-square test was used to establish comparisons. P-value was considered statically significant if less than 0.05. Microsoft Excel 2020 and SPSS 22.0.0 (Chicago, IL) were employed to make the statistical description and analysis.

RESULTS

Sociodemographic characters of patients at baseline

The total number of patients included in our analysis was 346, with an overall mean age of (55.1±13.6) years. Moreover, a majority of patients were male (70.2%) from urban areas (88.4%), and smokers (28.6%)

Table 1. Sociodemographic characters of the patients at baseline

Variables	Frequencies (N=346)	Percentage
Age (years) 18-34 35-50 51-65 >65	 17 107 127 95	 4.9% 30.9% 36.7% 27.5%
Female	103	29.8%
Male	243	70.2%
Employed	86	24.8%
Not employed	260	75.2%
Rural residence	40	11.6%
Urban residence	306	88.4%
Smokers	99	28.6%
Nonsmokers	247	71.4%

Comorbidities of patients at baseline

Most patients had hypertension (38.2%), diabetes (35.3%) and ischemic heart disease (16.2%).

Table 2. Comorbidities of patients at baseline

Variables	Frequencies (N=346)	Percentage
Hypertension	132	38.2%
Diabetic	122	35.3%
IHD	56	16.2%
Asthma/ COPD	15	4.3%
CKD	11	3.2%
Others	6	1.7%
No comorbidities	4	1.2%

IHD: Ischemic heart disease, COPD: Chronic obstructive airway disease, CKD: Chronic kidney disease

Patient clinical presentation at baseline

Most of the patients presented the respiratory manifestations of coronavirus disease - cough (74.3%) and shortness of breath (73.4%). Some had fever (25.1%).

Table 3. Patient clinical presentations at baseline

Variables	Frequencies (N=346)	Percentage
Cough	257	74.3%
Shortness of breath	254	73.4%
Fever	87	25.1%
Headache	49	14.2%
Sore throat	35	10.1%
Fatigue	34	9.8%
Nausea and vomiting	10	2.9%
Others	6	1.7%

Patient clinical and laboratory data at Baseline

According to health guidelines, patients were designated as severe cases and hospitalized when SPO_2 was 93%. In the study, the included patients demonstrated an overall mean SPO_2 of 83.7 Regarding D-dimer, creatinine, AST and ALT, the data was not normally distributed and thus is presented as medians (interquartile range). The Median value of D-dimer level was 911 and IQR – 312-2499.

Table 4. Patient clinical and laboratory data at baseline.

Variables	Mean (±SD) or Median (IQR)
Temperature (°C)	37.5±0.7
HR (bpm)	88.0±15.8
SPO_2 (%)	83.7±6.9
WBC (103/ul)	9.6±5.0
Lymphocyte count (103/ul)	1.2±0.7
Platelet count (103/ul)	236.4±88.4
Creatinine#(IQR) (mg/dl)	0.7 (0.6-0.8)
D-dimer#(IQR) (ng/ml)	911 (312-2499)
Ferritin (ng/ml)	686.0±439.6
AST#(IQR)(U/L)	42.4 (31.5-55.9)
ALT#(IQR)(U/L)	35 (25-72.6)

HR: Heart rate, SpO_2: oxygen saturation; WBC: white blood cells; AST: aspartate aminotransferase; ALT: alanine transaminase. IQR: interquartile range; SD (standard deviation)

Type of oxygen therapy

Most of the patients received high-flow oxygen therapy (78%). This procedure was mandated with patients who were at the severe stage – with SPO_2 ≤93%, wherein high-flow oxygen therapy was stipulated.

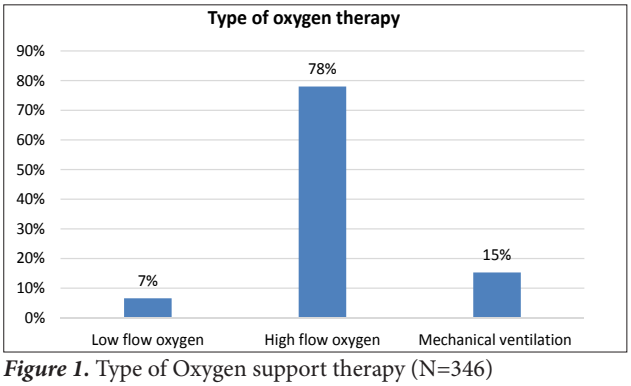

Figure 1. Type of Oxygen support therapy (N=346)

Specific medications for COVID-19

The majority of the patients were treated with dexamethasone (81%). Also, convalescent plasma therapy was applied in some of the patients (44%), while favipiravir and hydroxychloroquine were prescribed in 23% of all patients. Moreover, azithromycin and lopinavir/ritonavir were given to 19% of all patients, while tocilizumab was administered to 9% of all patients, as illustrated in Figure 2.

Most patients received supportive medications. These included enoxaparin received by 93% of the patients and acetaminophen prescribed to 89% of all patients, while tonics was recommended to 86% of the patients. Regarding antibiotics, meropenem was the most frequently prescribed in 60% of the patients. Other different supportive medications were used as shown in Figure 3.

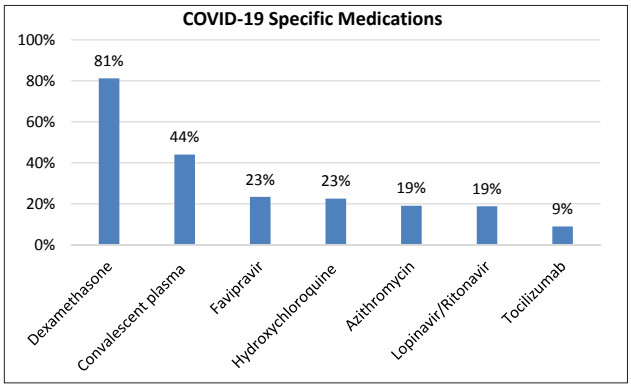

Figure 2. Type of COVID-19 specific medications (N=346)

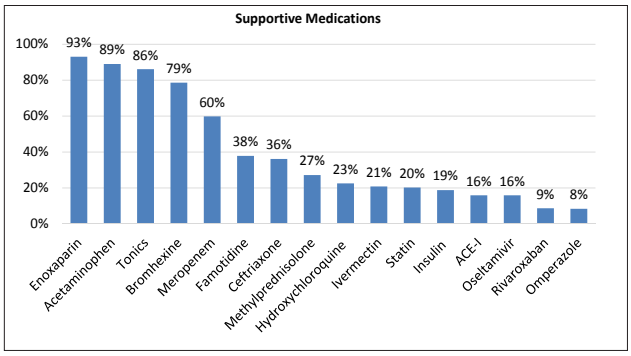

Figure 3. Type of supportive care medications (N=346)

Hospitalization outcomes

The majority of patients recovered and were discharged alive (66%) while in-hospital mortality was 26%, and the remaining patients were transferred to other hospitals (8%) because they needed specialized intervention for their coexisting comorbidities – such as dialysis and cardioangiography, as shown in Figure 4.

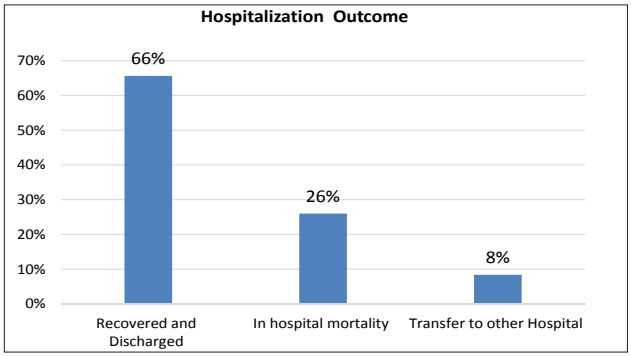

Figure 4. Patient hospitalization outcome (N=346)

Patients with comorbidities such diabetes and hypertension (46.4% and 52.2%, respectively) in the dead group were higher than that in the discharged alive patient group. Also, high D-dimer levels were noted to be more common among the dead group patients than those who were discharged alive. Use of high flow oxygen therapy (88%), dexamethasone (90%) or plasma therapy (39.7%) were also observed in higher proportion in the discharged alive than in

the dead group. In contrast, the broad spectrum meropenem was prescribed to a higher percent among the dead group. Interestingly, a combination of enoxaparin with hydroxychloroquine or a combination of dexamethasone plus plasma therapy were prescribed at a higher rate among the survived patients (Table 5).

Table 5. Comparison of patient variables between the discharged alive and discharged dead patients

Variables	Discharged alive (N=228)	Dead in hospital (N=90)	P value
Diabetes	36.2%	46.4%	0.003
Hypertension	35.7%	52.2%	0.002
D-dimer#(IQR) (ng/ml)	1745±667	4081±771	0.000
High flow oxygen therapy	88%	60%	0.000
Enoxaparin	94%	86%	0.04
Plasma therapy	52.2%	39.7%	0.013
Meropenem	54.4%	85%	0.004
Enoxaparin + Hydroxychloroquine	27.8%	8%	0.003
Dexamethasone plus plasma	49%	31%	0.04

Categorical variable compared by Chi square test , nonparametric variable compared by Mann-Whitney U test

DISCUSSION

Coronavirus disease 2019 is a challenging disease. To date, many treatment options have been used, either based on emergency approval or evidence-based medicine [13,14]. This pharmacological therapy ranges between COVID-19-specific medications and COVID-19-nonspecific medications [15]. Therefore, we designed this study to assess the prescribing patterns of medications used for the treatment of hospitalized patients with severe and critical COVID-19 and the clinical outcome.

In this retrospective observational study, which was conducted on 346 patients, we found that most patients (about 81%) received corticosteroid as dexamethasone, while convalescent plasma therapy was applied as a quickly available immune therapy in almost half the patients (44%). Also, a few patients were given antiviral favipiravir (23%) and lopinavir/ritonavir (19%). In addition, hydroxychloroquine was prescribed in 23% of all patients, and azithromycin was given to 19% of all patients. As supportive care medications, anticoagulants as low molecular weight heparin, enoxaparin were administered to most of the patients (93%), while meropenem was the most frequently used broad-spectrum antibiotic (60% of all patients).

These prescribing patterns can be attributed to Iraq health authorities' recommendations at the beginning of the COVID-19 outbreak, wherein treatment with hydroxychloroquine, azithromycin and oseltamivir was used and then stopped in July 2020 and another regimen was initiated that included lopinavir/ritonavir, favipiravir and remdesivir. In addition, adjunctive immunomodulatory therapy with corticosteroids and tocilizumab and other medications (antibiotics, low molecular heparin and tonics) were included in the Iraq Ministry of health released standard guidelines that were adapted from those of different international organizations [12,16]. These medications prescription patterns for COVID-19 are consistent with findings from other cohort studies conducted on more than 20,000 patients with COVOD-19 that also demonstrated that steroid, anticoagulant, and antiviral medicaments were frequently used [17].

Beyond the aforementioned, it is worth mentioning that the disease severity stage is an important factor to be considered in the selection of COVID-19 specific therapy and oxygen therapy, as well as supportive therapy – as shown in the current study in which most patients received high flow oxygen therapy, steroid, and convalescent plasma, as well as broad-spectrum antibiotics. This is in agreement with findings from previous studies [15]. The antiviral, Remdesivir, showed superiority in the effectiveness against COVID-19 [18,19], however, this was not administered to patients due to a lack of availability at that time.

Interestingly, in this study, most of the patients (66%) recovered and were discharged alive and only 26% of all patients died in hospital. This finding is in line with that outcome of a study conducted on 2821 patients that revealed that the overall discharge alive was (77%) compared to in-hospital mortality (14%) [15]. This good survival rate as demonstrated by discharged alive can be explained by the effective use of steroid, anticoagulant and plasma therapy to most patients. As supporting evidence, a recovery trial conducted on 6426 hospitalized patients showed that the use of dexamethasone was associated with a low rate of mortality [10]. Moreover, the use of antiviral agents such as favipiravir showed a beneficial effect in the treatment of COVID-19 patients and this in line with finding from a retrospective cohort study conducted on 247 patients in Thailand that demonstrated day-7 clinical improvement in patients received favipiravir [20]. Additionally, convalescent plasma therapy was proven to be effective in enhancing survival in patients with COVID-19 [21,22].

Arshad *et al*., 2020 demonstrated a reduction in COVID-19 associated mortality in patients who received hydroxychloroquine alone or in combination with azithromycin [23], and this was confirmed in our findings. Additionally, the use of tocilizumab, an immunomodulatory agent, revealed a positive effect on COVID-19, as showed by a retrospective observational study conducted on 51 hospitalized patients (28 patients received tocilizumab, while 23 patients did not) with severe COVID-19 demonstrating a shorter median time to clinical improvement in tocilizumab vs. no tocilizumab groups (8 days vs. 13 days) [11]. Regarding the off-label use of bromhexine, ivermectin and famotidine, this was based on evidence-based medicine supported by finding of previous studies [24,26].

CONCLUSION

This retrospective cohort study showed that the prescribing pattern of COVID-19 specific medications and supportive care are consistent with guideline recommendations. Patients with comorbidities such diabetes and hypertension are associated with high in hospitable mortality. High flow oxygen therapy, anticoagulants and plasma therapy, as well as a combination of enoxaparin plus hydroxychloroquine or a combination of steroid with plasma therapy were prescribed at greater rates among patients who were discharged alive from hospital.

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