Original Article

Comparison of the Eight Different Treatment Regimens for the Hospitalized Patients with COVID-19: A Retrospective Cohort Study

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Abstract

Background: Coronavirus disease 2019 (COVID -19), characterized by a mild to severe respiratory illness, has been affecting the world since late 2019 and leading to an increase in hospitalizations and deaths. There is still no specific, highly effective treatment for this disease. This study aimed to compare the efficacy of the eight treatment regimens for hospitalized patients with COVID-19.

Materials and Methods: This retrospective cohort study was conducted on hospitalized patients with laboratory-confirmed COVID-19 by a real-time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) of nasopharyngeal samples.

Results: Among all patients hospitalized with COVID-19 between March to September 2020, 861 patients were included in the study. This study indicated that treatment protocols included either remdesivir or favipiravir were superior to hydroxychloroquine in reducing the risk of in-hospital mortality of the patients with confirmed COVID-19, especially in critical patients defined as those who were ICU admitted or under mechanical ventilation (HR, 0.43; 95% CI, 0.23 to 0.82; P=0.011 and HR, 0.45; 95% CI, 0.22 to 0.90; P=0.024, respectively). Whereas receiving lopinavir/ritonavir in combination with either hydroxychloroquine plus interferon β and corticosteroids (HR, 1.85; 95% CI, 1.17 to 2.94; P=0.009), hydroxychloroquine plus interferon β (HR, 1.66; 95% CI, 1.01 to 2.74; P=0.046), or interferon β (HR, 1.80; 95% CI, 1.12 to 2.89; P=0.015) was associated with a significant increase in this risk.

Conclusion: Our findings indicate that using remdesivir and favipiravir in combination with interferon β and corticosteroids might be beneficial in hospitalized patients with COVID-19, especially critical ones.

Keywords: Coronavirus disease 2019, Critically ill, In-hospital mortality, Treatment regimens

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Introduction

Coronavirus disease 2019 (COVID -19) is caused by Severe Acute Respiratory Syndrome- related Coronavirus 2 (SARS-CoV-2) (1). This disease is characterized by a mild to severe respiratory illness affecting the world since late 2019, leading to an increase in hospitalizations and deaths. According to World Health Organization (WHO), over 117 million confirmed cases of COVID-19, including 2.61 million deaths, had been reported globally until 11 March 2021 (2). There are many factors involved in differences between the crude fatality rate (CFR) of COVID-19 throughout the world, including the proportion of older individuals diagnosed with this disease, the prevalence of comorbidities, obesity, and smoking habits, psychological factors, genetic, healthcare-related factors such as heterogeneity in testing, reporting approaches, and healthcare system capacities, availability of drugs, different virus strains, and even political regime and environmental-related factors like air pollution (3-9).

The majority of existing treatment protocols for COVID-19 have focused on a combination of supportive therapy and antivirals, and anti-inflammatory drugs (10-13). In this retrospective cohort study, we evaluated eight different treatment regimens recommended by the Iranian ministry of health for hospitalized patients with COVID-19 and compared their efficacy on the outcome of the patients. Treatment regimens consisted of an antiviral (remdesivir, favipiravir, lopinavir/ritonavir), interferon, corticosteroids, and/or corticosteroids hydroxychloroquine. Although there are various RCTs behind the mentioned regimens in the manuscript, the advantage of our study was evaluating the combined effect of drugs in the treatment of COVID-19.

Methods

Setting and study population: This retrospective cohort study was conducted at Imam Hossein Hospital, a tertiary care teaching hospital affiliated with Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran. The inclusion criteria were hospitalized patients between March to September 2020 who had laboratory-confirmed COVID-19 by a real-time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) of nasopharyngeal samples. The protocol of this study was approved by the Ethics Committee of SBMU (IR.SBMU.RETECH.REC.1399.686).

The treatment regimens used for COVID-19 encompassed 8 main protocols: 1) remdesivir + interferon β + corticosteroids, (Rem + INF + GCs), 2) favipiravir + interferon β + corticosteroids, (Favipiravir + INF + GCs), 3) lopinavir/ritonavir + hydroxychloroquine + interferon β + corticosteroids, (LPV/r + HCQ + INF + GCs), 4) lopinavir/ritonavir + interferon β + corticosteroids, (LPV/r + INF + GCs), 5) lopinavir/ritonavir + hydroxychloroquine + interferon β, (LPV/r + HCQ + INF), 6) lopinavir/ritonavir + interferon β, (LPV/r + INF), 7) lopinavir/ritonavir + hydroxychloroquine, (LPV/r + HCQ), 8) hydroxychloroquine (HCQ). The dose and duration of drugs were as recommended in international COVID-19 protocols. According to the effect of COVID-19 on the thromboembolic events, all patients received an anticoagulant based on recommended prophylaxis doses.

Data gathering: demographic data and clinical information of the patients, including the Respiratory Rate (RR), peripheral capillary Oxygen Saturation (SpO2), and COVID-19 related symptoms of the patients on the first day of their admission to the hospital, underlying diseases, treatment regimens used for COVID-19, and outcome of the patients (need to ICU admission and mechanical ventilation, duration of hospitalization, Length of Stay in the ICU (ICULS), duration of mechanical ventilation, and in-hospital mortality) were extracted from their medical records.

Outcome: The efficacy of the eight treatment regimens on in-hospital mortality of hospitalized patients with COVID-19 was evaluated as the study's primary outcome.

Data analysis: Categorical variables were expressed as frequency [n (%)], and continuous variables were described by mean ± standard deviation (SD) or median [interquartile range (IQR)] for normal and non-normal distributions data, respectively. The normality assumption has been examined by checking kurtosis, skewness, box plot, and Q-Q plot, due to a large number of data. Analysis of variance (ANOVA) in the case of normality and Kruskal–Wallis or Mann-Whitney analysis in case normality assumption violated were used to compare the mean of different study variables between our different treatment regimens. Also, the Cox proportional hazard regression model was performed to assess the

association between treatment protocols and survival. First, a crude analysis was done for selecting the most associated and best predictor variables. The selection of best predictors was based on a P-value of less than 0.2 in univariable analysis.

The Multivariable stepwise Cox regression model consists of the selected variables performed to the assessment. The final model was selected according to backward Wald. All study variables, including demographic data and clinical information of the patients, were considered in the crude analysis and finally in selecting a model based on stepwise methods. Data were reported as Hazard Ratio (HR) and 95% Confidence Interval (95% CI). A two-sided *P*-value less than 0.05 was considered statistically significant. Analyzing was done using the STATA 14 Package. We considered protocol 8 (HCQ) as the reference protocol to compare the efficacy of other treatment regimens according to the study period and wide use of hydroxychloroquine at the beginning of the COVID-19 pandemic as a potentially helpful treatment (14, 15).

Results

Among all patients hospitalized with confirmed COVID-19 between the time of March to September

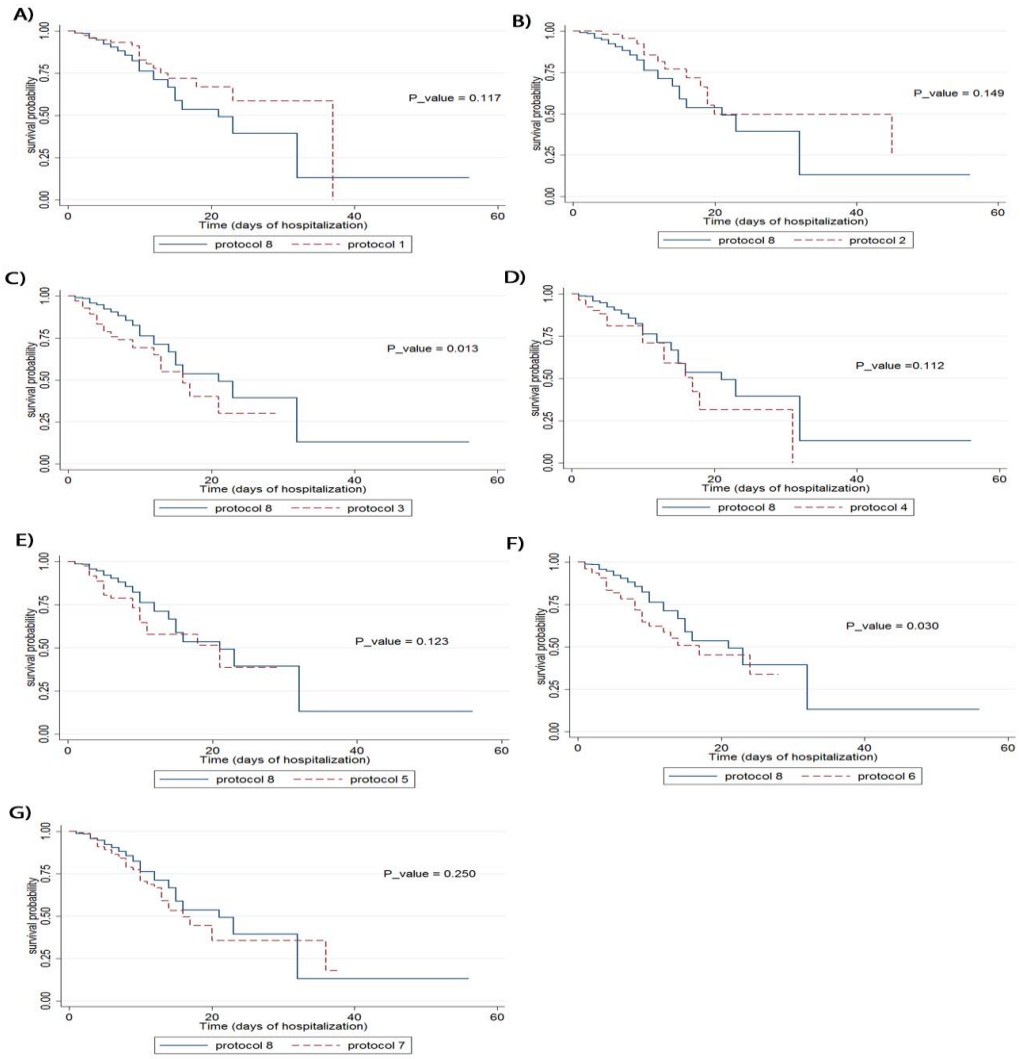

Figure 1. Kaplan Meier Curves; Comparison of survival probability between: A) protocol 1, remdesivir + interferon β + corticosteroids; B) protocol 2, favipiravir + interferon β + corticosteroids; C) protocol 3, lopinavir/ritonavir + hydroxychloroquine + interferon β + corticosteroids; D) protocol 4, lopinavir/ritonavir + interferon β + corticosteroids; E) protocol 5, lopinavir/ritonavir + hydroxychloroquine + interferon β; F) protocol 6, lopinavir/ritonavir + interferon β; and G) protocol 7, lopinavir/ritonavir + hydroxychloroquine and reference protocol (protocol 8, HCQ).

Table 1: Demographic characteristics and clinical information of the patients with COVID-19 in each treatment group*

Variables	Protocol 1 (n=75)	Protocol 2 (n=51)	Protocol 3 (n=95)	Protocol 4 (n=53)	Protocol 5 (n=80)	Protocol 6 (n=77)	Protocol 7 (n=158)	Protocol 8 (n=272)	P-value
Male gender, [n (%)]	46 (61.3)	33 (64.7)	56 (58.9)	32 (60.4)	36 (45.0)	36 (46.8)	88 (55.7)	147 (54.0)	0.197
Age, years [mean±SD]	55.2±17.8	57.4±15.8	62.1±14.4	59.2±16.3	60.9±15.7	64.4±17.4	61.3±17.2	61.4±16.5	0.197
Body mass index, [mean±SD]	28.7±5.1	26.9±4.0	27.7±4.5	27.3±4.2	27.9±5.8	26.7±5.2	27.3±5.0	27.0±5.1	0.218
Base SpO2, [median(IQR)]**	86(10)	87(9)	88(8)	88(7)	90(6)	88(8)	90(7)	90(5)	<0.001
Base RR*, [median(IQR)]**	19(2)	19(3)	20.3	20(2)	20(7)	18(2)	19(5)	19(5)	0.541
History of respiratory disorders, [n (%)]	2 (2.7)	1 (2)	10 (10.5)	5 (9.4)	4 (5)	7 (9.1)	12 (7.6)	18 (6.6)	0.357
Hypertension, [n (%)]	26 (34.7)	23 (45.1)	35 (36.8)	21 (39.6)	40 (50.0)	38 (49.4)	62 (39.2)	110 (40.4)	0.386
Diabetes, [n (%)]	22 (29.3)	18 (35.3)	24 (25.3)	10 (18.9)	27 (33.8)	31 (40.3)	47 (29.7)	86 (31.6)	0.239
Coronary artery disease, [n (%)]	3 (4.0)	3 (5.9)	15 (15.8)	7 (13.2)	14 (17.5)	10 (13.0)	29 (18.4)	63 (23.2)	0.002
Malignancy, [n (%)]	0 (0.0)	4 (7.8)	2 (2.1)	0 (0.0)	3 (3.8)	5 (6.5)	3 (1.9)	16 (5.9)	0.046
Symptoms, [n (%)]									
Fever	37 (49.3)	26 (51.0)	54 (56.8)	27 (50.9)	46 (57.5)	40 (51.9)	79 (50.0)	147 (54.0)	0.926
Cough	48 (64.0)	33 (64.7)	48 (50.5)	28 (52.8)	42 (52.5)	32 (41.6)	93 (58.9)	166 (61.0)	0.037
Sore throat	0 (0.0)	1 (2.0)	2 (2.1)	1 (1.9)	1 (1.3)	1 (1.3)	2 (2.3)	5 (1.8)	0.969
Fatigue	28 (37.3)	23 (45.1)	44 (46.3)	25 (47.2)	29 (36.3)	30 (39.0)	55 (34.8)	104 (38.2)	0.545
Muscle pain	23 (30.7)	16 (31.4)	31 (32.6)	21 (39.6)	25 (31.3)	23 (29.9)	50 (31.6)	106 (39.0)	0.594
Dyspnea	60 (80.0)	37 (72.5)	61 (64.2)	29 (54.7)	54 (67.5)	53 (68.8)	101 (63.9)	173 (63.6)	0.100
Chest pain	6 (8.0)	1 (2.0)	8 (8.4)	3 (5.7)	3 (3.8)	5 (6.5)	8 (5.1)	24 (8.8)	0.505
Headache	11 (14.7)	4 (7.8)	17 (17.9)	9 (17.0)	11 (13.8)	12 (15.6)	24 (15.2)	26 (19.6)	0.334
Vertigo	0 (0.0)	0 (0.0)	5 (5.3)	1 (1.9)	3 (3.8)	2 (2.6)	7 (4.4)	0 (0.0)	0.010
Loss of taste and/or smell	1 (1.3)	0 (0.0)	1 (1.1)	2 (3.8)	0 (0.0)	1 (1.3)	2 (1.3)	0 (0.0)	0.188
Altered state of consciousness	3 (4.0)	2 (3.9)	9 (9.5)	6 (11.3)	7 (8.8)	13 (16.9)	11 (7.0)	16 (5.9)	0.045
Abdominal pain	3 (4.0)	2 (3.9)	3 (3.2)	2 (3.8)	3 (3.8)	3 (3.9)	13 (8.2)	15 (5.5)	0.654
Anorexia	10 (13.3)	17 (33.3)	54 (56.8)	28 (52.8)	48 (60.0)	44 (57.1)	81 (51.3)	125 (46.0)	<0.001
Nausea and/or vomiting	11 (14.7)	4 (7.8)	18 (18.9)	10 (18.9)	20 (25.0)	12 (15.6)	33 (20.9)	58 (21.3)	0.285
Diarrhea	6 (8.0)	4 (7.8)	9 (9.5)	6 (11.3)	6 (7.5)	6 (7.8)	21 (13.3)	26 (9.6)	0.815
Sleep disorder	4 (5.3)	8 (15.7)	17 (17.9)	14 (26.4)	19 (23.8)	16 (20.8)	40 (25.3)	63 (23.2)	0.022
Anxiety	0 (0.0)	5 (9.8)	5 (5.3)	7 (13.2)	7 (8.8)	8 (10.4)	11 (7.0)	50 (18.4)	<0.001
ICU admission, [n (%)]	42 (56.0)	22 (43.1)	11 (11.6)	7 (13.2)	11 (13.8)	20 (26.0)	18 (11.4)	24 (8.8)	<0.001
Mechanical ventilation, [n (%)]	15 (20.0)	10 (19.6)	15 (15.8)	10 (18.9)	13 (16.3)	10 (13.0)	23 (14.6)	32 (11.8)	0.585

Duration of hospitalization, days [median (IQR)]	10.0 (7.0-15.0)	10.0 (6.0-18.0)	6.0 (4.0-10.0)	6.0 (4.0-10.0)	6.0 (3.3-10.0)	7.0 (4.0-11.0)	6.0 (4.0-10.0)	6.0 (4.0-9.8)	<0.001
Length of stay in ICU, days [median (IQR)]	7 (4.75-11.25)	7 (5.95-12.93)	6 (4-9)	5 (3-9)	6(3-10)	6 (4-10)	6(4-9)	6(4-9)	0.011
Duration of mechanical ventilation, days [median (IQR)]	10 (6-15)	9(6-17)	6 (3-9)	5 (3-8)	6(3-10)	7 (4-10.5)	6(4-9)	6(4-9)	0.002
In-hospital mortality, [n (%)]	17 (22.7)	13 (25.5)	29 (30.5)	17 (32.1)	23 (28.8)	27 (35.1)	40 (25.3)	50 (18.4))	0.047

* Treatment protocols: Protocol 1 (remdesivir + interferon β + corticosteroids), Protocol 2 (favipiravir + interferon β + corticosteroids), Protocol 3 (lopinavir/ritonavir + hydroxychloroquine + interferon β + corticosteroids), Protocol 4 (lopinavir/ritonavir + interferon β + corticosteroids), Protocol 5 (lopinavir/ritonavir + hydroxychloroquine + interferon β), Protocol 6 (lopinavir/ritonavir + interferon β), Protocol 7 (lopinavir/ritonavir + hydroxychloroquine), Protocol 8 (hydroxychloroquine); Categorical variables were expressed as frequency [n (%)] and continuous variables were described by mean ± standard deviation [SD] or median [interquartile range (IQR)] for normal and non-normal distributions data, respectively; ** Base SpO2, Peripheral capillary Oxygen Saturation (SpO2) of the patients on the first day of their admission to the hospital; *** Base RR, Respiratory Rate (RR) of the patients on the first day of their admission to the hospital; Categorical variables were expressed as frequency [n (%)] and continuous variables were described by mean ± standard deviation [SD] or median [interquartile range (IQR)] for normal and non-normal distributions data, respectively.

2020, 861 patients were eligible to be included in the study. The mean age of included patients was 60.8±16.6 years, and 474 of them (55.1%) were males. The demographic data and clinical information of the patients in each treatment group are summarized in Table 1.

In this study, we used the Respiratory Rate (RR) and peripheral capillary Oxygen Saturation (SpO2) of the patients on the first day of admission to the hospital to evaluate the severity of their disease (16). There was no statistically significant difference between treatment groups in terms of the RR of the patients (P=0.541). In contrast, SpO2 was statistically significantly different between them (P<0.001) (Table 2).

The risk of in-hospital mortality among the total population, critical patients, and non-critical ones were assessed by Cox proportional hazard model compared to reference protocol (Tables 3, 4, and 5, respectively). Kaplan Meier Curve for each treatment protocol is available in Figure 1.

In the total population, we detected a significantly higher risk of in-hospital mortality among patients treated with LPV/r + HCQ + INF + GCs (HR, 1.85; 95% CI, 1.17 to 2.94; P=0.009), LPV/r + HCQ + INF (HR, 1.66; 95% CI, 1.01 to 2.74; P=0.046), and LPV/r + INF (HR, 1.80; 95% CI, 1.12 to 2.89; P=0.015). This association also was showed by age (HR, 1.04; 95% CI, 1.03 to 1.05; P<0.001) and male gender (HR, 1.42; 95% CI, 1.07 to 1.88; P=0.015).

There was observed a lower risk of in-hospital mortality only with protocols 1 (Rem + INF + GCs) and 2 (Favipiravir + INF + GCs) that were non-significant for both of them (Table 3).

The significantly lower survival with protocols 3 (LPV/r + HCQ + INF + GCs) and 6 (LPV/r + INF) also was shown with Kaplan Meier Curves (Figure 1).

Among Critical patients, defined as those who were ICU admitted or under mechanical ventilation, the risk of in-hospital mortality was significantly lower in those who were treated with Rem + INF + GCs (HR, 0.43; 95% CI, 0.23 to 0.82; P=0.011) and Favipiravir + INF + GCs (HR, 0.45; 95% CI, 0.22 to 0.90; P=0.024). Whereas age (HR, 1.02; 95% CI, 1.01 to 1.03; P=0.003) and history of respiratory disorders (HR, 1.98; 95% CI, 1.03 to 3.79; P=0.040) were associated with a significant increase in this risk (Table 4).

Table 2: Peripheral capillary Oxygen Saturation (SpO2) on the first day of their admission to the hospital.

Treatment protocols	Median(IQR) *	Sig. **
1 (remdesivir + interferon β + corticosteroids)	86(10)	<0.001
2 (favipiravir + interferon β + corticosteroids)	87(9)	<0.001
3 (lopinavir/ritonavir + hydroxychloroquine + interferon β + corticosteroids)	88(8)	<0.001
4 (lopinavir/ritonavir + interferon β + corticosteroids)	88(7)	0.001
5 (lopinavir/ritonavir + hydroxychloroquine + interferon β)	90(6)	0.244
6 (lopinavir/ritonavir + interferon β)	88(8)	0.003
7 (lopinavir/ritonavir + hydroxychloroquine)	90(7)	0.172

* SpO2 of patients in each treatment group was compared with the reference group (protocol 8); Continuous variables were described median [interquartile range (IQR)] for non-normal distributions data

Table 3: Cox proportional hazard model for in-hospital mortality in the total population.

Variables	Crude HR, 95% CI	P-value	Adjusted HR, 95% CI	P-value
Treatment protocols*:				
1 (Rem + INF + GCs)	0.69 [0.40-1.20]	0.188	0.88 [0.50-1.53]	0.649
2 (Favi + INF + GCs)	0.68 [0.37-1.27]	0.226	0.79 [0.43-1.48]	0.470
3 (LPV/r + HCQ + INF + GCs)	1.73 [1.09-2.74]	0.019	1.85 [1.17-2.94]	0.009
4 (LPV/r + INF + GCs)	1.57 [0.90-2.73]	0.108	1.56 [0.89-2.70]	0.118
5 (LPV/r + HCQ + INF)	1.45 [0.88-2.37]	0.144	1.66 [1.01-2.74]	0.046
6 (LPV/r + INF)	1.63 [1.02-2.61]	0.041	1.80 [1.12-2.89]	0.015
7 (LPV/r + HCQ)	1.28 [0.85-1.95]	0.236	1.29 [0.85-1.96]	0.228
Age	1.04 [1.03-1.05]	0.000	1.04 [1.03-1.05]	0.000
Gender, male	1.32 [1.00-1.75]	0.046	1.42 [1.07-1.88]	0.015

* Treatment protocols: Protocol 1 (remdesivir + interferon β + corticosteroids), Protocol 2 (favipiravir + interferon β + corticosteroids), Protocol 3 (lopinavir/ritonavir + hydroxychloroquine + interferon β + corticosteroids), Protocol 4 (lopinavir/ritonavir + interferon β + corticosteroids), Protocol 5 (lopinavir/ritonavir + hydroxychloroquine + interferon β), Protocol 6 (lopinavir/ritonavir + interferon β), Protocol 7 (lopinavir/ritonavir + hydroxychloroquine); Data of multivariable stepwise Cox regression model were reported as Hazard Ratio (HR) and its 95% Confidence Interval (95% CI)

In non-critical patients, receiving LPV/r + HCQ + INF + GCs (HR, 2.46; 95% CI, 1.21 to 4.99; P=0.013) and LPV/r + INF (HR, 2.63; 95% CI, 1.29 to 5.38; P=0.008) regimens, and also age (HR, 1.06; 95% CI, 1.04 to 1.08; P=0.001) and male gender (HR, 1.97; 95% CI, 1.23 to 3.17; P=0.005) were associated with significant increased risk of in-hospital mortality compared to reference protocol. We only detected a decrease in in-hospital mortality in patients treated with protocols 1 (Rem + INF + GCs) and 2 (Favipiravir + INF + GCs) that were non-significant for both of them (Table 5).

Discussion

This study indicated that treatment protocols included either remdesivir (protocol 1) or favipiravir (protocol 2) were superior to HCQ in reducing the risk of in-hospital mortality of patients with COVID-19, especially in critical patients defined as those who were ICU admitted or under mechanical ventilation. Whereas treatment protocols included LPV/r (protocols 3, 4, 5, 6, and 7) were associated with worse clinical outcomes. We considered Protocol 8 (HCQ) the reference protocol to compare the efficacy of other treatment regimens according to the study period and

Table 4: Cox proportional hazard model for in-hospital mortality in critical patients (ICU admitted or under mechanical ventilation).

Variables	Crude HR, 95% CI	P-value	Adjusted HR, 95% CI	P-value
Treatment protocols*:				
1 (Rem + INF + GCs)	0.34 [0.18-0.63]	0.001	0.43 [0.23-0.82]	0.011
2 (Favi + INF + GCs)	0.39 [0.19-0.78]	0.008	0.45 [0.22-0.90]	0.024
3 (LPV/r + HCQ + INF + GCs)	1.14 [0.62-2.10]	0.662	1.29 [0.70-2.40]	0.411
4 (LPV/r + INF + GCs)	0.94 [0.46-1.93]	0.874	0.99 [0.48-2.04]	0.985
5 (LPV/r + HCQ + INF)	1.12 [0.58-2.14]	0.740	1.28 [0.66-2.48]	0.460
6 (LPV/r + INF)	0.74 [0.39-1.40]	0.355	0.87 [0.45-1.66]	0.668
7 (LPV/r + HCQ)	1.17 [0.68-1.99]	0.574	1.11 [0.64-1.92]	0.718
Age	1.02 [1.01-1.04]	0.000	1.02 [1.01-1.03]	0.003
History of respiratory disorder	2.13 [1.14-3.98]	0.017	1.98 [1.03-3.79]	0.040

* Treatment protocols: Protocol 1 (remdesivir + interferon β + corticosteroids), Protocol 2 (favipiravir + interferon β + corticosteroids), Protocol 3 (lopinavir/ritonavir + hydroxychloroquine + interferon β + corticosteroids), Protocol 4 (lopinavir/ritonavir + interferon β + corticosteroids), Protocol 5 (lopinavir/ritonavir + hydroxychloroquine + interferon β), Protocol 6 (lopinavir/ritonavir + interferon β), Protocol 7 (lopinavir/ritonavir + hydroxychloroquine); Data of multivariable stepwise Cox regression model were reported as Hazard Ratio (HR) and its 95% Confidence Interval (95% CI)

wide use of HCQ at the beginning of the COVID-19 pandemic as a potentially useful treatment (14, 15, 17). Most of our patients (31.6%) were assigned to protocol 8. Some studies reported conflicting results on the efficacy of HCQ in improving the outcome of the patients with COVID-19 (18-22). A multicenter study on 1395 admitted patients to 176 UK hospitals did not report a significant effect of high dose HCQ on the 28-day mortality rate (26.8%) compared to patients who did not receive it (25.0%) (23). A systematic review and meta-analysis of seven clinical trials on 4984 patients found no difference in outcomes between patients who received HCQ and those who did not (24). However, a newly published nationwide observational cohort study on 1064 patients showed a 53% reduction in the risk of ICU admission by early HCQ administration (within one day of ward admission) (25). Remdesivir is a nucleoside analog mainly known for its therapeutic effects in patients with the Ebola virus. It binds to viral RNA and leads to premature termination (21, 26, 27). Following some in-vitro reports about the efficacy of remdesivir on inhibiting SARS-CoV-2, it was considered a new promising therapeutic option for COVID-19 (28, 29). Spinner CD et al. evaluated the efficacy of adding remdesivir to the treatment protocol of hospitalized patients with moderate to severe COVID-19 and reported a significantly higher clinical improvement in patients who received 5-day treatment with remdesivir (odds ratio, 1.65; 95% CI, 1.09 to 2.48; P=0.02). However, this clinical benefit was not significant following 10-day treatment with remdesivir (P=0.18) (27). Remdesivir also showed a significant effect on reducing the recovery time and the rate of mortality of patients with COVID-19 in a double-blind, randomized, placebo-controlled trial. Recovery time decreased from 15 days in the placebo arm to 10 days in the remdesivir group (RR, 1.29; 95% CI, 1.12 to 1.49; P<0.001), and the mortality rate reduced from 11.9% to 6.7%, respectively (HR, 0.55; 95% CI, 0.36 to 0.83) (30). The last update of the National Institutes of Health (NIH) guideline for therapeutic management of adults with COVID-19 on 23 February 2021 noted remdesivir as a treatment option in hospitalized patients who require minimal supplemental oxygen the moderate rating of recommendation (BIIa). However, there is no clear recommendation about its use in hospitalized patients with increasing supplemental oxygen. In these patients, it is suggested to use remdesivir in combination with dexamethasone according to expert opinion for those who do not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or Extra Corporeal Membrane

Oxygenation (ECMO), and also those who require oxygen delivery through a high-flow device or noninvasive ventilation. Dexamethasone is the only strongly recommended treatment in hospitalized patients who require invasive mechanical ventilation (31). According to our data, although the severity of the disease was significantly worse in patients of the remdesivir group ($p<0.001$), the risk of mortality was lower among them. This association especially was significant among hospitalized patients with COVID-19 who were ICU admitted or under mechanical ventilation.

Favipiravir and Rem are among the most commonly studied antivirals in COVID-19 patients (30). Favipiravir is a purine nucleoside analog that selectively inhibits the viral RNA-dependent RNA polymerase (32). Similar to remdesivir, the efficacy of Favipiravir against SARS-CoV-2 first was shown in in-vitro studies (28, 33) and then was evaluated by some clinical studies. Some studies reported the significant effect of Favipiravir on a higher improvement rate of chest imaging (Computed Tomography(CT) scan), faster viral clearance, and higher clinical improvement of patients with COVID-19 (33-37).

Treatment protocols included LPV/r were associated with increased in-hospital mortality in this study. This effect was significant following the use of LPV/r in combination with either HCQ plus INF-β and GCs (protocol 3), HCQ plus INF-β (protocol 5), or INF-β (protocol 6). LPV/r could decrease in-hospital mortality in critical patients when combined with INF-β plus GCs (protocol 4) and INF-β (protocol 6) that were non-significant for both regimens. Lopinavir and ritonavir are protease inhibitors and bind competitively to the viral protease substrate site. They are commonly used as anti-HIV agents (38). Evaluation of the efficacy of LPV/r in patients with COVID-19 did not significantly affect clinical improvement and patients' mortality rate in some studies (39-41). A large clinical trial conducted by RECOVERY Collaborative Group reported no difference between the patients who received this combination (1616 patients) compared to those who received usual care (3424 patients) regarding 28-day mortality, hospital discharge within 28 days, and receipt of invasive mechanical ventilation (40). According to the lack of clinical benefit and reduction in mortality rate with using LPV/r in patients with COVID-19, NIH guidelines strongly recommended against the use of this combination for the treatment of COVID-19 in both hospitalized and non-hospitalized patients (31). We also observed worse clinical outcomes and increased mortality risk with treatment protocols included. This study had some

Table 5: Cox proportional hazard model for in-hospital mortality in non-critical patients.

Variables	Crude HR, 95% CI	P-value	Adjusted HR, 95% CI	P-value
Treatment protocols*:				
1 (Rem + INF + GCs)	0.68 [0.16-2.93]	0.608	0.77 [0.18-3.32]	0.725
2 (Favi + INF + GCs)	0.63 [0.15-2.70]	0.532	0.73 [0.17-3.16]	0.675
3 (LPV/r + HCQ + INF + GCs)	2.20 [1.09-4.47]	0.028	2.46 [1.21-4.99]	0.013
4 (LPV/r + INF + GCs)	2.04 [0.85-4.85]	0.108	2.12 [0.89-5.08]	0.091
5 (LPV/r + HCQ + INF)	1.59 [0.73-3.44]	0.240	1.81 [0.83-3.95]	0.134
6 (LPV/r + INF)	2.76 [1.36-5.60]	0.005	2.63 [1.29-5.38]	0.008
7 (LPV/r + HCQ)	1.34 [0.69-2.61]	0.390	1.29 [0.66-2.52]	0.454
Age	1.06 [1.04-1.08]	0.000	1.06 [1.04-1.08]	0.001
Gender, male	1.76 [1.11-2.79]	0.016	1.97 [1.23-3.17]	0.005

* Treatment protocols: Protocol 1 (remdesivir + interferon β + corticosteroids), Protocol 2 (favipiravir + interferon β + corticosteroids), Protocol 3 (lopinavir/ritonavir + hydroxychloroquine + interferon β + corticosteroids), Protocol 4 (lopinavir/ritonavir + interferon β + corticosteroids), Protocol 5 (lopinavir/ritonavir + hydroxychloroquine + interferon β), Protocol 6 (lopinavir/ritonavir + interferon β), Protocol 7 (lopinavir/ritonavir + hydroxychloroquine); Data of multivariable stepwise Cox regression model were reported as Hazard Ratio (HR) and its 95% Confidence Interval (95% CI)

limitations. This was a retrospective cohort study, and we could not control confounding factors between study groups. Also, we didn't analyze the safety profile of treatment protocols due to a lack of data.

Conclusion

In conclusion, our findings indicate that using Remdisivir and Favipiravir might be beneficial in hospitalized patients with COVID-19, especially in ICU admitted or under mechanical ventilation. In comparison, LPV/r was associated with worse clinical outcomes. Further randomized clinical trials are needed to evaluate the safety and efficacy of these antivirals more rigorously.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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