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The effect of hydroxychloroquine in COVID-19 patients who did not receive corticosteroids

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ABSTRACT

Background and Objective: At the beginning of the pandemic, Hydroxychloroquine (HCQ) was one of the most widely used drugs prescribed to patients admitted to hospitals with coronavirus disease 2019 (COVID-19). We try to find the effect of HCQ on the severity and mortality of patients who did not receive corticosteroids.

Methods: In this retrospective study, patients with COVID-19 disease were collected from February 20, 2020, to July 21, 2020, at Rouhani Hospital in Babol. Patients were followed up until December 6, 2021. In this study, 170 patients in case and control groups were studied. We used logistic and COX regression models to explore the effects of drugs. Data were analyzed by SPSS version 22.

Findings: The use of HCQ did not affect mortality (p=0. 46, 95%CI= 0.63 to 2.71, OR= 1.31) and final severity (p= 0.75, 95%CI= 0.59 to 2.06, OR= 1.10) at admission time. However, azithromycin remained in the final model but did not have a significant effect (P= 0.08, HR= 0.28, 95%CI= 0.06 to 0.18). Heparin use was not associated with severity improvement (p= 0.06, 95%CI= 0.97 to 2.81, HR= 1.65), while ceftriaxone remained a factor affecting severity in the model (p = 0.03, 95% CI= 0.29 to 0.95, HR = 0.52).

Conclusion: In this study, HCQ harmed mortality admission time and was ineffective in the long term. The use of ceftriaxone compared to other drugs showed protective effects against the mortality hospitalization time. Heparin is not recommended without considering the risk of bleeding in COVID-19 patients.

Keywords: COVID-19, HCQ, Hydroxychloroquine, Mortality, Coronavirus

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Introduction

In December 2019, an acute respiratory disease spread in Wuhan, China, identified as the novel coronavirus, or coronavirus-disease 2019 (COVID-19). Reports show that infection with the virus leads to acute respiratory distress syndrome (ARDS). The virus is transferred to surrounding persons by respiratory particles created by sneezing and coughing of the infected or the carrier (at a distance of about 2 to 4 meters) (1-3). The major symptoms of coronavirus are fever, cough, sore throat, and shortness of breath (4). According to statistics from the Center for Infectious Diseases (CDC) and the World Health Organization (WHO), the virus has spread around the world, and more than 213 million have been afflicted, and more than 4.5 million people have died, which is growing every day (5, 6). Different diagnostic tests are performed to diagnose coronavirus disease. Kits that have gained emergency diagnostic authorization from the Food and Drug Administration (FDA) include reverse transcription-polymerase chain reaction (PCR), IgM / IgG serology, and antigen testing (7). One of the most extensively utilized medications in the treatment of COVID-19 is hydroxychloroquine. It is beneficial in treating rheumatoid arthritis, systemic lupus erythematosus, and the prevention of malaria (8, 9). Although hydroxychloroquine has been proven to have an antiviral mechanism in vitro, there is insufficient evidence of its potential effectiveness in the clinical environment (10). Contrary to promising results in vitro, in a recent randomized controlled study done by the WHO for the treatment of coronavirus, hydroxychloroquine showed little or no influence on overall mortality, ventilation, and duration of hospital stay in hospitalized patients, while its effectiveness in the early stages of the disease must be proved (11). In a long-term follow-up, we decided to evaluate the effects of hydroxychloroquine in patients who did not receive corticosteroids.

Methods

Study design & setting

In this retrospective analysis, patients with COVID-19 were gathered from February 20, 2020, to July 21, 2020, at the Rouhani Hospital in Babol, Mazandaran, Northern Iran after receiving ethical approval (ethical code: IR.MUBABOL.HRI.REC.1400.092) by the ethical committee of Vice Chancellor for Research, Babol University of Medical Sciences. Follow-up of patients has been done from the time of admission until December 6, 2021. It should be mentioned that the follow-up of patients in case of discharge was done via telephone.

Patients

In this study, patients over 18 years of age who were hospitalized with COVID-19 and whose diagnosis was confirmed by clinical symptoms and computerized tomography scan (CT-scan) or PCR results were considered in the study period. Patients who have been treated as outpatients but have not been able to follow up or who have not been given hydroxychloroquine because of arrhythmias, high Q-T intervals, or psoriasis, as well as patients who have been given corticosteroids (because of corticosteroid are effective in the treatment of the disease, excluding these patients would help find more reliable results), were excluded from the study. In this study, patients were separated into the intervention group (case) and the non-intervention group (control). The intervention group comprised patients who received hydroxychloroquine, while the non-intervention group included patients who did

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not receive hydroxychloroquine. Follow-up of patients was until the cut points of death or December 6, 2021.

Variables

In terms of disease severity, patients were categorized into severe and nonsevere groups. The initial severe condition of patients was according to National Early Warning Score 2 (NEWS2) (12)), and the final disease severity of the patients was according to intensive care unit (ICU) admission, receiving invasive ventilation, or being expired. Mortality during hospitalization and mortality after discharge, age, age over 65 years and under, gender, ventilator use, ICU admission, underlying diseases such as diabetes, hypertension, cardiac, lung, and kidney disease, malignancy, CT-Scan findings such as consolidation, ground-glass opacity, and other pulmonary complications such as fibrosis and bronchiectasis, and the formation of bands and thickening of septae, Group therapy including case (patients receiving hydroxychloroquine) and control (patients not receiving hydroxychloroquine), other drugs like anticoagulant group (aspirin, enoxaparin, heparin, Plavix), antibiotic group (meropenem, vancomycin, ceftriaxone, and azithromycin), and antiviral group (kaletra and ribavirin), length of hospital stay until discharge and length of hospital stay until cut points were recorded. In this investigation, disease severity (baseline state compared to the final disease severity of patients to assess treatment effectiveness) is characterized according to the modified NEWS2 criteria (12)).

Statistical methods

Using SPSS software version 22, qualitative data were examined using the Chi-square test, and quantitative data were evaluated by t-test. If required, we separated the data based on mortality and final disease severity and independently evaluated the connection of variables in each group. We utilized the Cox regression model using the backward stepwise technique to analyze the survival of patients and determine the factors impacting the mortality risk ratio and their final disease severity. The events evaluated in the different models included mortality at the time of admission, final disease severity and mortality at the time of follow-up, and timeframes also include the duration of hospitalization and the duration of follow-up. In all models, the male gender was included, and the availability of criteria for bi-dimensional data such as underlying disorders, drug usage, or even CT-scan findings was considered. In this study, P-value < 0.05 is significant.

Results

In this study, 170 patients with coronavirus disease in case and control groups (85 patients each) were analyzed to evaluate the effect of hydroxychloroquine on severity and mortality. The age range of patients was between 19-91 years with a mean and standard deviation of 60.16 ± 15.68 years, and 58.2 percent were over 65 years old. The majority of male patients had a history of underlying diabetes, cardiovascular disease, and hypertension. Forty patients (23.5 %) were in the mild group, 20 (11.8 %) were in the mild-to-moderate group, 44 (25.9 %) were in the moderate group, and 66 (38.8 %) were in the severe group. In terms of final disease severity. There were 108 (63.5%) in the nonsevere group and 62 (36.5%) in the severe group. The mean and standard deviation of hospital stays were 4.72 ± 8.31 days, and the patients were monitored for 380.20 ± 233.25 days.

Thirty-eight individuals expired during hospitalization, while thirteen others expired during follow-up (Table 1). In the analysis of patients based on pre-drug results such as medical history, age, and sex, as well as CT-scan findings and initial severity, there was no statistically significant difference between

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the two groups (P > 0.05 in all cases). As shown in Table 1, there was a significant gender correlation between the case and control groups (P = 0.028) among the expired patients. In research comparing the length of hospital stays for expired patients who received hydroxychloroquine with those who did not, a statistically significant difference of about four days was discovered, and the expired patients who received hydroxychloroquine had more extended hospital stays (P = 0.010). According to Table 2, ceftriaxone is the most frequently recommended medicine for patients, regardless of whether they use hydroxychloroquine, whereas ribavirin is the least frequently used prescription.

Table 1. Primary characteristics of patients and their relationship with mortality based on case and control groups

Variable**		Frequency N=170	mortality					
			alive			expired		
			Case N=64	Control N=68	P-value*	Case N=21	Control N=17	P-value*
age (Mean±SD)		60.16±15.68	57.88±15.04	59.22±14.74	0.605	64.19±16.01	67.53±19.31	0.563
gender	female	67 (39.4)	29 (45.3)	23 (33.8)	0.177	5 (23.8)	10 (58.8)	**0.028**
	male	103 (60.6)	35 (54.7)	45 (66.2)		16 (76.2)	7 (41.2)	
age	<65	99 (58.2)	39 (60.9)	42 (61.8)	0.922	12 (57.1)	6 (35.3)	0.180
	≥65	71 (41.8)	25 (39.1)	26 (38.2)		9 (42.9)	11 (64.7)	
renal diseases	no	161 (94.7)	60 (93.8)	64 (94.1)	0.930	21 (100)	16 (94.1)	0.260
	yes	9 (5.3)	4 (6.3)	4 (5.9)		0 (0)	1 (5.9)	
lung disease	no	158 (92.2)	57 (89.1)	65 (95.6)	0.157	20 (95.2)	16 (94.1)	0.878
	yes	12 (7.1)	7 (10.9)	3 (4.4)		1 (4.8)	1 (5.9)	
CVD	no	104 (61.2)	41 (64.1)	43 (63.2)	0.921	14 (66.7)	6 (35.3)	0.054
	yes	66 (38.8)	23 (35.9)	25 (36.8)		7 (33.3)	11 (64.7)	
hypertension	no	111 (65.3)	40 (62.5)	46 (67.6)	0.535	15 (71.4)	10 (58.8)	0.415
	yes	59 (34.7)	24 (37.5)	22 (32.4)		6 (28.6)	7 (41.2)	
DM	no	102 (60)	38 (59.4)	41 (60.3)	0.914	13 (61.9)	10 (58.8)	0.847
	yes	68 (40)	26 (40.6)	27 (39.7)		8 (38.1)	7 (41.2)	
cancer	no	163 (95.9)	62 (96.9)	64 (94.1)	0.447	20 (95.2)	17 (100)	0.362
	yes	7 (4.1)	2 (3.1)	4 (5.9)		1 (4.8)	0 (0)	
ICU admission	no	138 (81.2)	57 (89.1)	56 (82.4)	0.272	14 (66.7)	11 (64.7)	0.899
	yes	32 (18.8)	7 (10.9)	12 (17.6)		7 (33.3)	6 (35.3)	
Ventilator use	no	129 (75.9)	53 (82.8)	56 (82.4)	0.945	10 (47.6)	10 (58.8)	0.492
	yes	41 (24.1)	11 (17.2)	12 (17.6)		11 (52.4)	7 (41.2)	
GGO	no	16 (9.4)	8 (17.8)	7 (15.2)	0.742	0 (0)	1 (10)	0.277
	yes	99 (58.2)	37 (82.2)	39 (84.8)		14 (100)	9 (90)	
consolidation	no	50 (29.4)	23 (51.1)	18 (39.1)	0.251	6 (42.9)	3 (30)	0.521
	yes	65 (38.2)	22 (48.9)	28 (60.9)		8 (57.1)	7 (70)	
OLA	no	44 (25.9)	16 (35.6)	17 (37)	0.889	6 (42.9)	5 (50)	0.729
	yes	71 (41.8)	29 (64.4)	29 (63)		8 (57.1)	5 (50)	

SD: Standard Deviation; CVD: Cardiovascular disease; DM: Diabetes Mellitus; ICU: Intensive Care Unit; GGO: Ground Glass Opacity; OLA: Other Lung Abnormality.

*P-value < 0.05 statistically significant.

**Qualitative variables are shown as Frequency (percentages).

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There was a significant relationship between not receiving enoxaparin and being discharged alive in the case group and between using vancomycin and being expired in the case group (P = 0.046 and P = 0.011, respectively). Similar to Tables 1 and 2, we analyzed the final disease severity and the connection between the initial and drug variables for the case and control groups. There was a statistically significant link between those with a history of lung disease and the case group (P = 0.024) in patients with nonsevere conditions. In addition, there was a statistically significant link between patients who received vancomycin and the case group (P = 0.005). We evaluated the effect of hydroxychloroquine on mortality in the following section. We utilized a logistic regression model using the Enter technique for this purpose. In this model, the group treatment variable was added, and the conclusion was that receiving hydroxychloroquine increases the risk of mortality by 31%, although this connection is not statistically significant (P = 0.462, Odds Ratio (OR) = 1.122, 95% CI = 0.636 to 2.710). In investigating the influence of hydroxychloroquine on the final disease severity, we utilized the Enter technique, in which only the case group was entered, and the outcome was a 10 percent probability of final disease severity in patients receiving hydroxychloroquine. This connection is similarly not significant (P = 0.57, OR = 1.107, 95% CI = 0.068 to 0.538) when the number of patients grows. The models shown in Table 3 provide an overview of the final results of the Cox regression. Medically, azithromycin during hospitalization and ceftriaxone have demonstrated long-term protective effects, but heparin has been linked to a long-term increase in patient mortality.

Table 2. Patient's drug findings and their relationship with mortality based on case and control groups

Variable**		Frequency N=170	mortality					
			alive			expired		
			Case N=64	Control N=68	P-value*	Case N=21	Control N=17	P-value*
aspirin	**no**	123 (72.4)	48 (75)	49 (72.1)	0.702	17 (81)	9 (52.9)	0.065
	yes	47 (27.6)	16 (25)	19 (27.9)		4 (19)	8 (47.1)	
enoxaparin	**no**	140 (82.4)	58 (90.6)	53 (77.9)	**0.046**	14 (66.7)	15 (88.2)	0.120
	yes	30 (17.6)	6 (9.4)	16 (22.1)		7 (33.3)	2 (11.8)	
heparin	**no**	107 (62.9)	47 (73.4)	41 (60.3)	0.109	10 (47.6)	9 (52.9)	0.744
	yes	63 (37.1)	17 (26.6)	27 (39.7)		11 (52.4)	8 (47.1)	
Plavix	**no**	150 (88.2)	59 (92.2)	57 (83.8)	0.141	20 (95.2)	14 (82.4)	0.198
	yes	20 (11.8)	5 (7.8)	11 (16.2)		1 (4.8)	3 (17.6)	
meropenem	**no**	93 (54.7)	40 (62.5)	41 (60.3)	0.759	4 (19)	8 (47.1)	0.065
	yes	77 (45.3)	24 (37.5)	27 (39.7)		17 (81)	9 (52.9)	
azithromycin	**no**	149 (87.6)	56 (87.5)	57 (83.8)	0.548	19 (90.5)	17 (100)	0.191
	yes	21 (12.4)	8 (12.5)	11 (16.2)		2 (9.5)	0 (0)	
ceftriaxone	**no**	45 (26.5)	13 (20.3)	21 (30.9)	0.165	6 (28.6)	5 (29.4)	0.955
	yes	125 (73.5)	51 (79.7)	47 (69.1)		15 (71.4)	12 (70.6)	
vancomycin	**no**	76 (44.7)	30 (46.9)	32 (47.1)	0.988	4 (19)	10 (58.8)	**0.011**
	yes	94 (55.3)	34 (53.1)	36 (52.9)		17 (81)	7 (41.2)	
kaletra	**no**	157 (92.4)	60 (93.8)	61 (89.7)	0.401	20 (95.2)	16 (94.1)	0.878
	yes	13 (7.6)	4 (6.2)	7 (10.3)		1 (4.8)	1 (5.9)	
ribavirin	**no**	164 (89.4)	62 (96.9)	65 (95.6)	0.699	20 (95.2)	17 (100)	0.362
	yes	6 (10.6)	2 (3.1)	3 (4.4)		1 (4.8)	0 (0)	

*P-value < 0.05 statistically significant. **Qualitative variables are shown as Frequency (percentages).

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Table 3. Last step of Cox regression models to find the risk factors affecting the desired event

Models*	variable		HR	95%CI		P-value**
				upper	lower	
Model 1	Severity	Mild-moderate	1.691	0.105	27.371	0.711
		moderate	6.687	0.810	55.223	0.078
		severe	7.363	0.968	56.024	0.054
Model 2	Azithromycin		0.284	0.068	1.183	0.084
Model 3	consolidation		1.939	0.995	3.779	0.052
	Lung disease		0.291	0.066	1.275	0.101
Model 4	ceftriaxone		0.526	0.291	0.950	**0.033**
	heparin		1.654	0.970	2.819	0.064
Model 5	age		1.032	1.012	1.053	**0.002**
	heparin		2.068	1.184	3.612	**0.011**

HR: Hazard Ratio; CI: Confidence Interval

*Event 1: in-hospital death (event=24), Time 1: length of stay in hospital, Covariates use in model 1: age, gender, history of lung disease, heart disease, DM, hypertension, severity, GGO, consolidation, OLA (censored=91). Event 2: in-hospital death (event=38), Time 2: length of stay in hospital, Covariates use in model 2 (censored=132): group therapy, aspirin, heparin, Plavix, meropenem, vancomycin, ceftriaxone, azithromycin, kaletra, ribavirin. Event 3: final disease severity (event=43), Time 3: length of stay in hospital, Covariate use in model 3: age, gender, history of lung, heart, kidney disease, DM, hypertension, severity, GGO, consolidation, OLA (censored=72). Event 4: final disease severity (event=62), Time 4: length of stay in hospital, Covariate use in model 4 (censored=108): like covariate in model 2. Event 5: ICU admission (event=51), Time 5: duration between admission to end point, Covariates use in model 5: age, sex, group therapy, aspirin, heparin, Plavix, meropenem, vancomycin, ceftriaxone, azithromycin, kaletra, ribavirin (censored=119).

**P-value < 0.05 statistically significant.

Discussion

We assessed the effects of receiving hydroxychloroquine on the treatment of COVID-19 and the relationship between receiving this medication and other findings. In several trials, hydroxychloroquine has lost its efficacy in boosting patient survival and decreasing prognosis and death in COVID-19 patients. According to Chen's research, the medicine was first approved for a limited amount for COVID-19, and since a better treatment had not been produced at the time, it was advised to give it with caution owing to its adverse effects (13). Currently, the FDA has authorized medications such as Ramsavir, Barsitinib, anti-antibody therapies, viral monoclonal antibodies, and others, as well as the use of pharmaceuticals such as dexamethasone, anticoagulants, etc. (14). In our investigation, hydroxychloroquine was shown to influence mortality and hospital stay substantially; these findings were consistent with those of several other studies (15-19). In contrast, Gatteau's study recommended low-dose hydroxychloroquine monotherapy for reducing hospital mortality (20).

In prior research, Yu et al. also linked hydroxychloroquine treatment to a substantial reduction in mortality among critically ill patients, which runs counter to our hypothesis (21). In the review of research by Gholami et al., he discussed the excellent benefits of therapy with hydroxychloroquine. However, he highlighted that the predicted extracellular concentration of this medication in the lungs is lower than laboratory values, indicating that this drug's in vivo action is diminished (22). The Hussain study stated that the FDA should approach this drug with extreme caution from the start due to its side

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effects and the exacerbation of those side effects when combined with other drugs such as azithromycin (15). Although azithromycin has a decent preventive effect, its effect on patient survival is not statistically significant. This result is comparable to the meta-analysis performed by Kamel et al. in 2021, who reported that this treatment had minimal and minor protective benefits on mortality and the need for ventilation; nevertheless, due to the high possibility of bacterial resistance, it is suggested that this drug no longer be used to treat infections caused by COVID-19 (23). Research by Bleyzac et al. in 2020 reported the positive antiviral effects of the drugs and considered that the drug's combination with hydroxychloroquine would be successful in vitro as opposed to Andreani et al. research (24, 25). Finally, it was suggested that in the event of a greater advantage, it should be administered therapeutically and with bacterial resistance in mind (24).

The research by Sultana et al. also evaluates the use of this medicine only in patients with COVID-19 if there is also a bacterial etiology; also, because of its synergistic effects with drugs that lower the QT interval (such as hydroxychloroquine), the administration of this drug in patients requires strict ECG monitoring and cautious administration (26). Regarding the influence of hospitalization duration on the ultimate intensity in this plan, the protective effect of ceftriaxone is considerable, but heparin has a non-significant and unfavorable effect on severity. This result is comparable to that of Maboud et al. 2021.'s study, which concluded that there was insufficient evidence to support the effect of prophylactic doses of heparin on mortality reduction. However, it should be noted that the majority of the studies in this review had small sample sizes and were retrospective (27). In our strategy, preventative doses of heparin were utilized for COVID-19, although therapeutic dosages have been added based on the patient's condition. However, it is essential to consider the danger of long-term bleeding and adequate patient follow-up. There is also relatively little research on the efficacy of ceftriaxone; however, antibiotics are routinely recommended for bacterial infections in COVID-19 patients. According to Grau et al., in March, the first wave of the corona saw a substantial rise in antibiotic use, led by ceftriaxone and azithromycin (28). Although the usage of antibiotics has decreased in successive waves due to increased antibiotic resistance and a defined course of action against COVID-19, they are still employed (29). Ceftriaxone is a viable medicine for people with COVID-19 if antibiotics are required.

In the research on patients' long-term survival, we assessed the influence of medicines, age, and gender on death at follow-up. With each year's increase in age, the risk of mortality increases by 3%, and with the administration of heparin, the risk of mortality increases to 2.5-fold. Both of these conclusions were statistically significant. The results are comparable to those of Costa et al., who discovered that age of more than 60 was a determinant of death. Contrary to our findings, this study reported the effect of 3.6 times non-use of heparin in both therapeutic and preventative doses on patient mortality (30). According to a review by Zhang et al. in 2020, the etiologies behind aging include increased comorbidity, decreased reserves of essential organs, increased viral load, and decreased levels of innate immune function (31). In relation to heparin usage, Godino et al. noted in their study the good benefits of heparin therapy and that, like anticoagulants, these medications have the least intermediate effects. The effects of antiplatelet medications also require further research. In the approach presented in this study, if anticoagulant treatment is required in patients with COVID-19, its severity should be assessed in the next step; if no treatment is required and if there is no risk of heart attack or coronary artery syndrome, anticoagulants are only recommended for moderate to severe patients with a risk of Disseminated intravascular coagulation (DIC) and Venous thromboembolism (VTE). Due to its direct antiviral effects and ability to prevent thromboembolism, the usage of this heparin has been deemed to be successful. However, the risk of bleeding associated with this medicine and the underlying heart conditions that affect individuals should be considered (32).

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In our study, we did not examine the risk of bleeding in patients, nor did we review the risk of readmission to the hospital and other diseases following the use of other medications, but it is essential to note that the use of pharmaceuticals is associated with an increased risk of disease. Various research (13, 33) has indicated that anticoagulants have beneficial short-term benefits; however, their long-term effects have not been investigated, and this is the first study to consider an average follow-up duration of more than one year. We suggest that if anticoagulants are prescribed, the risk of long-term bleeding, underlying diseases, and age should be taken into account and that in the treatment of patients with COVID-19, corticosteroids or other WHO-approved drugs should be prescribed in addition to COVID-19 treatment, as patients admitted to our study did not receive any dose of corticosteroids at the time of admission.

The retrospective nature of the design and the limited sample size used to examine the pharmacological impact are among the limitations of our study. Given that the drug's efficacy is being evaluated, it may be preferable to include only patients with a definitively positive COVID-19 test (positive PCR). Another issue is that the patient's bleeding status is not evaluated. In the early days of the COVID-19 pandemic, there was neither a good drug nor a set of approved recommendations, so most of these drugs were given based on experience and initial recommendations that have since changed. Because of this, it is recommended to design a study that takes the risk of bleeding into account and reconsiders the status of some medications, such as heparin. A further shortcoming of the plan is that patients were solely monitored for death. Most of the people who took part in the study did not need a revisit to the hospital after they were released. However, some patients did need a revisit, which can lead to the use of new drugs or even the development of new diseases, which messes up the study results. This study, however, has advantages. To our knowledge, this is the first research to assess the pharmacological effects of COVID-19 patients for an average of more than a year and the initial severity of the condition according to the stated and authorized NEWS2 criteria. Since corticosteroid medicines have already established a favorable position in treating patients with COVID-19, the accuracy of the data is enhanced by the fact that none of the patients used corticosteroids, allowing for a more accurate evaluation of the drugs' efficacy.

Conclusion

According to the findings of this study, hydroxychloroquine has been associated with disease severity and higher mortality at the time of admission; thus, this medicine is not recommended for hospitalized patients. Compared to other antibiotics such as meropenem, azithromycin, and vancomycin, ceftriaxone is a more successful therapy for people with COVID-19. Heparin has long been associated with a higher risk of death; thus, the risk of bleeding, underlying disorders and clinical conditions, and the use or non-use of other essential medications such as corticosteroids should be evaluated before prescribing this medication, and be followed up after discharge.

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None.

Compliance with Ethics Guidelines

This study is approved by the ethics committee of Babol University of Medical Sciences with the code IR.MUBABOL.HRI.REC.1400. 092.

Data Availability

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

Competing Interests

The authors declare that they have no competing interests.

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