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Effect of Hydroxychloroquine on Clinical Improvement and Mortality Among Patients with COVID-19 Admitted to Four General Hospitals in Saudi Arabia

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Abstract

Background: The use of hydroxychloroquine in coronavirus disease (COVID-19) pandemic raised significant concerns as regards safety and efficacy in hospitalized patients. The objective was to examine the effect of hydroxychloroquine on clinical improvement and mortality among hospitalized patients with COVID-19.

Methods: A prospective cohort study was conducted at four general hospitals in the Western region, Saudi Arabia. Patients who had absolute or relative contraindication for using hydroxychloroquine were excluded. Patients concomitantly receiving other medications including azithromycin, antivirals, and supportive treatment were not excluded.

Results: A total 267 patients were included in the current analysis; 185 (69.3%) on hydroxychloroquine and 82 (30.7%) on non -hydroxychloroquine treatments. The average age was 46.0±13.3 years and 78.3% of the patients were males. Approximately 95.9% of the patients were symptomatic with mild (50.6%), moderate (32.6%), severe (8.2%), or ARDS symptoms (4.5%). Compared with no hydroxychloroquine, those on hydroxychloroquine had significantly longer length of stay (11.5±7.1 versus 7.8±4.3 days, p<0.001), more ICU admission (22.7% versus 9.8%, p=0.012), and more intubation (12.4% versus 3.7%, p=0.026).

Improvement of symptoms (84.3% versus 81.7%, p=0.595) and hospitalization death (7.0% versus 1.2%, p=0.071) were not significantly different between groups. With exception of length of stay, the association of hydroxychloroquine with the above negative outcomes disappeared after adjustment for several factors including disease severity and concomitant use of azithromycin.

Conclusions: Hydroxychloroquine is not associated with better improvement of symptoms compared with other treatments. Moreover, it is associated with longer length of stay but not mortality or ICU admission in adjusted analysis.

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Introduction

Since its first appearance in Wuhan (China) in late 2019, more than 30 million patients globally were infected with severe acute respiratory syndrome coronavirus number 2 (SARS-CoV-2) with more than 950 thousands related deaths by mid-September 2020 [1, 2]. Although the mortality observed in the current coronavirus disease (COVID-19) pandemic (4.1% of closed cases) is much lower than other coronaviruses such as SARS-CoV (10%) and the Middle East Respiratory Syndrome-CoV (MERS-CoV, 35%)[3], the rapid and universal spread of COVID-19 caused unprecedented global public health emergency and major healthcare crises [4, 5].

With the lack of recognized therapeutic medications or effective vaccine, the management of COVID-19 was largely dependent on off-label use of available medications [6, 7]. Several medications have been tried during the pandemic including anti-viral drugs, antimalarial drugs, and immunomodulatory agents (such as tocilizumab and interferons) [6, 7].

Chloroquine and hydroxychloroquine have been used for decades in the prevention and treatment of malaria and then the treatment of some autoimmune diseases [8]. Their earlier use in the COVID pandemic was based on pre-pandemic reports that showed their ability to inhibit viral replication of several viruses including SARS and human immunodeficiency virus (HIV) [8, 9]. Additionally, in vitro reports published early in the pandemic showing the ability of hydroxychloroquine to inhibit SARS-CoV-2 replication [10]. The use of hydroxychloroquine in the COVID pandemic raised significant concerns as regards safety and efficacy, specially among cardiac patients [11]. Accumulating evidence and scientific debates forced several international organizations such as the World Health Organization (WHO) and the US Food and Drug Administration (FDA) to limit or halt the use of hydroxychloroquine in the management of patients with COVID-19 [11, 12]. The objective of the current study was to examine the effect of hydroxychloroquine on clinical improvement and mortality among patients with COVID-19 admitted earlier in the pandemic to general hospitals in Saudi Arabia.

Methods

Setting

The current study was conducted at four general hospitals at Western region, Saudi Arabia. The hospitals included 700-bed King Fahad General Hospital, 500-bed Alnoor Specialist Hospital, 300-bed East Jeddah Hospital, and 300-bed King Abdullah Medical Complex. All were located in Jeddah with exception of Alnoor Specialist Hospital which is located at Mecca. The hospitals were allowed to provide healthcare services for patients with COVID-19 in addition to other types of patients. The hospitals were following the guidelines of

Saudi Ministry of Health (MOH) as regards testing, diagnosis, admission, isolation, management, and discharge [13, 14].

Design

It was a prospective cohort study conducted between March 1, 2020 and May 30, 2020. The study design obtained all required ethical approvals from the Institutional Review Board (IRB) of the Saudi MOH. Informed consent was obtained from patients or their immediate family members after explaining the objectives of the study.

Sample Size Calculation

Assuming an improvement rate of 50% and assuming that hydroxychloroquine is used in the majority of patients, 240 patients (160 use hydroxychloroquine and 80 do not use hydroxychloroquine) would be required to detect 20% difference (60% versus 40%) in improvement using 80% power and 95% level of significance.

Population

The study targeted adult patients (age >18 years) with polymerase chain reaction (RT-PCR)-confirmed COVID-19 diagnosis admitted to any of the included four hospitals during the study duration. The patients were divided into two cohorts based on the status of hydroxychloroquine treatment, as per the Saudi MOH guidelines. Patients who had absolute or relative contraindication for using hydroxychloroquine were excluded from the study. These included known hypersensitivity to hydroxychloroquine or similar compounds, Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency, decompensated heart failure, prolonged QTc interval, and preexisting retinopathy. Patients concomitantly receiving other medications including azithromycin, antivirals, and supportive treatment were not excluded.

Recruitment and Data Collection

Patients were conveniently recruited after obtaining informed consent. Structured study data collection sheet was used to collect the patient information. These included socio-demographic characteristics, exposure history, symptoms, comorbidity, chest imaging findings, relevant laboratory examinations, and outcomes.

Outcome Definitions

Clinical improvement was based on comparing the assessments of symptoms, disease severity, and chest imaging before and after the use of treatments. Disease severity was categorized into five groups; asymptomatic, mild (symptomatic without evidence of pneumonia or hypoxia), moderate (clinical signs of pneumonia but no hypoxia), severe (severe pneumonia or hypoxia), and acute respiratory distress syndrome (ARDS) [14, 15]. Other outcome measures included length of stay, need for intensive care unit (ICU) admission, need for intubation, need for inotropic support, and hospitalization death.

Statistical Analysis

Categorical variables were presented as frequencies and percentage while continuous variables were presented as means and standard deviations (SD) or median and inter-quartile range (IQR), as appropriate. Demographic, clinical, and outcome variables were compared between those who received and those who did not receive hydroxychloroquine. Chi-square or Fisher's exact test, as appropriate, were used to examine differences in categorical variables while student t-test or Mann–Whitney test, as appropriate, were used to examine differences in continuous variables. To detect independent differences in outcome variables between those who received and those who did not receive hydroxychloroquine, multivariate logistic regression analysis models (for categorical outcomes) and general linear models (for length of stay) were run after adjusting for the variables that were significantly associated with hydroxychloroquine in univariate analysis. All P-values were two-tailed. P-value <0.05 was considered as significant. SPSS software (release 25.0, Armonk, NY: IBM Corp) was used for all statistical analyses.

Results

A total 267 patients have been included in the current analysis; 185 (69.3%) on hydroxychloroquine and 82 (30.7%) on non-hydroxychloroquine treatments. As shown in Table 1, the average age was 46.0±13.3 years and 78.3% of the patients were males. More than half (53.6%) of the patients were from Asian countries while Saudi patients represented less than a quarter

Table 1. Socio-demographic characteristics and exposure history of patients with confirmed COVID-19 by the treatment status

	Hydroxychloroquine		Total	P-value
	No	Yes		
Age (years)				
Mean±SD	44.0±14.0	47.0±12.8	46.0±13.3	0.093
<35	29 (35.8%)	33 (18.6%)	62 (24.0%)	0.017
35-44	15 (18.5%)	41 (23.2%)	56 (21.7%)	
45-54	15 (18.5%)	53 (29.9%)	68 (26.4%)	
≥55	22 (27.2%)	50 (28.2%)	72 (27.9%)	
Gender				
Male	60 (73.2%)	149 (80.5%)	209 (78.3%)	0.178
Female	22 (26.8%)	36 (19.5%)	58 (21.7%)	
Nationality				
Saudi	16 (19.5%)	46 (24.9%)	62 (23.2%)	0.084
Arab	24 (29.3%)	32 (17.3%)	56 (21.0%)	
Asia	39 (47.6%)	104 (56.2%)	143 (53.6%)	
Others	3 (3.7%)	3 (1.6%)	6 (2.2%)	
Employment				
Currently employed	20 (24.4%)	32 (17.3%)	52 (19.5%)	0.002
Not working	21 (25.6%)	31 (16.8%)	52 (19.5%)	
Retired	0 (0.0%)	2 (1.1%)	2 (0.7%)	
Umrah	6 (7.3%)	2 (1.1%)	8 (3.0%)	
Unknown	35 (42.7%)	118 (63.8%)	153 (57.3%)	
Exposure				
Recent travel within 14 days of symptoms	10 (12.2%)	11 (5.9%)	21 (7.9%)	0.080
Contact with patients with confirmed COVID-19	25 (30.5%)	74 (40.0%)	99 (37.1%)	0.138
Other characteristics				
Healthcare workers (HCWs)	4 (4.9%)	8 (4.3%)	12 (4.5%)	>0.99
Smoking	9 (11.0%)	36 (19.5%)	45 (16.9%)	0.088
Pregnancy	2 (9.1%)	0 (0.0%)	2 (3.4%)	0.140

Table 2. Clinical characteristics at admission among patients with confirmed COVID-19 by the treatment status

	Hydroxychloroquine		Total	P-value
	No	Yes		
Comorbidity				
None	54 (65.9%)	99 (53.5%)	153 (57.3%)	0.081
One	17 (20.7%)	40 (21.6%)	57 (21.3%)	
Two or more	11 (13.4%)	46 (24.9%)	57 (21.3%)	
Type of comorbidity				
Hypertension	14 (17.1%)	49 (26.5%)	63 (23.6%)	0.095
Diabetes	16 (19.5%)	66 (35.7%)	82 (30.7%)	0.008
Chronic lung disease	0 (0.0%)	6 (3.2%)	6 (2.2%)	0.182
Heart disease	4 (4.9%)	9 (4.9%)	13 (4.9%)	>0.99
Symptoms				
Asymptomatic	9 (11.0%)	2 (1.1%)	11 (4.1%)	0.001
Symptomatic	73 (89.0%)	183 (98.9%)	256 (95.9%)	
Type of symptoms				
Fever	51 (62.2%)	123 (66.5%)	174 (65.2%)	0.497
Cough	43 (52.4%)	144 (77.8%)	187 (70.0%)	<0.001
Shortness of breath	13 (15.9%)	76 (41.1%)	89 (33.3%)	<0.001
Chest pain	2 (2.4%)	2 (1.1%)	4 (1.5%)	0.589
Nausea or vomiting	8 (9.8%)	11 (5.9%)	19 (7.1%)	0.264
Diarrhea	6 (7.3%)	9 (4.9%)	15 (5.6%)	0.404
Severity of symptoms				
Asymptomatic	9 (11.0%)	2 (1.1%)	11 (4.1%)	<0.001
Mild	50 (61.0%)	85 (45.9%)	135 (50.6%)	
Moderate	21 (25.6%)	66 (35.7%)	87 (32.6%)	
Severe	2 (2.4%)	20 (10.8%)	22 (8.2%)	
ARDS	0 (0.0%)	12 (6.5%)	12 (4.5%)	
Chest imaging findings				
Unremarkable	49 (59.8%)	37 (20.1%)	86 (32.3%)	<0.001
Findings detected	33 (40.2%)	147 (79.9%)	180 (67.7%)	
Other related examinations				
Systolic BP (mm Hg)	124.6±13.3	125.6±13.2	125.3±13.2	0.546
Diastolic BP (mm Hg)	77.0±8.3	76.5±9.6	76.7±9.2	0.728
Temperature (C°)	37.2±0.7	37.4±0.7	37.4±0.7	0.035
Oxygen saturation at room air	97.0±3.2	94.0±6.7	94.9±6.0	<0.001
Hemoglobin (g/dl)	13.6±2.3	12.7±2.1	13.0±2.2	0.009
White blood cell count (x10 ^9/L)	6.7±3.2	7.3±3.4	7.1±3.3	0.163
Absolute lymphocyte count (x10 ^9/L)	2.0±1.3	1.7±1.4	1.8±1.4	0.186
Platelet count (x10 ^9/L)	248.7±124.3	251.0±112.3	250.3±115.8	0.884
C-reactive protein (mg/dL)	1.6 (0.4-9.1)	7.5 (3.0-13.2)	6.7 (1.5-11.8)	0.001
Creatinine (mg/dL)	0.9 (0.7-1.1)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.053
D.dimer (mg/L)	0.6 (0.3-1.3)	0.9 (0.5-1.5)	0.8 (0.5-1.4)	0.076
Ferritin (ug/L)	311(102-668)	634(334-1159)	517(254-1031)	0.001
QTc duration (ms)	406.5±27.7	417.7±44.0	414.8±40.6	0.121

ARDS, acute respiratory distress syndrome

(23.2%). One-fifth (19.5%) of the patients were currently employed and only 4.5% were healthcare workers (HCWs). Approximately 16.9% of the patients were smokers and only 3.4% of the females were pregnant. Contact with patients with confirmed COVID-19 (37.1%) was much more common than recent travel within 14 days of symptoms (7.9%). Compared with no hydroxychloroquine, those who received hydroxychloroquine were more likely to be between 35 and 54 years and with unknown employment status.

Table 2 shows the clinical characteristics of the patients at admission. Approximately 42.7% of the patients had one or more comorbid disease, specially diabetes (30.7%) and hypertension (23.6%). The majority (95.9%) of the patients were symptomatic; with mainly cough (70.0%), fever (65.2%), and shortness of breath (33.3%). The severity ranged between mild (50.6%), moderate (32.6%), severe (8.2%), or ARDS symptoms (4.5%). Approximately two-thirds (67.7%) of chest imaging were abnormal (mainly opacities and consolidations). The average temperature was 37.4±0.7 C°, oxygen saturation was 94.9%±6.0% at room air, and QTc duration was 414.8±40.6. Median C-reactive protein (CRP) was 6.7 (1.5-11.8) mg/dL and ferritin was 517 (254-1031) ug/L. Compared with no hydroxychloroquine, those who received hydroxychloroquine were more likely to be symptomatic and have cough, shortness of breath, severer form of disease, diabetes, abnormal chest imaging, higher temperature, lower oxygen saturation at room air, lower hemoglobin, higher CRP, and higher ferritin at admission.

Irrespective of hydroxychloroquine, patients included in the study were receiving azithromycin (73.0%), supportive treatment (48.7%), antivirals (17.6%), and zinc (9.0%). Table 3 shows the clinical characteristics of the patients after receiving hydroxychloroquine or non-hydroxychloroquine treatments. Approximately 58.8% of the patients were still symptomatic. Approximately 10.9% of the patients still had severe disease or ARDS. Approximately 60.0% of chest imaging was still abnormal. The average temperature slightly decreased to 37.1±0.4 C° and oxygen saturation slightly increased to 96.5%±3.3% at room air. Compared with no hydroxychloroquine, those who received hydroxychloroquine were more likely to use azithromycin, still symptomatic with more fever, cough, and shortness of breath, have severer form of disease, abnormal chest imaging, lower levels of oxygen saturation at room air and hemoglobin, and higher levels of white blood cell (WBC) count, platelet count, creatinine, D-dimer, and ferritin after receiving hydroxychloroquine.

As shown in Table 4, patients experienced clinical improvement mainly in symptoms (83.5%), disease severity (47.9%), and to less extent chest imaging (10.6%) after receiving hydroxychloroquine or non-hydroxychloroquine treatments. The average length of stay was 10.4±6.6 days. Approximately 18.7% of the patients required ICU admission, 9.7% required intubation, 2.6% required inotropic support, and 5.2% died during admission. Compared with no hydroxychloroquine, those on hydroxychloroquine had significantly longer length of stay (11.5±7.1 versus 7.8±4.3 days, $p<0.001$), more ICU admission (22.7% versus 9.8%, $p=0.012$), and more intubation (12.4% versus 3.7%, $p=0.026$). The difference in ICU admission and intubation but not length of stay disappeared after stratification by disease severity and to less extent by the presence of comorbidity (data not shown).

Table 5 shows the results of multivariate analysis of study outcomes. With two exceptions, patients who received hydroxychloroquine had generally similar outcomes compared with those who received non-hydroxychloroquine treatments after adjusting for several factors that were significantly different between the two groups in univariate analysis (Tables 1 through 4). Nevertheless, the length of stay was significantly longer (9.8±2.4 versus 7.6±2.0, $p=0.006$) and the improvement in chest imaging was significantly lower (odds ratio was 0.02, 95% CI 0.001-0.20, $p=0.001$) among patients who received hydroxychloroquine compared with those who received non-hydroxychloroquine treatments.

Discussion

The current study examined the efficacy and safety of hydroxychloroquine among admitted patients with COVID-19 of different disease severity. The findings showed that hydroxychloroquine was the second most commonly used single medication (69.3%) after azithromycin (73.0%). It was used approximately

Table 3. Clinical characteristics after using hydroxychloroquine among patients with confirmed COVID-19 by the treatment status

	Hydroxychloroquine		Total	P-value
	No	Yes		
Other medication				
Azithromycin	45 (54.9%)	150 (81.1%)	195 (73.0%)	<0.001
Lopinavir/ritonavir (Kaletra)	16 (19.5%)	27 (14.6%)	43 (16.1%)	0.313
Oseltamivir (Tamiflu)	2 (2.4%)	2 (1.1%)	4 (1.5%)	0.589
Zinc	8 (9.8%)	16 (8.6%)	24 (9.0%)	0.770
Supportive treatment	45 (54.9%)	85 (45.9%)	130 (48.7%)	0.178
Symptoms				
Asymptomatic	43 (52.4%)	67 (36.2%)	110 (41.2%)	0.013
Symptomatic	39 (47.6%)	118 (63.8%)	157 (58.8%)	
Type of symptoms				
Fever	1 (1.2%)	17 (9.2%)	18 (6.7%)	0.017
Cough	3 (3.7%)	32 (17.3%)	35 (13.1%)	0.002
Shortness of breath	4 (4.9%)	32 (17.3%)	36 (13.5%)	0.006
Nausea or vomiting	0 (0.0%)	1 (0.5%)	1 (0.4%)	>0.99
Diarrhea	0 (0.0%)	2 (1.1%)	2 (0.7%)	>0.99
Severity of symptoms				
Asymptomatic	43 (52.4%)	67 (36.2%)	110 (41.2%)	0.033
Mild	29 (35.4%)	69 (37.3%)	98 (36.7%)	
Moderate	7 (8.5%)	23 (12.4%)	30 (11.2%)	
Severe	2 (2.4%)	10 (5.4%)	12 (4.5%)	
ARDS	1 (1.2%)	16 (8.6%)	17 (6.4%)	
Chest imaging findings				
Unremarkable	39 (79.6%)	33 (25.2%)	72 (40.0%)	<0.001
Findings detected	10 (20.3%)	98 (74.8%)	108 (60.0%)	
Other related examinations				
Systolic BP (mm Hg)	121.9±7.6	121.2±8.8	121.4±8.5	0.595
Diastolic BP (mm Hg)	75.1±7.6	74.9±8.8	74.9±8.5	0.863
Temperature (C°)	37.0±0.3	37.1±0.5	37.1±0.4	0.144
Oxygen saturation at room air (%)	97.5±2.4	96.1±3.5	96.5±3.3	0.010
Hemoglobin (g/dl)	13.6±2.3	12.7±2.1	13.0±2.2	0.009
White blood cell count (x10 ^9/L)	6.7±3.4	8.7±5.6	8.1±5.1	0.011
Absolute lymphocyte count (x10 ^9/L)	2.4±1.7	2.1±1.8	2.2±1.8	0.478
Platelet count (x10 ^9/L)	288.1±150.8	354.4±149.9	335.0±152.8	0.005
C-reactive protein (CRP, mg/dL)	2.5 (0.9-11.9)	6.2 (2.4-11.8)	5.3 (1.5-11.6)	0.118
Creatinine (mg/dL)	0.8 (0.7-1.0)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.018
D.dimer (mg/L)	0.8 (0.2-1.2)	1.2 (0.7-4.3)	1.0 (0.6-3.1)	0.018
Ferritin (ug/L)	346(178-769)	771(370-1248)	691(301-1140)	0.021

ARDS, acute respiratory distress syndrome

Table 4. Study outcomes among patients with confirmed COVID-19 by treatment status

	Hydroxychloroquine		Total	P-value
	No	Yes		
Improved symptoms	67 (81.7%)	156 (84.3%)	223 (83.5%)	0.595
Reduced severity	42 (51.2%)	86 (46.5%)	128 (47.9%)	0.475
Improved chest imaging	8 (16.3%)	11 (8.5%)	19 (10.6%)	0.128
Length of stay (days)	7.8±4.3	11.5±7.1	10.4±6.6	<0.001
Length of stay (days)	7 (5-9)	10 (7-14)	9 (6-13)	<0.001
ICU admission	8 (9.8%)	42 (22.7%)	50 (18.7%)	0.012
Intubation	3 (3.7%)	23 (12.4%)	26 (9.7%)	0.026
Inotropic support	0 (0.0%)	7 (3.8%)	7 (2.6%)	0.104
Death	1 (1.2%)	13 (7.0%)	14 (5.2%)	0.071

Table 5. Adjusted outcomes* (multivariate analysis) among patients with confirmed COVID-19 who received hydroxychloroquine compared with those who received non-hydroxychloroquine treatments

	Odds ratio (OR)	95% confidence interval of OR		P-value	Adjusted R-square
		Lower	Upper		
Improved symptoms	1.14	0.42	3.10	0.797	0.280
Reduced severity	0.58	0.27	1.21	0.146	0.305
Improved chest imaging	0.02	0.001	0.20	0.001	0.499
ICU admission	1.02	0.39	2.69	0.967	0.215
Intubation	1.76	0.37	8.49	0.480	0.351
Inotropic support	>10	0.00	.	0.996	0.325
Death	1.04	0.07	15.66	0.978	0.575
		Hydroxychloroquine		Total	P-value
		No	Yes		
Length of stay (days)		7.6±2.0	9.8±2.4	8.6±2.5	0.006

* Adjusted for age, employment status, diabetes, symptoms (cough and shortness of breath), temperature, severity of disease, oxygen saturation at room air, chest imaging findings, use of azithromycin, and levels of hemoglobin and creatinine.

four-folds higher than all antiviral medications. The heavy use of hydroxychloroquine is probably reflecting the MOH guidelines at the time of study (March through May) which placed hydroxychloroquine as a first-line drug for all patients (mild to ARDS) while adding antivirals for severe and critical patients [14]. The high use of hydroxychloroquine underscores the importance of reviewing local efficacy and safety data.

The patients in the current study experienced a significant clinical improvement specially in symptoms and disease severity after treatment. However, hydroxychloroquine was not associated with better clinical improvement (including symptoms and severity) than non-hydroxychloroquine treatments in both univariate and multivariate analysis. On the other hand, improvement of chest imaging was significantly slower among those receiving hydroxychloroquine. Consistent with current findings, meta-analysis studies could not detect significant clinical improvement (mainly symptoms) in patients receiving hydroxychloroquine [16-18]. However, the results of these studies were conflicting as regards the ability of hydroxychloroquine to limit the radiologic progression [17-19]. Variability may be related to the difference in disease severity and time of re-assessment of chest imaging in different study designs.

Hydroxychloroquine in the current study was associated with longer length of stay in both univariate and multivariate analysis. Similarly, hydroxychloroquine with or without azithromycin was associated with longer length of stay in both univariate and multivariate analysis in a retrospective cohort design [20]. However, most of the previous studies either did not focus on the length of stay as an outcome or could not find benefit of hydroxychloroquine on the length of stay [21, 22]. It should be mentioned that the length of stay may be easily affected by the hospital capacity and discharge polices [20].

The patients in the current study who were receiving hydroxychloroquine experienced negative outcomes including ICU admission and intubation, which largely disappeared in multivariate analysis adjusted for several factors including disease severity and concomitant use of azithromycin. This finding may indicate that the above negative outcomes were not caused by hydroxychloroquine itself but rather by the difference between treatment groups as regards clinical picture, severity, and other received treatments. Similarly, previous studies could not detect any significant increase in ICU admission or intubation in patients receiving hydroxychloroquine [19, 21, 23].

The current study showed that hydroxychloroquine was associated with an insignificant increase in mortality that completely disappeared in multivariate analysis. Previous studies examining the impact of hydroxychloroquine on all-cause mortality were conflicting and probably changing overtime. For example, earlier meta-analysis reports that included few studies published before the end of April 2020 showed a significant increase in mortality among patients receiving hydroxychloroquine, with risk ratios above two [19, 24]. However, the majority of include studies were observation with high level of heterogeneity due to variable doses, disease severity, and concomitant treatments. Later meta-analysis reports that included more recent studies published up to June or July 2020 found no significant increase in mortality among patients receiving hydroxychloroquine [16, 17, 25, 26]. A recent local prospective cohort study (pre-review publication) showed that hydroxychloroquine was associated with lower hospital admission and mortality among outpatients with mild-moderate COVID-19 symptoms [27]. The apparently conflicting finding may underscore the variability of the outcome by the type of patient and severity of the disease. Interestingly, a two recent report showed a significant increase in mortality only among patients who were receiving both hydroxychloroquine and azithromycin [25, 26]. Consistently, a sub-analysis of the current data showed that this group had the worst outcome in univariate analysis, probably because physicians were reserving hydroxychloroquine/azithromycin combination for severe/critical patients (data not shown). Additionally, adjustment for concomitant azithromycin use was a major factor that pushed the adjusted odds ratio for mortality towards null.

The current study is considered the first study in Saudi Arabia to comprehensively examine the efficacy and safety of hydroxychloroquine in admitted patients. The study used a prospective multi-hospital design, included patients with different severity, and reported both univariate and multivariate analysis. Nevertheless,

we acknowledge a number of limitations. The lack of randomization may have introduced selection bias. However, the observational design allowed for evaluation of actual treatment practices while adjusting for group differences at admission in multivariate analysis. The concomitant use of other types of treatments represented an important confounding factor for the current outcomes. However, it is probably unethical to deprive patients from other potential treatments at the time of pandemic with limited therapeutic information. Additionally, this has been adjusted for in multivariate analysis.

In conclusion, hydroxychloroquine have been heavily used to treat patients with COVID-19 admitted to general hospitals in Saudi Arabia during the time of the study. Hydroxychloroquine was not associated with better clinical improvement and it was associated with longer length of stay. The observed univariate associations between hydroxychloroquine and negative outcomes such as ICU admission, intubation, and may be mortality can be can be largely explained by the differences between treatment groups in clinical severity and other received treatments. The current findings represent a significant addition to the debate about hydroxychloroquine use in COVID-19 pandemic.

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Statement

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