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Evaluation of the prophylactic effect of hydroxychloroquine on people in close-contact with patients with COVID-19

Minoosh Shabani [a,b,1], Mehdi Totonchi [c,d,1], Omidvar Rezaeimirghaed [e], Latif Gachkar [a,b], Mohammadreza Hajiesmaeili [f], Ali Khoshkar [g], Mahdi Amirdosara [f], Ali Saffaei [h], Shervin Shokouhi [a,b], Masoud Mardani [a,b], Ilad Alavi Darazam [a,b], Alireza Karami [i], Milad Sharifi [i], Mana Zaman [j], Elham Abedheydari [k], Zahra Sahraei [l,m,*]

[a] Department of Infectious Diseases and Tropical Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Genetics, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran
[d] Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
[e] Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[f] Anesthesiology Research Center, Loghman Hakim Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[g] General Surgery Department, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[h] Student Research Committee, Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[i] Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[j] Student Research Committee, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[k] Department of Embryology, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran
[l] Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[m] Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Introduction: The coronavirus disease 2019 (COVID-19) pandemic has caused significant mortality worldwide. The disease attacks the lung tissue and may lead to acute respiratory distress syndrome. An in vitro study showed that hydroxychloroquine (HCQ) has a prophylactic effect against COVID-19 due to its anti-inflammatory effects. The present study aimed to evaluate the prophylactic effect of HCQ on individuals in close contact with patients with COVID-19.

Method: In this quasi-trial study, we prescribed HCQ for 7 days to all people who had close contact with a patient with COVID-19. All contacts underwent a nasal swab in two steps, and those positive for COVID-19 were excluded from the study. After 14 days of follow-up, the clinical and laboratory manifestations of COVID-19 were evaluated.

Results: A total of 113 participants completed the study. The HCQ group comprised 51 (45.13%) contacts, and 62 (54.86%) contacts were allocated to the control group. According to the results of clinical examination and real-time polymerase chain reaction test, 8 (12.90%) contacts in the control group were reported to have contracted COVID-19. In the HCQ group, 7 (13.72%) contacts were confirmed to have contracted COVID-19. There was no relationship between HCQ use and age, sex, underlying disorders, and laboratory data (all $p > 0.05$). In terms of HCQ side effects, five participants experienced gastrointestinal and cutaneous side effects that subsided on discontinuation of HCQ.

Conclusion: The current study showed that HCQ had no prophylactic effect with regard to COVID-19 prevention.

* Corresponding author. Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Niyayesh Highway, Valiasr St, Tehran, Iran.
E-mail address: z.sahraei@sbmu.ac.ir (Z. Sahraei).
[1] Co-first Authors: Minoosh Shabani and Mehdi Totonchi.

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1. Introduction

In December 2019, a new member of the Coronoviridae family, called the severe acute respiratory syndrome of coronavirus 2 (SARS-CoV-2), was detected in the Wuhan Province of China, and spread globally [1].

Many efforts have focused on developing preventive strategies against the coronavirus disease 2019 (COVID-19). Frequent hand washing and wearing a face mask are among the essential preventive strategies [2]. However, no specific medication has been found for COVID-19 prevention or prophylaxis. This virus is highly contagious, and recent studies have demonstrated that every patient can infect two other persons on average. The transmission of SARS-CoV-2 by asymptomatic carriers is another vital issue [3]. Healthcare providers and those with a history of close contact with a patient with confirmed COVID-19 are highly at risk of infection [4]. An effective vaccine is a necessary tool to fight the COVID-19 pandemic, but the vaccine development process generally takes years or even decades. Monoclonal antibodies provide an alternative option for the prevention of COVID-19. Passive infusion of monoclonal antibodies as pre-exposure or post-exposure prophylaxis might offer immediate protection from infection that could last weeks or months. Even if a vaccine is available, a few weeks are required to achieve an effective immune response. This emphasizes the benefits of passive immunity in healthcare settings and households [5]. Chloroquine analogs were shown to suppress endosome acidification and to demonstrate at high micromolar concentrations in vitro non-specific antiviral activity against a wide variety of circulating viruses, such as HIV, hepatitis C, influenza, Ebola, severe acute respiratory syndrome, and Middle East respiratory syndrome viruses, and more recently, SARS-CoV-2 [6]. A recent report indicated the efficacy of chloroquine against SARS-CoV-2 in vitro. Hydroxychloroquine (HCQ), which is more soluble than chloroquine, has similar beneficial effects and fewer adverse effects. Similar to chloroquine, HCQ raises the pH and causes antiviral effects. HCQ also has a modulating effect on activated immune cells [7].

Recent research in China in patients with COVID-19 demonstrated no difference in the rate of virological clearance at seven days and no difference in clinical results (duration of hospitalization, temperature normalization, radiological progression) with or without five days of HCQ use. The above findings are consistent with the lack of virological or therapeutic value of chloroquine in a range of viral infections where it was evaluated for treatment or prophylaxis [8]. In contrast, another study confirmed 100% virus clearance in nasopharyngeal swabs of six patients after 5–6 days of a combination of HCQ and azithromycin. This viral clearance rate was lower with HCQ alone (57.1%) and 12.5% in patients who did not receive HCQ [9]. No data are available on the efficacy and safety of post-exposure prophylaxis for COVID-19. Post--exposure prophylaxis using HCQ was administered for 14 days in a Korean sample. The follow-up polymerase chain reaction (PCR) test results were negative [10].

Considering the effects of HCQ against COVID-19, this study aimed to investigate the prophylactic effect of HCQ in individuals in close contact with patients with COVID-19.

2. Materials and methods

This quasi-experimental trial was conducted between April and June 2020 at the Loghman Hakim Hospital, which is affiliated to the Shahid Beheshti University of Medical Sciences, Tehran, Iran. This hospital was the referral center for COVID-19 in Tehran, Iran. The Ethics Committee of Shahid Beheshti University of Medical Sciences approved this study (IR.SBMU.RETECH.REC.1399.026). The study protocol was registered in the Iranian Registry of Clinical Trials (IRCT20130917014693N10). All enrolled patients provided complete and signed informed consent forms. An independent investigator who was not involved in the data analysis was employed in this regard.

Inclusion criteria were adults who had household exposure to a patient with confirmed COVID-19 at a distance of <6 ft for >10 min [11]. At least 48 h, and not >5 days had passed since their first contact with the patient. This time was based on the incubation period for SARS-CoV-2 [12]. The exclusion criteria were age <18 years, pregnant and/or breastfeeding women, people with underlying disorders such as arrhythmia, favism, chronic kidney diseases, chronic liver diseases, drug allergies, retinopathy, and those with abnormal findings on electrocardiography (which was performed at the beginning of the study). In addition, we excluded people with flu-like symptoms (fever > 37.5 °C, sore throat, cough, dyspnea, myalgia, and diarrhea) during the visit and in the past month or a history of COVID-19. All patients who received other prophylactic medicines, such as ivermectin and convalescent plasma, and those who refused to receive HCQ were also excluded. History and physical examination, including vital signs and oral temperature measurement (°C), was performed for all participants. The researchers evaluated age, sex, weight, smoking status, blood group, underlying disorders, COVID-19 signs and symptoms, and laboratory data (WBC, BUN, Cr, AST, ALT, ALP, albumin, and CRP) for all participants. Nasopharyngeal swabs were collected for testing for COVID-19 by real-time PCR (RT-PCR) on days 0 and 7.

In this study, a simple sampling method was selected. The first participant was allocated to the HCQ group. The next participant was allocated to the control group. Participants in the HCQ group received 200 mg of HCQ sulfate (Amin Pharmaceutical Company, Isfahan, Iran) three times a day for one week. Two days after initiation of the intervention, the RT-PCR test results for both groups were available, and those with positive results were excluded from the study. All participants were advised to follow home isolation. The primary outcome was defined as PCR-confirmed COVID-19 on day 7. The secondary outcome was defined as the number of people with symptoms compatible with COVID-19 and the number of people who developed adverse drug reactions. The participants were followed-up every other day by telephone until 14 days from intervention initiation or the occurrence of any suspected clinical symptoms compatible with COVID-19, and the occurrence of adverse effects was recorded. In addition, participants were instructed to call the investigators in cases of any symptom occurrence. On day 7, all participants were clinically re-evaluated for any evidence of COVID-19, and nasopharyngeal swabs were collected for testing for COVID-19 using RT-PCR. The clinic maintained appropriate standards for receiving suspected patients with COVID-19, and all instruments were disinfected after each visit. All contacts with clinical symptoms (the presence of two or more of the following symptoms — fever, chills, myalgia, headache, sore throat, ageusia, and anosmia — according to the United States Council for State and Territorial Epidemiologists criteria) or positive RT-PCR test were classified as having COVID-19. In each step of the study, patients with confirmed COVID-19 were referred to the clinic for treatment.

2.1. SARS-CoV-2 nucleic acid detection

Viral RNA was purified from 200 μL of nasopharyngeal or throat swab fluid based on the manufacturer-recommended methods using the NORGEN Kit (Biotek Corporation, Canada) to detect SARS-CoV-2 nucleic acid. RT-PCR assay was then performed to detect the ORF1ab and N genes of SARS-CoV-2, which encode RNA-dependent RNA polymerase and N nucleocapsid protein, respectively. Synthetic viral RNA was used as a positive control, and the RNase P gene was used as an internal control to assess the quality of the viral RNA purification process. A novel coronavirus (2019-nCoV) nucleic acid diagnostic kit (PCR fluorescence probing, Sansure Biotech) was used for gene detection. For this purpose, 5 μL of purified RNA was added to the 20 μL PCR mix and the qRT-PCR thermocycling program (50 °C for 20 min, followed by one cycle of 95 °C for 60 s, one cycle of 95 °C for 15 s and 60 °C for 60 s, and 45 cycles) was performed on a Corbett Instrument.

2.2. Statistical analysis

Data were analyzed using SPSS version 16 (IBM, NY, USA). The Kolmogorov-Smirnov test was used, and descriptive results were reported as medians and interquartile ranges. Post-hoc analysis was performed using the Mann-Whitney *U* test with a pre-per-protocol approach.

3. Results

Of the 178 participants enrolled in this study, 65 were excluded according to the exclusion criteria. Fifty-four participants were diagnosed with COVID-19 at the beginning of the study (15 patients had only positive RT-PCR test results, and 13 had only clinical symptoms compatible with COVID-19; 26 patients had both positive RT-PCR test results and COVID-19 symptoms), and 5 participants were lost to follow-up due to adverse effects. Six participants discontinued the drug due to poor compliance. Finally, 113 participants (51[82.25%] and 62 [75.60%] participants in the HCQ and control groups, respectively) completed the study. Fig. 1 shows the CONSORT diagram for the current study. As shown in Table 1, there were no statistically significant differences between the groups with regard to age, weight, sex, smoking status, blood groups, and underlying disorders (all $p \geq 0.05$).

The hazard ratio for RT-PCR test positivity in the entire patient population after exposure was 1.5 (95% confidence interval, 1.372–1.642) but no differences were seen between the control group and those treated with hydroxychloroquine [7 (12.90%) vs. 7 (13.72%), $p = 0.625$], respectively.

In addition, clinical evaluations revealed that 2 (3.92%) and 3 (4.83%) contacts in the HCQ and control groups, respectively, developed COVID-19 symptoms. All of these contacts had positive RT-PCR results, except for one patient in the HCQ group. Table 2 shows the results of outcomes according to the group and time of study.

Table 3 shows the results of laboratory studies in both groups. Although the mean ALT level was higher in COVID-19-positive participants who took HCQ, there was no statistically significant difference between them. There were no statistically significant differences in laboratory test results between the HCQ and control groups ($p \geq 0.05$).

In terms of adverse effects in the HCQ group, five patients developed an adverse drug reaction – three participants had diarrhea and two developed a maculopapular rash on the trunk and limbs, which was accompanied by swelling of the hands in one participant. All patients recovered after drug discontinuation. No adverse cardiac effects were observed in the HCQ group. None of the patients in the control group experienced adverse effects.

Lastly, of the patients who tested positive for the disease, none required hospitalization, and all recovered after receiving HCQ.

4. Discussion

In this study, we aimed to evaluate the prophylactic effects of HCQ after exposure to COVID-19. There was no statistically significant difference between the HCQ and control groups in the current study involving COVID-19.

Yao et al. conducted an in vitro study to evaluate the effects of chloroquine and HCQ as pre-exposure prophylaxis against COVID-19. Cell lines derived from the African green monkey kidney were treated with chloroquine or HCQ before exposure to SARS-CoV-2. They found

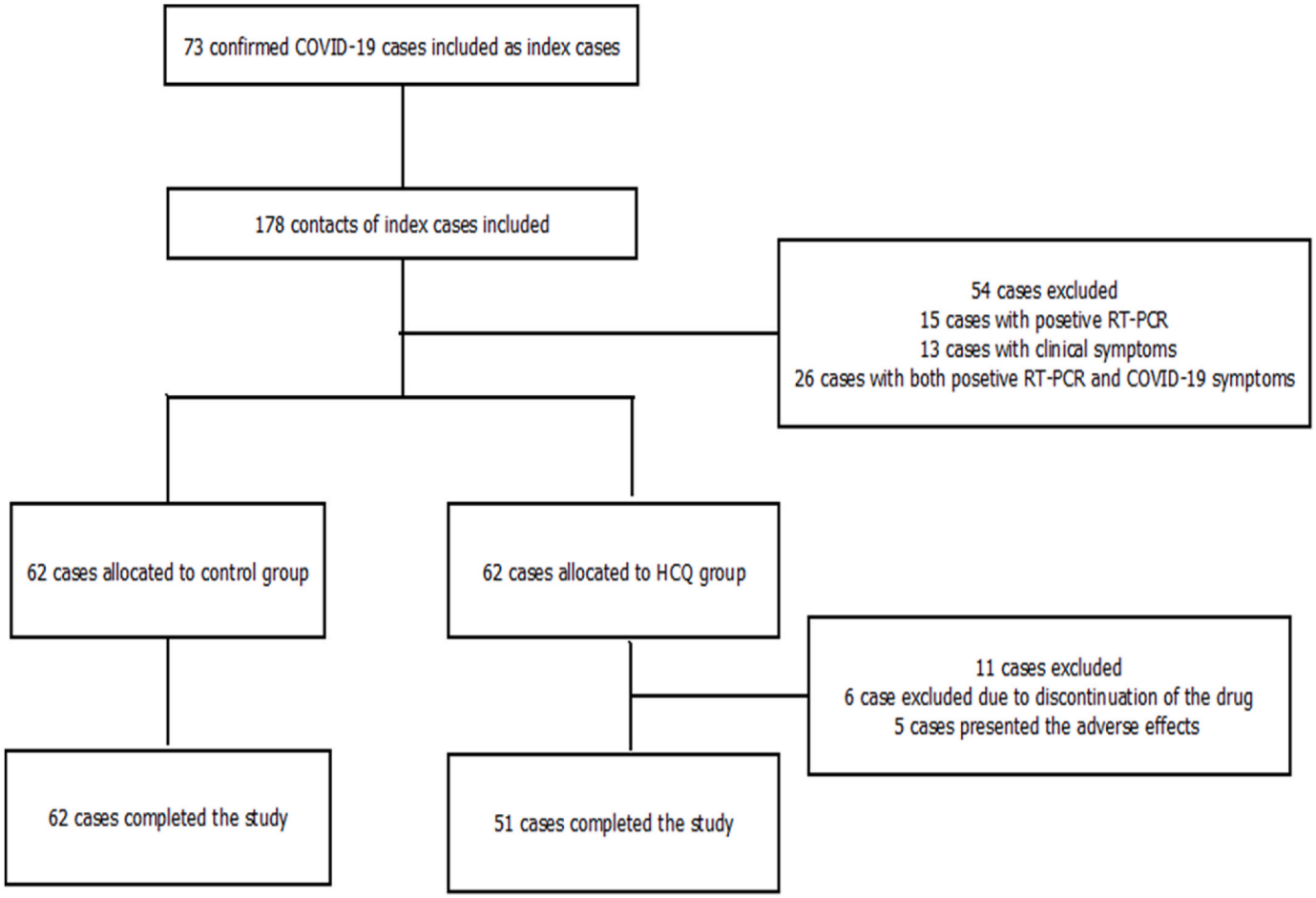

Fig. 1. The CONSORT diagram of the study.

Table 1
Demographic features of participants.

Characteristics		Control group (N = 62)		Hydroxychloroquine group (N = 51)		P value
Status		Negative (n = 54)	Positive (n = 8)	Negative (n = 44)	Positive (n = 7)	
Age-years (mean-IQR)		41 (43.5)	47 (42.5)	43.5 (42)	35.5 (36)	0.951
Weight-kg (mean-IQR)		73 (72)	81.5 (77.5)	75 (77.5)	75 (79.5)	0.252
Sex-male (%)		27 (43.54%)	3 (4.83%)	20 (39.21%)	5 (9.80%)	0.09
Smokers (%)		9 (14.51%)	1 (1.61%)	8 (15.68%)	3 (5.88%)	0.095
Blood group (%)	A	13 (24.07%)	1 (1.61%)	15 (2.94%)	2 (3.92%)	0.485
	B	13 (24.07%)	1 (1.61%)	7 (13.72%)	0 (0%)	
	AB	1 (1.61%)	0 (0%)	3 (5.88%)	0 (0%)	
	O	11 (17.74%)	3 (4.83%)	9 (17.64%)	1 (1.96%)	
	Unknown	24 (38.70%)	3 (4.83%)	10 (19.60%)	4 (7.84%)	
HTN (%)		4 (6.45%)	2 (3.22%)	3 (5.88%)	0 (0%)	0.355
DM (%)		3 (4.83%)	1 (1.61%)	2 (3.92%)	0 (0%)	0.360
CHD (%)		1 (1.61%)	0 (0%)	1 (1.96%)	0 (0%)	0.512
COPD (%)		0 (0%)	0 (0%)	1 (1.96%)	0 (0%)	0.412
CVA (%)		0 (0%)	0 (0%)	2 (3.92%)	0 (0%)	0.450
Malignancy (%)		0 (0%)	0 (0%)	1 (1.96%)	0 (0%)	0.363
Asthma (%)		3 (4.83%)	0 (0%)	2 (3.92%)	0 (0%)	0.451
Hepatic diseases (%)		0 (0%)	0 (0%)	2 (3.92%)	1 (1.96%)	0.489
Renal diseases (%)		3 (4.83%)	1 (1.61%)	2 (3.92%)	0 (0%)	0.147
Autoimmune disorder (%)		1 (1.61%)	0 (0%)	1 (1.96%)	0 (0%)	0.518

Table 2
The outcomes of study according to the group and time of the study.

Time/Group		HCQ group **(N = 51)**	Control **(N = 62)**	P-Value
Day 7	RT-PCR positive	7	7	–
	Sign or symptom of COVID-19	2	3	>0.05
Day 14	sign or symptom of COVID-19	1	1	–

that HCQ was more potent than chloroquine in achieving a concentration of 50% of the maximally effective concentration. Their study led to an interest in designing clinical trials on the prophylactic role of HCQ in COVID-19. In vitro, the research showed that HCQ could be a prophylactic drug in close contacts of patients with COVID-19 [13].

In another in vitro study, Principi et al. concluded that chloroquine and HCQ could be used for prophylaxis of COVID-19. The half-maximal inhibitory concentration of chloroquine for inhibition of SARS-CoV-2 replication in Vero E6 cells was 8.8 μmol/L. This concentration is substantially lower than the plasma concentrations that are reached in humans when the drug is prescribed to treat malaria at a dose of 25 mg/kg over 3 days. This finding prompted us to use higher doses of HCQ (200 mg) three times a day [14].

Dhibar et al. studied the post-exposure prophylactic effects of HCQ. They administered an 800 mg loading dose of HCQ, followed by 400 mg p.o. weekly for three weeks. After four weeks of follow-up, 10.6% of patients who took HCQ developed COVID-19. Dhibar et al.'s study had a longer duration of prophylaxis than the current study, and they reported mild adverse drug reactions in patients who received HCQ. They also included healthcare workers, and their study population was diverse [15].

Rajasingham et al. conducted a study on HCQ as a pre-exposure prophylaxis in healthcare workers. They found that pre-exposure prophylaxis with HCQ once or twice weekly did not significantly reduce the number of laboratory-confirmed cases. Their study included healthcare workers with continued exposure to COVID-19. Participants were randomized to 400 mg of HCQ once or twice weekly for 12 weeks, which was different from the protocol in the current study [16].

Boulware et al. investigated post-exposure prophylaxis with HCQ in COVID-19. Participants had close contact with a patient with COVID-19. Their study showed that HCQ had no prophylactic effect on people who had close contact with patients with confirmed COVID-19. HCQ was associated with more side effects, but no serious adverse reactions were reported. These findings are similar to those of the current study [12].

In comparison with Boulware et al.'s study, the current study evaluated participants with more details, including the nasopharyngeal RT-PCR in two stages, and regular telephonic follow-up. In their study, the participants were divided into high-risk and moderate-risk groups according to the type of exposure to COVID- 19. The contacts who did not use face masks were categorized as the high-risk group and those who used face masks were categorized as the moderate group. They included health care providers, and followed their patients entirely through the mail. However, the current study evaluated patients at the office with more details.

The present study had some limitations. One of the significant limitations was the small sample size due to limited resources, such as RT-PCR. However, the researchers believed that the enhanced checkpoints could eliminate, to some extent, the effects of limitations.

Table 3
Laboratory tests in participants.

Characteristics	Control group (N = 62)		Hydroxychloroquine group (N = 51)		P value
Status	Negative (N = 54)	Positive (N = 8)	Negative (N = 44)	Positive (N = 7)	
WBC (*10^3)	6.50 (4.20–10.30)	7.60 (4.70–12.50)	5.80 (4.70–12.20)	6.80 (3.90–13.60)	**0.112**
BUN (mg/dL)	26.00 (14.00–36.00)	30.00 (27.00–33.00)	26.00 (20.00–35.00)	21.00 (14.00–30.00)	**0.940**
Cr (mg/dL)	1.00 (0.92–1.10)	1.30 (0.60–2.00)	1.00 (0.90–1.12)	1.10 (0.90–1.20)	**0.531**
AST (U/L)	19.00 (15.00–24.00)	14.00 (14.00–14.00)	19.50 (15.50–28.50)	14.00 (10.00–28.00)	**0.775**
ALT (U/L)	25.00 (15.00–35.00)	12.00 (12.00–12.00)	21.00 (17.00–34.50)	42.00 (17.00–68.00)	**0.992**
ALP (U/L)	154.50 (134.00–193.50)	293.00 (293.00–293.00)	169.50 (147.00–214.00)	136.00 (130.00–185.00)	**0.858**
Albumin (g/dL)	4.50 (4.30–40.70)	4.10 (4.10–4.10)	4.70 (4.50–4.90)	4.70 (4.20–5.10)	**0.066**
CRP (mg/L)	**2.80 (2.00–5.30)**	-	**4.00 (2.00–6.00)**	-	**0.146**

5. Conclusion

In conclusion, the present study found no clinical benefit of HCQ use post exposure to SARS-CoV-2, and it may not help in COVID-19 prophylaxis. However, it is necessary to design trials with larger sample sizes to achieve a definitive conclusion.

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Author statement

Minoosh Shabani Barzegar: Conceptualization, Methodology, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Project administration. Mehdi Totonchi: Conceptualization, Data Curation, Formal analysis Writing - Review & Editing. Omidvar Rezaeimirghaed: Conceptualization, Data Curation, Writing - Review & Editing. Latif Gachkar: Conceptualization, Data Curation, Writing - Review & Editing. Mohammadreza Hajiesmaeili: Conceptualization, Data Curation, Writing - Review & Editing. Ali Khoshkar: Conceptualization, Data Curation, Writing - Review & Editing. Mahdi Amirdosara: Conceptualization, Data Curation, Writing - Review & Editing. Ali Saffaei: Conceptualization, Data Curation, Formal analysis, Writing - Review & Editing. Shervin Shokouhi: Conceptualization, Data Curation, Writing - Review & Editing. Masoud Mardani: Conceptualization, Data Curation, Writing - Review & Editing. Ilad Alavi Darazam: Conceptualization, Data Curation, Writing - Review & Editing. Alireza Karami: Conceptualization, Data Curation, Writing - Review & Editing. Milad Sharifi: Conceptualization, Data Curation, Writing - Review & Editing. Mana Zaman: Conceptualization, Data Curation, Writing - Review & Editing. Elham Abedheydari: Conceptualization, Data Curation, Writing - Review & Editing. Zahra Sahraei: Conceptualization, Methodology, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision.

Declaration of competing interest

The authors have declared that no conflicts of interest exist.

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