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International Immunopharmacology 96 (2021) 107636

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting

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ARTICLE INFO

Keywords:
COVID-19
Outpatient
Hydroxychloroquine

ABSTRACT

The role of hydroxychloroquine (HCQ) in early outpatient management of mild coronavirus disease 2019 (COVID-19) needs further investigation.

This study was a multicenter, population-based national retrospective-cohort investigation of 28,759 adults with mild COVID-19 seen at the network of Comprehensive Healthcare Centers (CHC) between March and September 2020 throughout Iran. The baseline characteristics and outcome variables were extracted from the national integrated health system database.

A total of 7295 (25.37%) patients who presented with mild COVID-19 within 3–7 days of symptoms onset received HCQ (400 mg twice daily on day 1 followed by 200 mg twice daily for the next four days and were then followed for 14 days).

The main outcome measures were hospitalization or death for six months follow-up. COVID-19-related hospitalizations or deaths occurred in 523 (7.17%) and 27 (0.37%) respectively, in HCQ recipients and 2382 (11.10%) and 287 (1.34%) respectively, in non-recipients. The odds of hospitalization or death was reduced by 38% (odds ratio [OR] = 0.62; 95% confidence interval [CI]: 0.56–0.68, p = < 0.001) and 73% (OR = 0.27; 95% CI: 0.18–0.41, p = < 0.001) in HCQ recipients and non-recipients. These effects were maintained after adjusting for age, comorbidities, and diagnostic modality. No serious HCQ-related adverse drug reactions were reported.

In our large outpatient national cohort of adults with mild COVID-19 disease who were given HCQ early in the course of the disease, the odds of hospitalization or death was reduced significantly regardless of age or comorbidities.

1. Introduction

Since the start of human transmission of Severe Acute Respiratory Coronavirus-2 (SARS CoV-2) to date (February 5, 2021), the virus has claimed 2,265,354 out of 104,165,006 confirmed cases globally.[1] Despite experiencing a year of the pandemic and the development and

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https://doi.org/10.1016/j.intimp.2021.107636
Received 25 February 2021; Received in revised form 30 March 2021; Accepted 31 March 2021
Available online 6 April 2021

deployment of multiple vaccines, efforts to find effective treatment with outcome benefits in patients with coronavirus disease 2019 (COVID-19) have remained futile.

Hydroxychloroquine (HCQ) was one of the first medications that were repurposed for the treatment of COVID-19. Following the publication of *in-vitro* and non-randomized clinical studies, [2–3] HCQ use rapidly increased to the extent that it was prescribed for about 60% of hospitalized patients with COVID-19 in the United States in March 2020.3 This level decreased to 12% in May 2020 owing to the ineffectiveness of HCQ as shown in subsequent studies. [4–5] Nevertheless, the controversy concerning its efficacy continued until randomized clinical trials (RCTs), such as the randomized evaluation of COVID-19 therapy (RECOVERY) and Solidarity trials confirmed the lack of efficacy of HCQ in hospitalized patients with COVID-19. [6–7]

Currently, most guidelines, such as those from the National Institutes Health (NIH) and infectious diseases society of America (IDSA), recommend against the use of HCQ for hospitalized patients. [8–9] Besides, from the early onset of its use, there was a concern about a potential property of HCQ in QTc interval prolongation as demonstrated on electrocardiography (ECG) tracings, particularly in patients with a history of cardiovascular diseases. Some studies have shown an increased in the risk of arrhythmias and ECG abnormalities following administration of HCQ, especially in combination with azithromycin. [10–12]

However, with the publication of subsequent studies, this concern has been somewhat alleviated. [6,13–14] Taken together, these factors once again led to attention being paid to HCQ use in outpatient settings.

The first confirmed case of COVID-19 in Iran was diagnosed on February 18, 2020. [15] A scientific COVID-19 taskforce was promptly assembled by the Iranian Ministry of Health (MOH) and five days later, the first national protocol for the management of the COVID-19 in outpatient settings was developed.

On February 29, 2020, the responsibility for providing outpatient services to the COVID-19 patients across a vast span of communities in Iran was assigned to the Comprehensive Health Centers (CHCs). The extensive CHC network of 5500 centers is the main provider of primary healthcare in Iran. These centers work free of charge in 16- or 24-h rosters and cover both rural and urban populations. These centers are governed by their regional medical science universities and health services authorities under the jurisdiction of the MOH throughout the whole country. [16,17] The health information of more than 90% of the population in Iran is registered in an electronic network of health records that are maintained by these centers. Allocation of these CHCs to function as the main body for primary care, data collection, and registration centers for COVID-19 facilitates the screening and follow-up of these patients, especially in the high-risk populations.

In this large population-based study, we evaluated the clinical outcomes of mild COVID-19 patients who were treated with HCQ in an outpatient setting.

2. Methods

In this outpatient national retrospective cohort study, the clinical outcomes of patients with mild COVID-19 were followed in two main groups of patients who received or did not receive HCQ.

HCQ was added to the supportive care for patients with mild COVID-19 illness who did not require referral to the hospital. Based on the national COVID-19 protocol, the mild disease was defined as the presence of mild cough, body ache, loss of smell or taste, a body temperature of $\leq 38\ ^{\circ}C$, peripheral oxygen saturation (SpO2) $\geq 93\%$, and the absence of shortness of breath, altered hemodynamics, and mental status instability.

HCQ was provided to the patients who presented with no clear contraindications and were not using it for other indications. They were instructed to take 400 mg twice daily on day 1 followed by 200 mg twice daily from days 2 to 5 if they had presented within 3 to 7 days of the initiation of their COVID-19 symptoms.

Patients were followed daily for 5 days and then on day 14, either in-person or by phone, for their disease trajectory, outcome variables, and adverse HCQ-related drug reactions. Baseline characteristics and outcome variables of hospitalization or death for all patients were also collected from the national integrated health system database.

COVID-19 was diagnosed based on the clinical presentation and either reverse transcriptase-polymerase chain reaction (RT-PCR) results from nasopharyngeal swab samples following World Health Organization (WHO) protocols or chest imaging. The clinical outcomes of our study were COVID-19-related hospitalizations or deaths during six-months of follow up.

Continuous and categorical variables are shown as mean ± standard deviation (SD) and frequency (percentage), respectively. OR and 95% CI were estimated for comparison of outcomes of the patients who were treated or not treated with HCQ by binary logistic regression models. The effect of confounding variables, including age, sex, body mass index (BMI), hypertension, respiratory diseases, diabetes mellitus, and cardiovascular diseases, other than hypertension, on the incidence of outcomes was examined by adjusted logistic regression models. The selection of these factors was based on their effects on the clinical outcomes of the patients with mild to moderate COVID-19 as described in previous studies.[18]

$$\text{Odds ratio} = \frac{\text{odds of hospitalization in the patients treated with HCQ}}{\text{odds of hospitalization in the patients who did not treat with HCQ}} \quad \text{Probability} = \frac{\text{odds}}{1 + \text{odds}}$$

To calculate cost saving of HCQ administration, the probability of hospitalization was estimated using following formulas:

3. Results

From March 2020 to September 2020, the COVID-19 related data concerning a total of 28,759 patients who presented to the CHCs were included in the integrated health system for final analysis. COVID-19 diagnosis was made by clinical parameters and RT-PCR in 22,784 (79.22%) and clinical parameters and chest imaging in the remaining patients (Table 1). Upon presentation, evaluation, and a brief education about COVID-19 and possible HCQ adverse reaction, a total of 7295 (25.37%) patients with mild symptoms consented to receive and use HCQ as prescribed.

The mean age ± SD of the patients was 45 ± 15 and 46 ± 15 years old in those who received and did not receive HCQ, respectively. No significant gender differences in both groups were noted (Table 1). Hypertension, chronic respiratory diseases, and diabetes mellitus were the most common underlying reported diseases. Hospitalization for COVID-19 worsening was required in 7.17% and 11.1% of patients who received and did not receive HCQ, respectively. HCQ reduced the odds of hospitalization by 38% (OR = 0.62; 95% CI: 0.56–0.68, p-value=< 0.001).

A total of 314 patients died of COVID-19 complications, 27 (0.37%) and 287 (1.34%) in those who receive and did not receive HCQ respectively, indicating a 73% mortality risk reduction on logistic

Table 1
Baseline characteristics and clinical outcomes of the patients who received and did not receive hydroxychloroquine.

Variable	Received HCQ (N = 7295)	Did not receive HCQ (N = 21,464)	OR (95% CI)	P-Value
Demographic characteristics				
Median age (IQR) - yr	43 (33–57)	43 (33–58)	–	0.112
Age category - no. (%)				
≤65 yr	6424 (88.06)	18,557 (86.45)	–	0.001
>65 to ≤85 yr	825 (11.31)	2710 (12.63)	–	
>85 yr	46 (0.63)	197 (0.92)	–	
Sex - no. (%)				
Male	3674 (50.36)	10,924 (50.89)	–	0.220
Female	3621 (49.64)	10,540 (49.11)	–	
COVID-19 risk factors - no. (%)				
Without risk	4724 (64,76)	14,365 (66.93)	–	<0.001
With at least 1 risk	2571 (35.24)	7099 (33.07)	–	
Hypertension	1023 (14.02)	2864 (13.34)	–	0.074
Respiratory diseases	636 (8.72)	1782 (8.30)	–	0.140
Diabetes mellitus	426 (5.84)	982 (4.58)	–	<0.001
Non-hypertensive cardiovascular diseases	308 (4.22)	907 (4.23)	–	0.508
Obesity (BMI > 30 kg/m^2)	122 (1.67)	415 (1.93)	–	0.085
History of corticosteroid use	110 (1.51)	281 (1.31)	–	0.114
Malignancy	43 (0.59)	126 (0.59)	–	0.526
Cancer therapy	32 (0.44)	98 (0.46)	–	0.462
Organ transplant recipient	14 (0.19)	33 (0.15)	–	0.292
HIV positive	9 (0.12)	21 (0.10)	–	0.344
COVID-19 diagnosis - no. (%)				
PCR positive	5964 (81.76)	16,820 (78.36)	–	<0.001
PCR negative	470 (6.44)	1418 (6.61)	–	
No test	861 (11.80)	3226 (15.03)	–	
Clinical outcomes - no. (%)				
Hospitalization (unadjusted)	523 (7.17)	2382 (11.10)	0.62 (0.56–0.68)	<0.001
Hospitalization (adjusted*)	–	–	0.62 (0.56–0.69)	<0.001
Death (unadjusted)	27 (0.37)	287 (1.34)	0.27 (0.18–0.41)	<0.001
Death (adjusted*)	–	–	0.30 (0.20–0.45)	<0.001
Hospitalization in patients with positive PCR	408 (6.84)	1598 (9.50)	0.70 (0.63–0.78)	<0.001
Hospitalization in patients with negative PCR	24 (5.11)	154 (10.86)	0.44 (0.28–0.69)	<0.001
Hospitalization in patients with no test	91 (10.57)	630 (19.53)	0.49 (0.39–0.62)	<0.001
Death in patients with positive PCR	18 (0.30)	151 (0.90)	0.33 (0.21–0.55)	<0.001
Death in patients with negative PCR	1 (0.21)	4 (0.28)	0.75 (0.08–6.76)	0.801
Death in patients with no test	8 (0.93)	132 (4.09)	0.22 (0.11–0.45)	<0.001

* Adjusted for age, sex, BMI, hypertension, respiratory diseases, diabetes mellitus and cardiovascular diseases other than hypertension.

regression model (OR = 0.27; 95% CI: 0.18–0.41, p ≤ 0.001) in the HCQ group.

The effect of HCQ on the outcome measures was maintained after adjusting for confounding factors and comorbidities. This effect remained significant whether patients were diagnosed based on positive RT-PCR or otherwise (Table 1).

According to the odds of hospitalization of patients who received (0.077) or did not receive (0.124) HCQ, the probability of this outcome was 0.07 and 0.11 respectively. Dividing the difference of these numbers by 0.11 it was estimated that hospitalization costs were reduced by about 36 percent.

Serious HCQ adverse drug reactions were not reported in any of the age groups with or without comorbidities.

4. Discussion

In this large national retrospective cohort study, we examined the clinical outcomes of the patients with mild COVID-19 following early treatment with HCQ in an outpatient setting. Our study demonstrated that a short course of HCQ, given in the outpatient setting and within seven days of symptoms, could significantly reduce hospitalizations and deaths. The odds of COVID-19-related hospitalizations and deaths in our study population who were treated with HCQ were reduced by more than one-third and two-thirds, respectively.

In our study, we included the effects of confounding factors on the occurrence of outcome measures and recorded any serious HCQ adverse reactions.

In the light of severe and prolonged burden caused by SARS-CoV-2, the importance of its early detection and management, and the lack of an effective, available, and cheap therapeutic option, our study along with others [19–21] may convey important messages regarding the outpatient management of mild COVID-19 disease.

In Iran, the mean direct medical cost for each hospitalized patient with COVID-19 was estimated to be 59,203,409 Rials (approximately $ 3755). [22] Administration of HCQ can reduce the hospitalization cost by about 36 percent. Assuming a population of 100 patients, the total costs of hospitalization are calculated as $ 41,305 (11 × 3755) without administration of HCQ while this cost will decrease to $ 26,285 (7 × 3755) with considering the medication. Of course, if indirect costs are also considered, the effect of HCQ will be far greater. It should be noted that mean indirect cost of each patient with COVID-19 was estimated as $ 11,634. [22]

The impact of triple therapy, including HCQ, azithromycin, and zinc on hospitalization rates and all-cause deaths was examined in a retrospective study. The dose of HCQ was 200 mg twice daily for five days in that study. Use of the triple regimen caused a significant reduction in the incidence rates of hospitalization and all-cause mortality (OR = 0.16 and 0.2, respectively). [19] Although this study was also retrospective, the number of included patients was much smaller than found in our study. In this study, concomitant medications, and adverse effects of HCQ were mentioned. The patients were risk-stratified based on age, symptoms, and comorbidities.

The impact of medications, such as HCQ, prednisolone, azithromycin, ivermectin, and oseltamivir on clinical outcomes of 717 COVID-19 patients was examined retrospectively in an outpatient setting in Brazil. The main outcomes of the study were the rates of hospitalization and deaths as in our study. The use of HCQ alone was associated with 55% reduction in the rate of hospitalization. While not significant, the same decrease was seen with respect to the incidence of death. Except for prednisolone, other medications had no significant effect on the outcomes. [20] Interestingly, cardiac and ECG abnormalities were not seen in any of the above studies. [19–20]

Beneficial effects of HCQ in outpatient were also described in a systematic review. [23] Currently, several random clinical trials (RCTs) are ongoing with the aim of evaluating the efficacy of HCQ, specifically in COVID-19 disease outpatient management. [24–25]

However, two recent RCTs for early HCQ use in non-hospitalized patients did not indicate any significant association with a reduction in the risk of hospitalization. [26–27]

Several studies especially RCTs demonstrated that HCQ can be administrated safely and without incidence of serious cardiac adverse events in outpatients and hospitalized patients with mild COVID-19. [14,28–30]

Some of the limitations of our study are the retrospective design, lack of laboratory data (as the patients were deemed to be mild and not followed for hospital laboratory values), lack of access to other medications received by the patients in each group, absence of data on patients who required hospital admission, and a short initial follow-up period.

However, our large, multicenter, national study and adjustment of the outcome variables for comorbidities are the strengths of our study.

5. Conclusion

Our investigation of a large national cohort appears to support early administration (within the first 3–7 days of COVID-19 diagnosis) of HCQ in mild COVID-19 disease in an outpatient setting for reducing hospitalizations and deaths without any serious adverse HCQ-related effects. If this finding is confirmed in future clinical trials, HCQ as a cheap and available drug may still play a role in a specific population with respect to reducing COVID-19 burden, particularly in resource-poor countries.

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.

Acknowledgment

Data were extracted from CHCs affiliated to following Medical Sciences Universities. We appreciate all staffs for data gathering and sharing.

Abadan University of Medical Sciences, Arak University of Medical Sciences, Ardabil University of Medical Sciences, Urmia University of Medical Sciences, Hamedan University of Medical Sciences (Asadabad branch), North Khorasan University of Medical Sciences (Esfarayen branch), Isfahan University of Medical Sciences, Alborz University of Medical Sciences, Iran University of Medical Sciences, Zahedan University of Medical Sciences (Iranshahr), Ilam University of Medical Sciences, Babol University of Medical Sciences, North Khorasan University of Medical Sciences (Bojnourd branch), Kerman North Khorasan University of Medical Sciences (Bam branch), Hormozgan University of Medical Sciences, Ahwaz Jundishapur University of Medical Sciences (Bahbahan branch), Bushehr University of Medical Sciences, Birjand University of Medical Sciences, Tabriz University of Medical Sciences, Mashhad University of Medical Sciences (Torbat Jam branch), Tehran University of Medical Sciences, Jahrom University of Medical Sciences, Jiroft University of Medical Sciences, Ardabil University of Medical Sciences (Khalkhal branch), Khomein University of Medical Sciences, Urmia University of Medical Sciences (Khoy branch), Dezful University of Medical Sciences, Rafsanjan University of Medical Sciences, Zabol University of Medical Sciences, Zanjan University of Medical Sciences, Mazandaran University of Medical Sciences, Saveh University of Medical Sciences, Sabzevar University of Medical Sciences, Tabriz University of Medical Sciences (Sarab branch), Semnan University of Medical Sciences, Sirjan University of Medical Sciences, Shahrood University of Medical Sciences, Shahrekord University of Medical Sciences, Shahid Beheshti University of Medical Sciences, Ahwaz Jundishapur University of Medical Sciences (Shushtar branch), Shiraz University of Medical Sciences, Fasa University of Medical Sciences, Qazvin University of Medical Sciences, Qom University of Medical Sciences, Kashan University of Medical Sciences, Kordestan University of Medical Sciences, Gonabad University of Medical Sciences, Gilan University of Medical Sciences, Shiraz University of Medical Sciences (Larestan branch), Lorestan University of Medical Sciences, Maragheh University of Medical Sciences, Neyshabur University of Medical Sciences, Yasuj University of Medical Sciences, Yazd University of Medical Sciences.

We would like to thank the nurses and other staffs of Imam Khomeini Hospital Complex for their kind supports and also Ms. Ava Khalili for English proofreading the manuscript.

Funding

The authors did not receive any fund for this work.

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