Original Article

The prophylactic effect of hydroxychloroquine on the severity of COVID-19 infection in an asymptomatic population: A randomized clinical trial

Termeh Tarjoman[1], Mahnaz Valizadeh[2], Parisa Shojaei[1], Behnam Farhoodi[2], Mehrangiz Zangen[3], Masood Najafi[1], Seyed Hamid Jamaldini[2], Masoumeh Mesgarian[2], Zahra Hanifezadeh[1], Faezeh abdollahi[1], Hamidreza Massumi naini[1], Mohsen Alijani[1], Hasti Ziaee[1], Arezoo Chouhdari[*1]

[1] Social Determinants of Health Research Center, Amir-al-Momenin Hospital, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran.

[2] Amir-Almomenin Hospital, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, IR Iran.

[3] Clinical Research Development Center, Amir-Almomenin Hospital, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, IR Iran.

[4] School of Medicine, University of Central Lancashire, Preston, England.

Corresponding author and reprints: Dr. Arezoo Chouhdari, Social Determinants of Health Research Center, Amir-al-Momenin Hospital, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran.

Email: chouhdariarezoo@gmail.com

Received: 20 Aug 2023 **Accepted:** 24 Nov 2023 **Published:** 22 Jan 2024

Abstract

Background: Laboratory and observational data suggest that hydroxychloroquine (HCQ) has biological activity against SARS-CoV-2, potentially permitting its use for disease prevention. This study aimed to evaluate the hydroxychloroquine effect as prophylaxis for SARS-CoV-2 infection.

Methods: In this double-blind randomized controlled trial, 1000 healthy people without any signs and symptoms of COVID-19 were randomly assigned in a 1:1 ratio to receive either 800 mg hydroxychloroquine or placebo (four 200 mg tablets in two divided doses on day 1 of the first week, followed by 200 mg (in a single dose) weekly for the next 6 weeks).

Results: Among 871 participants who remained and followed within 10 weeks 97(11.1%) became SARS-CoV-2 positive. there were statistically significant differences between infected or non-infected in the hydroxychloroquine (36 of 97 [37.1%]) and placebo (61 of 97 [62.9 %]) groups with a risk ratio of 2.1 (95% confidence interval (CI) 1.01 - 3.21; p = 0.005). The incidence of severe forms of COVID-19 (hospitalized in the coronavirus ward or the ICU) was 2 of 97 (0.02 %) in participants who received a placebo compared to hydroxychloroquine. The proportion of non-infected people who received hydroxychloroquine prophylaxis was nearly twice higher than that of placebo users (1.87, 95% CI: 1.19 - 2.84, p = 0.05). There were no significant differences between the two groups regarding side effects (1.1% vs. 0.9%), and no severe adverse reactions were observed.

Conclusion: Pre-exposure therapy with hydroxychloroquine appears to prevent moderate and severe illness caused by COVID-19 in asymptomatic persons.

Keywords: Adverse Drug Reactions; Hydroxychloroquine; Pre-Exposure Prophylaxis; SARS-CoV-2 COVID-19.

Cite this article as: Tarjoman T, Valizadeh M, Shojaei P, Farhoodi B, Zangeneh M, Najafi M, Jamaldini S.H, Mesgarian M, Hanifezadeh Z, Abdollahi F, Massumi naini H, Alijani M, Ziaee H, Chouhdari A. Evaluation of the prophylactic effect of hydroxychloroquine on the incidence of moderate or severe forms of COVID-19 infection in an asymptomatic population: A randomized clinical trial. *Soc Determinants Health*. 2024;10(1):1-10. DOI: http://dx.doi.org/10.22037/sdh.v10i1.43032

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-COV2) is a new form of coronavirus that causes COVID-19 disease. The virus initially broke out in Wuhan, China at the end of 2019 and spread rapidly around the world. The number of patients infected with the virus increased rapidly, leading to the current pandemic (1). SARS-COV-2 infected 266,680,657 people and caused more than 5,277,356 deaths around the world by December 7th, 2021.(2) Brazil, one of the countries greatly affected by the pandemic, had 29,432,157 infected patients and more than 655,585 deaths (2).

Since COVID-19 is a new disease, efforts are ongoing to find a suitable treatment for it. To date, the only approved drug with significant efficacy in the clinical treatment of patients with COVID-19 is Paxlovid (3-6). Therapeutic agents for the treatment of COVID-19 are selected because of their previously documented antiviral activity against MERS and SARS or other viral infections. There is an urgent need for a drug or vaccine with proven efficacy to treat or prevent COVID-19(4). After the recent announcement of the effectiveness of several COVID-19 vaccine candidates in protecting against the disease, a comprehensive strategy is now needed to ensure the vaccination of the global population at a later stage, and it remains unclear whether these vaccines can end the COVID-19 pandemic (5).

Current infection control strategies rely on vaccination and non-pharmacological interventions including hand hygiene, universal masking, physical distancing, case and contact detection, tracing and isolation (7). Despite these measures, infection outbreak among vaccinated people was observed, and a large proportion of the population have not yet received the vaccine. Therefore, having an effective prophylactic regimen enhances the capability to control the pandemic and its burden. Chloroquine an antimalarial drug, has an inhibitory effect on the growth of the virus in vitro (8). Hydroxychloroquine like chloroquine has been proved to inhibit virus growth in vitro (9) and has a safer profile than Chloroquine, especially when taken for a long time, allowing for higher daily doses (10); additionally, hydroxychloroquine causes less concern for drug interactions than Chloroquine (11).

For this purpose, we conducted a study to evaluate the effects of hydroxychloroquine in preventing the progression of COVID-19 and hospitalization in Tehran.

Methods

Trial design

The study was designed in March 2020, when the information about SARS-COV- 2 transmission was not very clear. This experiment was performed by clinical evaluation of two groups of healthy volunteers randomized to treatment with either hydroxychloroquine or placebo. The initial sample size was based on an attack rate of 5%. Epidemiologists recommended that the sample size should be end point–driven for ease of monitoring, thus, the design was changed to an endpoint–driven trial and would stop when the prespecified number of endpoints was observed. Participants were enrolled between August 20, 2020, to October 20, 2020.

The participants were followed for 10 weeks to observe SARS-CoV-2 infection. The study was registered with https://irct.behdasht.gov.ir (IRCT20200421047153N1).

Participants

Study participants were men and women between the ages of 18 and 65 years who were willing to participate in the study and were not suspected of having COVID-19 symptoms at the time of enrollment or a history of COVID-19 infection. We excluded individuals with a history of allergy to hydroxychloroquine, retinopathy, long QT syndrome (LQTS), glucose-6-

phosphate dehydrogenase (G6PD), porphyria, cardiovascular disease, arrythmia, or COVID-19, patients positive for human immune deficiency virus (HIV), patients with autoimmune diseases (e.g. lupus or rheumatoid arthritis), those who receive immunosuppressive drugs, people with BMI >40, patients with diabetes or chronic kidney disease (CKD), pregnant women, those using drugs that are contraindicated with hydroxychloroquine or drugs that interact with hydroxychloroquine and cannot be discontinued, and any individuals who could not be observed in the follow-up period.

Interventions

Both the intervention and control groups were given 10 tablets—four to be taken in the first day in two divided doses, and one tablet weekly for the remaining six weeks. Both intervention and control groups were followed up on a weekly basis by telephone to monitor any COVID-19 symptoms and adverse drug reaction. During the telephone call, regular and weekly use of the drug was emphasized. Individuals were advised to call and refer to the hospital for assessment of health status and collection of nasopharyngeal swabs if they experience any symptoms. Suspected or confirmed COVID-19 cases were treated according to the Iran Ministry of Health protocol.

Outcomes

The primary outcome of the study included severe forms of COVID-19 disease (shortness of breath, persistent chest pain or pressure, decreased level of consciousness, bruising of the lips and face, and a positive reverse transcriptase polymorphism chain reaction (RT-PCR) test), requiring hospital admission (including COVID-19 ward or ICU), or death. The secondary outcomes were confirmed or probable COVID-19 and HCQ side effects. Probable COVID-19 was defined based on clinical characteristics and/or Computed Tomography (CT) findings. Confirmed cases indicated patients with positive SARS-CoV2 RT-PCR testing.

Sample size

The study participants were recruited from August 20, 2020 to October 20, 2020. About 40 people were invited to the site daily to receive medication, provide consent and fill out the initial information form. A total of 1000 persons (439 in HCQ group and 432 in placebo group) participated in the study and 129 were lost during follow up.

Randomization

The study analyst performed the balance block randomization allocation. For each person a unique code was assigned and the study staff did not have access to the randomization codes. Once eligibility was confirmed and the enrollment visit completed, the table of codes was sent to the drug manufacturer (Tehran Darou Pharmaceutical Co.).

Sequence generation

According to the table, participants were categorized into A or B groups. The company put the drugs and the placebos in the envelopes according to the code of each person and provided the researchers with the label on which the code of the people was written.

Allocation concealment mechanism

This action allowed random allocation blinding and concealment.

Implementation

They were randomly assigned in a 1:1 ratio to receive either 800 mg hydroxychloroquine (four 200 mg tablets in two divided doses on day 1 of the first week, followed by 200 mg (in a single dose) weekly for the next 6 weeks) or 800 mg placebo (four 200 mg tablets in two divided doses on day 1 of the first week, followed by 200 mg (in a single dose) weekly for the next 6 weeks). Participants were advised to take the pills following meals. Both the hydroxychloroquine and placebo tablets

were round, white, and had a bitter taste. The labeling and packaging of the drug was identical in both groups.

Blinding

Participants were randomly assigned to the list to prevent unblinding between them. The participants, investigators, laboratory technicians, and study team members were blinded to participant allocation.

Statistical methods

We anticipated that illness caused by COVID-19 would develop in 5% of community. Using G-power, z test method with a 50% reduction in new symptomatic infections, a two-sided alpha of 0.05, and 80 % power, we estimated that 714 persons would need to be enrolled in each group. Because the estimates for both incident symptomatic COVID-19 and the limited resources in early March 2020, we recruited 871 asymptomatic adult participants who were randomly assigned to the hydroxychloroquine group (439 participants) or the placebo group (432 participants). The study was conducted with the code of ethics issued to the ID IR.IAU.PS.REC.1399.003.

Statistical analysis was performed by descriptive methods and analytical tests including independent ANOVA, Chi-square, multivariable logistic regression and Tukey post hoc tests in SPSS software version 24.

Results

Participants

1000 participants were screened for study eligibility and enrolled (Figure 1). They were randomly assigned to the hydroxychloroquine group (500 participants) and to the control group (500 participants).

For the 871 participants followed during 10 weeks completely, the mean age in the hydroxychloroquine group was reported 40.19±12.33 and the placebo group was 40.50±12.23. In addition, 663 (76%) were married and 137 (15%) were illiterate. A total of 108 (12.4%) participants reported chronic health conditions, with hypertension being the most common (6.4%), followed by diabetes (2.6%). (Table 1)

Among the participants who enrolled, none reported contact with COVID-19 patients or suspicious symptoms.

Primary Outcome

Overall, new COVID-19 (either RT- PCR-confirmed or symptomatic cases) developed in 97 participants (11.1%) during the 10 weeks of follow-up (Table 2). The incidence of new illness caused by COVID-19 differs significantly between those receiving hydroxychloroquine (37.1%) and those receiving placebo (62.9%) (P = 0.005). The odds ratio was 2.1 (95% CI 1.01 - 3.21).

Two hospitalizations were reported in the placebo group. One patient was hospitalized in the COVID-19 ward and another in the ICU due to clinical conditions and underwent mechanical ventilation. No arrhythmias or deaths occurred.

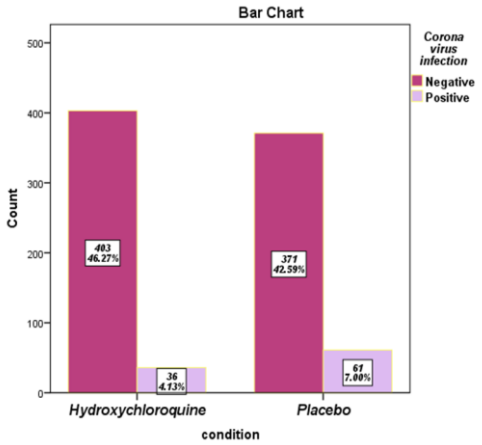

Figure 1: the incidence rate of Coronavirus infection in hydroxychloroquine and Placebo group (4.13% in Hydroxychloroquine Vs 7% in Placebo group)

Overall, 12.9% of the participants (61 in the hydroxychloroquine group and 68 in the placebo group) did not complete the 10-week survey of persons in whom symptomatic illness developed. In the

hydroxychloroquine group, 8 (21.6%) had clinical symptoms; 12 (32.4%) had clinical symptoms and positive RT- PCR; 3 (8.1%) had clinical diagnosis and CT scan of the lungs; 1 (2.7%) had a clinical diagnosis, CT scan and RT- PCR test; and 13 (35.1%) had only RT- PCR test. In the placebo group, 5 (8.9%) had clinical symptoms; 24 (42.9%) had clinical diagnosis and RT- PCR; 11 (19.6%) had a clinical diagnosis and lung CT scan; and 16 (28.6%) had only diagnosis with RT- PCR. About 3% of people infected with COVID-19 had a drug complication (headache or gastrointestinal complication); in the non-COVID-19 group, only 0.8% had a drug complication, however this difference was not significant (p=0.06). Also, there was no significant difference between the two treatment groups in terms of complications (1.1% in hydroxychloroquine group vs. 0.9% in placebo group, p – 0.07).

Adherence and Safety

Adherence among the trial participants was moderate. Full adherence to the trial intervention differed according to trial group, with 0.87% of participants in the hydroxychloroquine group (439 of 500) and 86.4% of those in the placebo group (432 of 500) having taken all 10 prescribed tablets over a period of 7 weeks.

Table 1: Demographic and Clinical Characteristics of the Participants at Baseline.

Variables	**Drug (n=439) N (%)**	**Placebo (n=432) N (%)**	**Variables**	**Drug (n=439) N (%)**	**Placebo (n=432) N (%)**
Age(Years) (Mean± SD)	40.19±12.33	40.50±12.23	Smoking		
			Yes	104(23.7)	97(22.5)
			No	335(76.3)	335(77.5)
Gender			Alcohol consumption		
Male	220(50.1)	204(47.2)	Yes	17(3.9)	20(4.6)
Female	219(49.9)	228(52.8)	No	422(96.1)	412(95.4)
Marital Status			Addiction		
Single, Divorced, Widow	107(24.4)	101(23.4)	Yes	4(0.9)	5(1.2)
Married	332(75.6)	331(76.6)	No	435(99.1)	427(98.8)
Mother ethnicity			Comorbidities		
Fars	175(39.9)	176(40.7)	Yes	49(11.2)	59(13.7)
Turk	188(42.8)	174(40.3)	No	390(88.8)	373(86.3)
Other	76(17.3)	82(19)			
Father ethnicity			Side effect		
Fars	178(40.5)	167(38.7)	Yes	434(98.9)	428(99.1)
Turk	184(41.9)	178(41.2)	No	5(1.1)	4(0.9)
Other	77(17.5)	87(20.1)			
Educational Level			Corona infection		
Illiterate	67(15.3)	70(16.2)	Yes	37(8.4)	61(14.1)
Under diploma	194(44.2)	200(46.3)	No	402(91.6)	37(85.9)
Academic	178(40.5)	162(37.5)			
Have a Job			Diagnosis		
Yes	259(59)	188(43.5)	Clinical	8(21.6)	5(8.9)
No	180(41)	244(56.5)	Clinical±RT-PCR±CT	16(43.2)	35(62.5)
			Only RT- PCR	13(35.1)	16(28.6)
			Cure after infection		
			Yes	37(8.4)	61(14.1)
			No	0(0)	0(0)

placebo was fear of side effects (20 participants in the hydroxychloroquine group and 31 in the placebo group).

In the bivariate analysis there was significant difference between Covid 19 infection and marital status of participants, statistically (p=0.04). 68% of patients with Covid 19 were married, and in the non-affected group, 77.1% were married. Married people were infected with Covid 1.4 times more (OR: 1.4, 95 CI: 1.01-2.28). As well as we found a statistically significant difference between contracting Covid 19 and receiving hydroxychloroquine as a prophylaxis agent (p=0.05). 62.9% of Covid 19 patients did not receive hydroxychloroquine as a prophylaxis agent.

Table 2: Outcomes of hydroxychloroquine Therapy for Prophylaxis against COVID-19 and the variables under study in the bivariate analysis

Variables	Positive COVID-19 infection N (%) 97(11.1%)	Negative COVID-19 infection N (%) 774(88.9%)	P. value
Age(Years) (Mean± *SD*)	39.44±12.18	40.45±12.29	0.4
Gender			0.7
Male	49(50.5)	375(48.4)	
Female	48(49.5)	399(51.6)	
Marital Status			0.04*
Single, Divorced, Widow	31(32)	177(22.9)	
Married	66(68)	597(77.1)	
Mother ethnicity			0.8
Fars	19(19.6)	139(18)	
Turk	40(41.2)	311(40.2)	
Other	38(39.2)	324(41.9)	
Father ethnicity			0.7
Fars	18(18.6)	146(18.9)	
Turk	42(43.3)	303(39.1)	
Other	37(38.1)	325(42)	
Educational Level			0.3
Illiterate	11(11.3)	126(16.3)	
Under diploma	44(45.4)	350(45.2)	
Academic	42(43.3)	298(38.5)	
Have a Job			0.6
Yes	58(59.8)	445(57.5)	
No	39(40.2)	329(42.5)	
Smoking			0.9
Yes	75(77.3)	595(76.9)	
No	22(22.7)	179(23.1)	
Alcohol consumption			0.6
Yes	5(5.2)	32(4.1)	
No	92(94.8)	742(95.9)	
Addiction			0.9
Yes	0(0)	9(1.2)	
No	97(11.3)	765(98.8)	
Prophylaxis groups			
Hydroxychloroquine	36(37.1)	371(47.9)	0.005*
Placebo	61(62.9)	403(52.1)	
Comorbidities			0.7
Yes	11(11.3)	97(12.5)	
No	86(88.7)	677(87.5)	
Side effect			0.06
Yes	3(3.1)	6(0.8)	
No	94(96.9)	768(99.2)	

Table 3: Multivariable analysis for predicting non infected people with COVID-19

Variable	OR (95%CI)	p.value
Prophylaxis groups		
Hydroxychloroquine	1.87 (1.19-2.84)	0.005*
Placebo(reference)		

Also, the chance of infection in the group did not receive hydroxychloroquine was 2.1 time (OR: 2.1, 95 CI: 1.01-3.21).Side effects were not more frequent with hydroxychloroquine than with placebo.
In the Hydroxychloroquine group 5 (1.1%) people had drug side effects and in placebo group 4 (0.9%) had side effects (p = 0.06) (Table 2).

On week 10, we assessed how well the masking of the trial interventions was maintained. A survey was conducted of 439 participants in the hydroxychloroquine group who completed week 7; 201(45.7%) correctly received hydroxychloroquine, 182 (41.4%) were unsure, and 56 (12.7%) believed that they received placebo. A survey was conducted of the 432 participants in the control group who completed week 7; 187 (43.2%) correctly identified that they received placebo, 195 (44.8%) were unsure, and 50 (11.5%) believed that they received hydroxychloroquine. In the absence of side effects, blinding was well maintained.
Finally, according to Multivariable analysis, we observed that the proportion of non-infected people who receive hydroxychloroquine prophylaxis is 1.87 times more than placebo users (OR 1.87, 95%CI: 1.19 - 2.84, p = 0.05) (Table 3).

Discussion

In this study, we found that consuming an average dose of 200mg per week of hydroxychloroquine prevented moderate and severe disease of COVID-19. There was a statistically significant difference between the rate of infection and the prophylaxis drug group in the study. The proportion of non-infection in people who received hydroxychloroquine prophylaxis was nearly twice as high compared to placebo users. There was no significant difference between the two groups in terms of side effects and no severe side effects were observed.

A wide range of studies have been conducted to evaluate prophylactic effect of hydroxychloroquine against COVID-19, and many of them show that HCQ has no definite effect but the use of this drug in many treatment protocols is still recommended, which indicates the practical effect of the drug (2, 12-25). In our study, we found that prophylactic use of hydroxychloroquine in the community reduces the incidence of severe and moderate forms of the disease. Our findings are consistent with prior literature; in a study conducted by Yu et al., the mortality rate of the group who received hydroxychloroquine was 18.8% while in the group that did not receive hydroxychloroquine mortality was 45.8% (4). Another study, conducted by Lammers, found that hydroxychloroquine had no effect on patients mortality but it significantly reduced the transfer of COVID-19 patients from normal to ICU wards (26). In another study conducted by Citeaux et al., the death rate in the group receiving hydroxychloroquine was 17.7% and 27.1% among the group who did not receive hydroxychloroquine; the death rate was lower in the hydroxychloroquine group than in the control group in multivariable analyses (27).

The absence of side effects of the drug in these doses was consistent with many similar studies, so that the clinical side effects of the drug in the treated groups compared with placebo were not significantly different (28-30). In a study conducted by Rentsch et al., it was shown that if hydroxychloroquine is given prophylactically to people who are not

infected with COVID-19, their mortality rate will be reduced (31). Our findings showed that there was no significant difference in disease severity between males and females, although some studies have suggested the role of sex hormones and the protective effect of X chromosome in the development of innate and acquired immunity (32, 33) and showed the male sex to be associated with the severity of COVID-19 disease (34). Other studies did not show a significant relationship between sex and disease severity or mortality (35). In our study, it was shown that there was a statistically significant relationship between patient's marital status and COVID-19 infection; the most moderate to severe cases were seen in unmarried people but this phenomena has not been reported in prior literature.

In this study, most of the participants were healthy during the 10-week follow-up period and had no symptoms of COVID-19 disease. A little over 10% of the participants developed confirmed COVID-19 infection. All patients recovered and no case of mortality was observed.

Study Limitations:

Limitations of this study include limited information available at the time of the study. Additionally, there was potential for selection bias due to lack of cooperation of some participants influenced by contradictory news surrounding the administration of hydroxychloroquine in the media. Our limited sample size may impact the ability to generalize results, however the randomized nature of our trial reduces the impact of this limitation. Finally, there was potential for recall bias during telephone call follow-up.

Conclusion

There was a statistically significant difference between the incidence and prophylaxis drug grouping in the study. Non-infection was nearly twice as high among patients treated with hydroxychloroquine compared to those treated with placebo. Future studies should be performed on a larger sample size, with a prophylactic dose over a longer period of time, thereby increasing the accuracy of the results obtained. Given these findings, and due to the lack of definitive treatment in severe cases of the disease, the drug with the mentioned dose should be prescribed in the community for prophylaxis of severe cases and requiring hospitalization

Acknowledgment

The authors would like to thank the Islamic Azad Tehran University of Medical Sciences for their support, cooperation, and assistance throughout the study.

Author's contribution

data analysis and interpretation: Arezoo Chouhdari; statistical analysis: Arezoo Chouhdari; supervision or mentorship: Termeh Tarjoman, Arezoo Chouhdari; write the first draft of the manuscript: Termeh Tarjoman, Arezoo Chouhdari; All authors contributed to the intellectual content, and manuscript editing and read and approved the final manuscript.

Ethical considerations

Questionnaires were filled with the participants' satisfaction and written consent was obtained from the participants in this study.

Funding

The project funding was provided by Islamic Azad University

Conflicts of interest

All authors declare no conflict of interest.

References:

1. Cao Y-c, Deng Q-x, Dai S-x. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel medicine and infectious disease. 2020;35:101647.

2. Shabani M, Totonchi M, Rezaeimirghaed O, Gachkar L, Hajiesmaeili M, Khoshkar A, et al. Evaluation of the prophylactic effect of hydroxychloroquine on people in close-contact with

patients with COVID-19. Pulm Pharmacol Ther. 2021;70:102069.

3. Najjar-Debbiny R, Gronich N, Weber G, Khoury J, Amar M, Stein N, et al. Effectiveness of Paxlovid in reducing severe coronavirus disease 2019 and mortality in high-risk patients. Clinical Infectious Diseases. 2023;76(3):e342-e9.

4. Huang F, Li Y, Leung EL-H, Liu X, Liu K, Wang Q, et al. A review of therapeutic agents and Chinese herbal medicines against SARS-COV-2 (COVID-19). Pharmacological research. 2020;158:104929.

5. Panahi Y, Gorabi AM, Talaei S, Beiraghdar F, Akbarzadeh A, Tarhriz V, et al. An overview on the treatments and prevention against COVID-19. Virology Journal. 2023;20(1):1-29.

6. De Francia S, Chiara F, Allegra S. COVID-19 Prevention and Treatment. MDPI; 2023. p. 834.

7. Honein MA, Christie A, Rose DA, Brooks JT, Meaney-Delman D, Cohn A, et al. Summary of Guidance for Public Health Strategies to Address High Levels of Community Transmission of SARS-CoV-2 and Related Deaths, December 2020. MMWR Morbidity and mortality weekly report. 2020;69(49):1860-7.

8. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell research. 2020;30(3):269-71.

9. Biot C, Daher W, Chavain N, Fandeur T, Khalife J, Dive D, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. Journal of medicinal chemistry. 2006;49(9):2845-9.

10. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology. 2016;123(6):1386-94.

11. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020;71(15):732-9.

12. Bhatt P, Patel V, Shah P, Parikh K. Hydroxychloroquine Prophylaxis against Coronavirus Disease-19: Practice Outcomes among Health-Care Workers. medRxiv. 2021:2021.08. 02.21260750.

13. Shabani M, Totonchi M, Rezaeimirghaed O, Gachkar L, Hajiesmaeili M, Khoshkar A, et al. Evaluation of the prophylactic effect of hydroxychloroquine on people in close-contact with patients with COVID-19. Pulmonary Pharmacology & Therapeutics. 2021;70:102069.

14. Khuroo MS. Chloroquine and hydroxychloroquine in coronavirus disease 2019 (COVID-19). Facts, fiction and the hype: a critical appraisal. International journal of antimicrobial agents. 2020;56(3):106101.

15. Dhibar DP, Arora N, Kakkar A, Singla N, Mohindra R, Suri V, et al. Post-exposure prophylaxis with hydroxychloroquine for the prevention of COVID-19, a myth or a reality? The PEP-CQ Study. International journal of antimicrobial agents. 2020;56(6):106224.

16. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medrxiv. 2020:2020.03. 22.20040758.

17. Jung S-Y, Kim M-S, Kim M-C, Choi S-H, Chung J-W, Choi ST. Effect of hydroxychloroquine pre-exposure on infection with SARS-CoV-2 in rheumatic disease patients: a population-based cohort study. Clinical Microbiology and Infection. 2021;27(4):611-7.

18. Kashour Z, Kashour T, Gerberi D, Tleyjeh IM. Mortality, viral clearance, and other clinical outcomes of hydroxychloroquine in COVID-19 Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clinical and translational science. 2021;14(3):1101-12.

19. Polo R, García-Albéniz X, Terán C, Morales M, Rial-Crestelo D, Garcinuño MA, et al. Daily tenofovir disoproxil fumarate/emtricitabine and hydroxychloroquine for pre-exposure prophylaxis of COVID-19: a double-blind placebo-controlled randomized trial in healthcare workers. Clinical Microbiology and Infection. 2023;29(1):85-93.

20. Bansal P, Goyal A, Cusick IV A, Lahan S, Dhaliwal HS, Bhyan P, et al. Hydroxychloroquine: a comprehensive review and its controversial role in coronavirus disease 2019. Annals of medicine. 2021;53(1):117-34.

21. Naggie S, Milstone A, Castro M, Collins SP, Lakshmi S, Anderson DJ, et al. Hydroxychloroquine for pre-exposure prophylaxis of COVID-19 in health care workers: a randomized, multicenter, placebo-controlled trial Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine (HERO-HCQ). International Journal of Infectious Diseases. 2023;129:40-8.

22. Monti M, Vertogen B, Masini C, Donati C, Lilli C, Zingaretti C, et al. Hydroxychloroquine as prophylaxis for COVID-19: a review. Frontiers in pharmacology. 2020;11:605185.

23.Cortegiani A, Ippolito M, Ingoglia G, Iozzo P, Giarratano A, Einav S. Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for COVID-19. Journal of critical care. 2020;59:176-90.

24.Smit M, Marinosci A, Agoritsas T, Calmy A. Prophylaxis for COVID-19: a systematic review. Clinical microbiology and infection. 2021;27(4):532-7.

25.Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020;383(21):2030-40.

26.Lammers AJJ, Brohet RM, Theunissen REP, Koster C, Rood R, Verhagen DWM, et al. Early hydroxychloroquine but not chloroquine use reduces ICU admission in COVID-19 patients. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2020;101:283-9.

27.Catteau L, Dauby N, Montourcy M, Bottieau E, Hautekiet J, Goetghebeur E, et al. Low-dose hydroxychloroquine therapy and mortality in hospitalised patients with COVID-19: a nationwide observational study of 8075 participants. International journal of antimicrobial agents. 2020;56(4):106144.

28.Sen S, Werner A, Shekhar A. Within a large healthcare system, the incidence of positive COVID-19 results and mortality are lower in patients on chronic hydroxychloroquine therapy. Drugs & therapy perspectives : for rational drug selection and use. 2020:1-2.

29.Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. The New England journal of medicine. 2020;383(6):517-25.

30.Cohen MS. Hydroxychloroquine for the Prevention of Covid-19 - Searching for Evidence. The New England journal of medicine. 2020;383(6):585-6.

31.Rentsch CT, DeVito NJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, et al. Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the OpenSAFELY platform. The Lancet Rheumatology. 2021;3(1):e19-e27.

32.Kloc M, Ghobrial RM, Kubiak JZ. The Role of Genetic Sex and Mitochondria in Response to COVID-19 Infection. International archives of allergy and immunology. 2020;181(8):629-34.

33.Ruggieri A, Anticoli S, D'Ambrosio A, Giordani L, Viora M. The influence of sex and gender on immunity, infection and vaccination. Annali dell'Istituto superiore di sanita. 2016;52(2):198-204.

34.Pradhan A, Olsson PE. Sex differences in severity and mortality from COVID-19: are males more vulnerable? Biology of sex differences. 2020;11(1):53.

35.Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? International journal of epidemiology. 2020;49(3):717-26.