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Original article

Comparing the impact of Hydroxychloroquine based regimens and standard treatment on COVID-19 patient outcomes: A retrospective cohort study

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ABSTRACT

Background: Pharmacological treatments including antivirals (Lopinavir/Ritonavir), Immuno-modulatory and anti-inflammatory drugs including, Tocilizumab and Hydroxychloroquine (HCQ) has been widely investigated as a treatment for COVID-19.

Despite the ongoing controversies, HCQ was recommended for managing mild to moderate cases in Saudi Arabia . However, to our knowledge, no previous studies have been conducted in Saudi Arabia to assess its effectiveness.

Methods: A hospital-based retrospective cohort study involving 161 patients with COVID-19 was conducted from March 1 to May 20, 2020. The study was conducted at Prince Mohammed bin Abdul Aziz Hospital (PMAH).

The population included hospitalized adults (age $\geq$ 18 years) with laboratory-confirmed COVID-19. Each eligible patient was followed from the time of admission until the time of discharge. Patients were classified into two groups according to treatment type: in the HCQ group, patients were treated with HCQ; in the SC group, patients were treated with other antiviral or antibacterial treatments according to Ministry of Health (MOH) protocols.

The outcomes were hospitalization days, ICU admission, and the need for mechanical ventilation.

We estimated the differences in hospital length of stay and time in the ICU between the HCQ group and the standard care (SC) group using a multivariate generalized linear regression. The differences in ICU admission and mechanical ventilation were compared via logistic regression. All models were adjusted for age and gender variables.

Results: A total of 161 patients fulfilled the inclusion criteria. Approximately 59% (n = 95) received HCQ-based treatment, and 41% (n = 66) received SC. Length of hospital stay and time in ICU in for patients who received HCQ based treatment was shorter than those who received SC. Similarly, there was less need for ICU admission and mechanical ventilation among patients who received HCQ based treatment compared with SC, (8.6% vs. 10.7 and 3.1% vs. 9.1%). However, the regression analysis showed no significant difference between the two groups in terms of patient outcomes.

Conclusion: HCQ had a modest effect on hospital length stay and days in ICU compared with SC. However, these results need to be interpreted with caution. Larger observational studies and

Abbreviations: COVID-19, Coronavirus Disease 2019; HCQ, Hydroxychloroquine; HESN, Health Electronic Surveillance Network; MOH, Ministry of Health; WHO, World health organization; SC, Standard care; PMAH, Prince Mohammed bin Abdul Aziz Hospital; ICU, intensive care unit.

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RCTs that evaluate the efficacy of HCQ in COVID-19 patients in the Saudi population are urgently needed.

1. Introduction

The World Health Organization (WHO) announced Coronavirus Disease 2019 (COVID-19) at the beginning of 2020, naming it a public health emergency of international concern (World Health Organization. WHO, 2020; World Health Organization. WHO, 2020; World Health Organization. WHO, 2020). As of July 2nd, 2020, the WHO has reported a total of 10,533,779 confirmed cases and 512,842 deaths (World Health Organization. WHO, 2020; World Health Organization. WHO, 2020; World Health Organization. WHO, 2020). COVID-19 has been associated with a substantial symptomatic burden, including dyspnea that leads to death due to respiratory and heart failure (Keeley et al., 2020). The economic burden of such a pandemic is also troublesome. In the United States, the direct medial cost for one patient is $3,045 per infection course (Bartsch et al., 2020). If 80% of the U.S. population becomes infected, the total direct medical cost will be approximately $654 billion. Direct medical costs are mainly incurred via hospitalization, intensive care unit (ICU) admissions, and ventilator use. The burden of COVID-19 therefore extends beyond health care and affects the societal and national economies of affected countries (Keni et al., 2020).

Because COVID-19 is an emerging disease, treatment protocols and guidelines are being developed and updated rapidly (National Institutes of Health, 2020; World Health Organization. WHO, 2020; World Health Organization. WHO, 2020; World Health Organization. WHO, 2020). Several observational and interventional studies have evaluated the effectiveness of various pharmacological treatments for COVID-19(Matera et al., 2020; Siemieniuk et al., 2020).

The main therapies being used to treat COVID-19 are antiviral drugs which include Remdesivir and Lopinavir/Ritonavir combination which inhibits viral protease (Pascarella et al., 2020). Other treatments such as respiratory therapy which delivers oxygen in case of hypoxia or symptoms of respiratory distress.

Chloroquine and Hydroxychloroquine (HCQ) is among the promising treatment modalities for COVID-19 patients (Chen et al., 2020; Geleris et al., 2020; Rosenberg et al., 2020; Shen et al., 2020). HCQ is an antimalarial drug that have been used for decades to treat autoimmune diseases such as systemic lupus erythromatus (SLE) and rheumatoid arthritis (RA) (Ponticelli and Moroni, 2017). HCQ work by increasing the endosomal pH and thus enhancing the fusion between the virus and host cell (Pascarella et al., 2020). In addition, it has some immunomodulatory effect by interfering with the ACE2 cell receptors. The recommended regimen is to start with a loading dose of 400 mg BID for the first day followed by 200 mg BID (Colson et al., 2020).

The common side effects include nausea, vomiting and diarrhea. Arrhythmogenic cardiotoxicity was also associated with the use of HCQ, which require QT interval monitoring.

Several in vitro studies demonstrated the antiviral efficacy of HCQ (Yao et al., 2020)

Not only have in vitro studies suggested HCQ's activity against the SARS-CoV-2 virus, but observational studies have also suggested its effectiveness in COVID-19 patients (Mahévas et al., 2020). Several ongoing clinical trials are aimed at examining the efficacy and safety of HCQ in COVID-19 patients (clinicaltrials.gov, 2020). Despite the large number of studies assessing the effectiveness of HCQ, evidence is still limited and inconclusive (Pascarella et al., 2020).

On March 19, 2020, the Saudi Ministry of Health (MOH) issued the first protocol for treating adults with a confirmed diagnosis of COVID-19 (Saudi MOH and CDC, 2020). In this version, HCQ was one of the recommended treatments for mild to moderate cases of the disease. For severe cases, the protocol still recommends HCQ, but alternatives such as lopinavir/ritonavir can also be used (Saudi MOH and CDC, 2020). Despite the recommendation to use HCQ in COVID-19 patients in the MOH protocol, no observational studies or RCTs that evaluate the efficacy of these drugs in the Saudi Arabian population have been published. Therefore, the objective of this observational study is to compare the effects of HCQ and standard care (SC) on length of hospital stay, ICU admission, and mechanical ventilation use among COVID-19 patients.

2. Methods

2.1. Study design

A hospital-based cohort study involving 161 confirmed cases of patients with COVID-19 was conducted retrospectively from March 1, 2020, to May 20, 2020. The STROBE guideline for cohort studies was followed (von Elm et al., 2014).

2.2. Study setting

We conducted the study at Prince Mohammed bin Abdul Aziz hospital (PMAH), an infectious disease center in Riyadh ("Prince Mohammed bin Abdulaziz Hospital (PMAH)," 2020). In the response to the COVID-19 pandemic, this hospital was among the leading hospitals designated as COVID-19 centers. As such, patients with COVID-19 symptoms were escorted to this hospital.

2.3. Study population

The population included hospitalized males and females (age $\geq$ 18 years) with laboratory-confirmed COVID-19 infections. Each eligible patient was followed from the time of admission until the time of discharge. To be included, patients had to be treated for COVID-19 in the hospital. Patients were classified into two groups according to treatment type: in the HCQ group, patients were treated with HCQ; in the SC group, patients were treated with other antiviral or antibacterial treatments according to MOH protocols (Saudi Ministry of Health (MOH), 2020; Saudi Ministry of Health (MOH) and The Saudi Center for Disease Prevention and Control (CDC), 2020).

Patients who were transferred to other facilities, had incomplete or missing data, or received supportive treatment that only included analgesics were excluded from the final dataset.

2.4. Data sources

Data were collected from patients' medical records by trained medical personnel. Collected data included patients' basic information (e.g. age, gender, nationality); medication prescribed; and information on hospitalization, cases requiring ICU care, and mechanical ventilation. A well-designed, organized checklist was

used to obtain and extract necessary information from patients' medical records.

2.5. Outcomes of interest

The primary outcomes of interest for this study were hospital length of stay (number of days from the patient's arrival at the hospital until discharge) and time in ICU (calculated as the number of calendar days from the day of admission to the day of discharge). We also assessed the patients' need for ICU care and mechanical ventilation.

2.6. Statistical analysis

Data were cleaned, edited, and entered into SAS version 9.4 for analysis. Descriptive data were reported for dichotomous polychotomous frequencies and percentages to examine the distribution of study variables among members of the HCQ and SC groups. A chi-square test was utilized to compare categorical variables between groups. Continuous variables were presented as means ± standard deviation (SD) and/or median with interquartile range (IQR). We estimated the differences in length of hospital stay and time in ICU between the two groups using a multivariate generalized linear model regression. The differences in the need for ICU admission and mechanical ventilation were compared via logistic regression. All models were adjusted for age and gender variables. No imputation was performed for all tests, and statistical significance was considered at a P-value of less than 0.05.

2.7. Ethical considerations

Ethical clearance was obtained from the Institutional Review Board (IRB) at King Fahad Medical City with IRB log No. 20–376. Hospital management's permission was obtained to conduct this study. The information and data collected were kept confidential. This study included no personal information or identifiers such as names or ID number.

3. Results

A total of 161 patients fulfilled the inclusion criteria and were included in the study. A total of 57 regimens were prescribed for these patients. In the HCQ group, HCQ, azithromycin, and ceftriaxone comprised the most prescribed regimen (26%), whereas in the SC group, an azithromycin and ceftriaxone regimen accounted for 36% of the participants (see Appendix A1 for additional information).

Approximately 59% of patients received HCQ based treatment, and 41% received SC treatment. No differences were observed between the two groups with respect to age, whereas the number of male and non-Saudi patients were more in the HCQ group (p = 0.016 and p = 0.021, respectively). Table 1 illustrates the demographic characteristics of the included study patients.

Length of hospital stay and time in ICU in for patients who received HCQ based treatment was shorter than those who received SC. Similarly, there was less need for ICU admission and mechanical ventilation among patients who received HCQ based treatment compared with SC, (8.6% vs. 10.7 and 3.1% vs. 9.1%), respectively; see Table 2).

The results of the regression analyses after controlling for age and gender are shown in Table 3. Despite the shorter length of hospital stay and time in ICU among patients who received HCQ based treatment, as well as the smaller proportions of patients who needed ICU care and mechanical ventilation in this group, the results indicated no significant differences in these outcomes between the two cohorts. (See Table A1.)

Table 2
Comparison of outcomes between the HCQ and SC groups.

Outcome	HCQ based treatment (N = 95)	SC (N = 66)
Hospital length of stay, days*	6.4 ± 5.7	8.5 ± 10.7
	6 [1, 9]	6 [2, 11]
Time in ICU, days*	8.8 ± 4.3	9.4 ± 8.4
	9.5 [6.5, 12.5]	6 [4, 11]
ICU admission, n (%)	8 (8.6)	7 (10.7)
Mechanical ventilation, n (%)	3 (3.1)	6 (9.1)

*Data expressed as mean ± SD and median (IQR).
Abbreviations: HCQ, hydroxychloroquine; SC, Standard care; ICU, intensive care unit.

Table 3
Regression analyses results of the outcomes for HCQ based treatment vs. SC.

Outcome	Estimates	SE	P-value
Hospital length of stay	−2.12	1.31	0.107
Time in ICU, days	−0.55	3.39	0.873
ICU admission	−0.12	0.27	0.648
Mechanical ventilation	−0.56	0.36	0.122

A Adjusted for age and gender.
Abbreviations: ICU, intensive care unit.

4. Discussion

In this study, we employed a multivariate linear regression with adjustment for gender and age and found that treatment with HCQ was associated with shorter length of hospital stay and fewer days in ICU when compared with SC treatment. However, the difference

Table 1
Demographic characteristics of patients infected with COVID-19.

Characteristic	Total patients (N = 161)		HCQ-based treatment (N = 95, 59%)		SC (N = 66, 41%)		P-value
	n	%	n	%	n	%	
Age, years							0.856
less than 30	33	20.5	19	20	14	21.21	
30–50	99	61.49	60	63.16	39	59.09	
> 50	29	18.01	16	16.84	13	19.7	
Gender							0.016
Female	49	30.43	22	23.16	27	40.91	
Male	112	69.57	73	76.84	39	59.09	
Nationality							0.021
Non Saudi	118	73.29	76	80	42	63.64	
Saudi	43	26.71	19	20	24	36.36	

Abbreviations: HCQ, hydroxychloroquine; SC, Standard care; ICU, intensive care unit.

Table A1
Treatment regimens for patients infected with COVID-19.

Treatment regimens	HCQ based (N = 95)		SC (N = 66)	
	n	%	n	%
Tazocin	0	0	1	1.52
Azithromycin	0	0	12	18.18
Azithromycin, tazocin	0	0	1	1.52
Azithromycin, tazocin, vancomycin	0	0	1	1.05
Azithromycin, ceftriaxone	0	0	24	36.36
Azithromycin, ceftriaxone, tazocin	0	0	1	1.52
Azithromycin, ceftriaxone, doxycycline	0	0	1	1.52
Azithromycin, ceftriaxone, doxycycline, tazocin, moxifloxacin	0	0	1	1.52
Azithromycin, ceftriaxone, levofloxacin, moxifloxacin	0	0	1	1.52
Azithromycin, ceftriaxone, piperacillin/tazobactam	0	0	1	1.52
Azithromycin, cefuroxime	0	0	1	1.52
Ceftriaxone	0	0	11	16.67
Ceftriaxone, doxycycline	0	0	3	4.55
Hydroxychloroquine	6	6.32	0	0
Hydroxychloroquine, tazocin, moxifloxacin	1	1.05	0	0
Hydroxychloroquine, azithromycin	9	9.47	0	0
Hydroxychloroquine, azithromycin, tazocin	4	4.21	0	0
Hydroxychloroquine, azithromycin, tazocin, vancomycin, meropenem	1	1.05	0	0
Hydroxychloroquine, azithromycin, cefepime	3	3.16	0	0
Hydroxychloroquine, azithromycin, cefepime, piperacillin/tazobactam, tazocin	1	1.05	0	0
Hydroxychloroquine, azithromycin, cefepime, linezolid	1	1.05	0	0
Hydroxychloroquine, azithromycin, cefepime, linezolid, levofloxacin, piperacillin/tazobactam	1	1.05	0	0
Hydroxychloroquine, azithromycin, ceftriaxone	25	26.32	0	0
Hydroxychloroquine, azithromycin, ceftriaxone, tazocin	1	1.05	0	0
Hydroxychloroquine, azithromycin, ceftriaxone, cefepime, tazocin, vancomycin	1	1.05	0	0
Hydroxychloroquine, azithromycin, ceftriaxone, doxycycline	1	1.05	0	0
Hydroxychloroquine, azithromycin, ceftriaxone, piperacillin/tazobactam	1	1.05	0	0
Hydroxychloroquine, azithromycin, ceftriaxone, piperacillin/tazobactam, tazocin	1	1.05	0	0
Hydroxychloroquine, azithromycin, ceftriaxone, linezolid	1	1.05	0	0
Hydroxychloroquine, azithromycin, ceftriaxone, linezolid, tazocin	1	1.05	0	0
Hydroxychloroquine, azithromycin, ceftriaxone, linezolid, meropenem	1	1.05	0	0
Hydroxychloroquine, azithromycin, ceftriaxone, moxifloxacin	1	1.05	0	0
Hydroxychloroquine, azithromycin, doxycycline	1	1.05	0	0
Hydroxychloroquine, azithromycin, doxycycline, piperacillin/tazobactam, tazocin	1	1.05	0	0
Hydroxychloroquine, azithromycin, piperacillin/tazobactam	1	1.05	0	0
Hydroxychloroquine, azithromycin, piperacillin/tazobactam, tazocin	1	1.05	0	0
Hydroxychloroquine, azithromycin, vancomycin	1	1.05	0	0
Hydroxychloroquine, azithromycin, linezolid, piperacillin/tazobactam	1	1.05	0	0
Hydroxychloroquine, cefepime	2	2.11	0	0
Hydroxychloroquine, ceftriaxone	6	6.32	0	0
Hydroxychloroquine, ceftriaxone, tazocin	1	1.05	0	0
Hydroxychloroquine, ceftriaxone, cefepime	1	1.05	0	0
Hydroxychloroquine, ceftriaxone, doxycycline	6	6.32	0	0
Hydroxychloroquine, doxycycline	1	1.05	0	0
Hydroxychloroquine, levofloxacin, tazocin	1	1.05	0	0
Hydroxychloroquine, piperacillin/tazobactam	1	1.05	0	0
Hydroxychloroquine, piperacillin/tazobactam, tazocin, vancomycin	1	1.05	0	0
Hydroxychloroquine, linezolid	1	1.05	0	0
Hydroxychloroquine, linezolid, piperacillin/tazobactam	1	1.05	0	0

Treatment regimens	HCQ based (N=95)		SC (N=66)	
	n	%	n	%
Oseltamivir	0	0	5	7.58
Oseltamivir, azithromycin	0	0	1	1.52
Oseltamivir, azithromycin, levofloxacin	0	0	1	1.52
Oseltamivir, ceftriaxone	0	0	1	1.52
Oseltamivir, hydroxychloroquine	0	0	1	1.05
Oseltamivir, hydroxychloroquine, ceftriaxone	0	0	1	1.05
Piperacillin/tazobactam, vancomycin	0	0	1	1.52
Cefuroxime	0	0	1	1.52

was not significant. In addition, the percentage of patients who required ICU admission and mechanical ventilation was lower in the HCQ group than in the SC group, but the difference was not significant.

Our results were consistent with those of other observational studies. For instance, a retrospective cohort study was conducted at New York-Presbyterian Hospital (NYP)–Columbia University Irving Medical Center (CUIMC) and published in NEJM (Geleris et al., 2020). In this study, the outcomes were intubation rate and death rate (Geleris et al., 2020). HCQ use was not associated with a significant decrease in intubation or death (Geleris et al., 2020). The second study that evaluated the effectiveness of HCQ in COVID-19 patients was a systematic review that evaluated the efficacy of HCQ based on peer reviewed articles and preprint studies. HCQ showed controversial results among studies (Das et al., 2020). In conclusion, our study results are consistent with other observational studies on the effectiveness of HCQ in COVID-19 patients.

Generally, the effectiveness of pharmacological treatments of COVID-19 including antivirals such as Remdesivir and lopinavir/ritonavir, Chloroquine and Hydroxychloroquine is limited and inconclusive (Cortegiani et al., 2020; Das et al., 2020; Siemieniuk et al., 2020). This is mainly due to small sample size of most studies, lack of randomization and potential risk of selection bias (Pascarella et al., 2020).

According to a recently published *meta*-analysis which aim to assess the effectiveness of pharmacological intervention in COVID-19 (Siemieniuk et al., 2020). The only promising treatment that demonstrated a substantial impact on mortality, length of stay and mechanical ventilation is glucocorticoids. However, glucocorticoid are only recommended for COVID-19 patients having severe acute respiratory distress syndrome (ARDS) (Ye et al., 2020). The potential benefits of glucocorticoid for patients with no symptoms of ARDS is still inconclusive (Matera et al., 2020).

4.1. Strengths and limitations

To our knowledge, this is the first study in Saudi Arabia that clearly describes treatment options for COVID-19 patients. Other published studies in Saudi Arabia mainly described patient characteristics with a minimal emphasis on treatments and outcomes (Alsofayan et al., 2020). The treatment options recommended by the MOH protocol (Saudi MOH and CDC, 2020) were summarized in a disaggregated method to fully understand the prescribing pattern of COVID-19 treatments. In addition, the choice of various outcomes, including hospitalization, ICU admission, and mechanical ventilations targeted various levels of disease severity and facilitated comparison with other published studies that used these outcomes to assess treatment success.

However, this study has some limitations. First, randomization was not feasible as this stage of study, which potentially limits the selection bias. Second, the study did not have sufficient power to detect any statistical difference due to small sample size. Therefore, inferential statistical analyses cannot capture the potential effect of the intervention.

Second, in Saudi Arabia, the MOH provides 60% of health care services, whereas other governmental sectors, including teaching hospitals, the Ministry of Defense, and security forces provide the remainder (Almalki et al., 2011). This diversity in the provision of health care generates some inevitable issues, including those related to the definition of SC and generalizability. The definition of SC for COVID-19 might vary considerably across various hospitals within the MOH and other referral hospitals. Moreover, this study recruited people from only one hospital; therefore, the sample might not be representative of people with COVID-19 throughout the kingdom.

4.2. Implications for policy and practice

COVID-19 treatment options and guidelines continue to evolve on a daily basis. Therefore, decision-makers need a dynamic source of data that captures such ongoing progress. The Health Electronic Surveillance Network (HESN) is a Web based platform managed by the MOH that records and analyzes infectious diseases and pandemic data (Saudi Ministry of Health MOH, 2020). The current use of the HESN is quite limited, as it only collects patient demographics and laboratory data (Alsofayan et al., 2020). Therefore, decision-makers should consider expanding the scope of such platforms to include treatment regimens and patient outcomes. In addition, decision-makers should mandate that all MOH and non-MOH hospitals register COVID-19 patients and record their treatments and outcomes on a daily basis. This will ultimately generate a valuable representative data source that could help clinicians, researchers, and decision-makers assess the impact of emerging treatments on patient outcomes.

In this study, The choice of Hydroxychloroquine and the comparators (mainly antivirals) was mainly informed by the MOH guidelines for managing COVD-19 patients (10). The guideline gave a range of therapeutic options according to the disease severity. Additionally, the guideline did not provide any preference as for 1st and 2nd line treatment. Therefore, it was left to the treating physician to start either with HCQ or antiviral. We believe that the selection of 1st line therapy was based on the availability of the medication and the potential side effect of HCQ which need to be used cautiously for patients with arrythmia. Future clinical practice guidelines should consider the cost, availability of medication, patient preference and potential side effect to ensure the consistency of clinical practice among different hospitals.

5. Conclusion

Despite that HCQ based regimens reduce hospitalization and ICU admission, the results were not statistically significant. This was mainly due to the small size. In addition, the study's participants were recruited from a single hospital, which limits the generalizability of our results. Larger observational studies and RCTs that evaluate the efficacy of HCQ in COVID-19 patients in the Saudi population are urgently needed.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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