Original Article

Open-label randomized control trial of hydroxychloroquine in patients with moderate to severe coronavirus disease 2019 infection

Salil Gupta, Prashant Kumar Dixit, Parthasarathi Ghana, Kumar Abhisheka, Harshit Khurana, Vijoy Kumar Jha, Debasish Mahapatra, Jitesh Goel, Safia Ahmed, G. Varadaraj

a Consultant & Head (Medicine & Neurology), Command Hospital (Air Force), Bengaluru, India
b Graded Specialist (Medicine), Command Hospital (Air Force), Bengaluru, India
c Commanding Officer, Air Force Hospital, Gorakhpur, India
d Senior Advisor (Medicine & Endocrinology), Command Hospital (Air Force), Bengaluru, India
e Senior Advisor (Medicine & Haematology), Command Hospital (Southern Command), Pune, India
f Classified Specialist (Medicine & Nephrology), Command Hospital (Air Force), Bengaluru, India
g Senior Advisor (Medicine & Nephrology), 7 Air Force Hospital, Kanpur, India
h Senior Advisor (Medicine & Neurology), Command Hospital (Air Force), Bengaluru, India
i Classified Specialist (Pulmonology), Command Hospital (Air Force), Bengaluru, India
j Classified Specialist (Medicine), Command Hospital (Air Force), Bengaluru, India

Article info

Article history:
Received 5 November 2020
Accepted 13 February 2021

Keywords:
COVID-19
Hydroxychloroquine
Hospitalization
Oxygen
Ventilator

Abstract

Background: At onset of coronavirus disease 2019 (COVID-19) pandemic, hydroxychloroquine (HCQ) was repurposed for treatment of patients based on reports that it had in vitro activity. The aim of this study was to find out if HCQ reduces number of days of hospitalization when given to patients with moderate to severe COVID-19 infections who require hospitalized care.

Methods: This was an open-label randomized control trial of HCQ administered 400 mg twice on day 1, then 400 mg once daily from day 2 to day 5 in patients with moderate to severe COVID-19 infection. Assessment was not blinded. Standard of care was given to both arms. Primary outcome was number of days of hospitalization till discharge or death.

Result: One hundred ten patients (55 in each arm) were included. Mean age was 58 years. Baseline characteristics were well matched. There was no difference in the primary outcome (13.67 vs 13.89; p = 0.98). Number of deaths were more in HCQ arm (RR: 1.81; 95% CI: 1.13–2.93; p = 0.03). There was no difference in number of days on oxygen or normalization of oxygen saturation, number who needed ventilator, days to ventilator requirement and days on ventilator. Twenty-nine patients in control arm received remdesivir. When adjusted analysis was done after removal of these patients, there was no difference in primary or secondary outcomes. Number of deaths in adjusted analysis were not significant (RR: 1.28; 95% CI: 0.87–1.88; p = 0.37).
Introduction

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan in China. It rapidly spread, resulting in a global pandemic. The disease was designated as COVID-19 (coronavirus disease 2019) by WHO. The virus that causes COVID-19 was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

There were initial reports that the drug hydroxychloroquine (HCQ) had in vitro activity against the SARS-CoV-2 virus. Based on such reports and uncontrolled clinical trials the Ministry of Health and Family Welfare, Government of India recommended in their guidelines on clinical management of COVID-19 issued on 31 March 20 page 18, an off-label use of HCQ in patients with severe disease and requiring ICU management.

With this background we designed and conducted an open label, parallel group randomized control trial with the aim of answering the question that in patients with moderate to severe COVID-19 infections who require hospitalized care does the administering of HCQ in the recommended doses reduce the number of days of hospitalization? In addition, we also attempted to answer if the drug reduced the number of days the patient required oxygen and subsequently the ventilator.

Material and methods

This open-label randomized control trial with unblinded assessment was conducted at a single tertiary care centre of Indian Armed Forces Medical Services located in a metropolis city. Patients were included in the study if they were COVID-19–positive based on real time reverse transcription polymerase chain reaction (rRT PCR), were symptomatic for 4 days, were willing to participate in the trial and satisfied at least two of the following four criteria: (i) oxygen saturation (SaO2) less than 95% as measured by digital pulse oximetry; (ii) respiratory rate more than 20/min; (iii) pulse rate more than 90/min or (iv) imaging evidence of lung infection in the form of reticulonodular opacities, ground glass opacities, consolidation or acute respiratory distress syndrome. Patients were excluded if they were 14 years or less in age. All included patients were randomized at admission or within 8 h to either the HCQ or control arm. Randomization was carried out by simple alternate allocation of patients in a 1:1 fashion by the first author to either the control or HCQ arm. The allocation was not concealed either from the patient or the physicians and other medical staff. Patients in the HCQ arm received the drug as per the following schedule: 400 mg twice on day 1, followed by 400 mg once daily from day 2 to day 5. Patients in both the arms were given standard of care which included intravenous (IV) antibiotics to cover respiratory pathogens, IV dexamethasone at a dose of 4 mg every 8 h for 5 days and subcutaneous low-molecular-weight heparin (LMWH) enoxaparin in dose of 40 mg (0.4 ml) once a day for 5 days. Discretion was given to the treating clinicians for the choice of antibiotics and for increasing dose of LMWH to twice a day depending on the severity of disease. Oxygen was to be started for all patients if the saturation went below 94%. Route of administration and the decision when, if needed, to place on ventilator was at the discretion of the treating clinician. Other standard critical care measure including IV fluids, vasopressors, proton pump inhibitors, and so on were used where indicated. As per previously approved COVID-19 management protocol of this institute, investigational therapies were to be avoided. Only the antiviral drug remdesivir could be used at the discretion of the treating clinician. The same protocol was followed in this study.

Epidemiological and clinical data were recorded for all patients at admission. The following tests were carried out for all patients at admission and on day 4: complete blood count serum biochemistry and certain predefined prognostic markers for COVID-19. These prognostic markers included: erythrocyte sedimentation rate (ESR), serum C reactive protein (quantitative) (CRP), serum procalcitonin levels, serum ferritin levels, serum creatine phosphokinase, serum troponin I levels, serum lactate dehydrogenase and D-dimer levels. Sequential organ failure assessment (SOFA) score and quick SOFA score were done for all patients at admission. Electrocardiogram and radiograph chest were carried out for all patients at admission and subsequently, where indicated. Computed tomogram chest was carried out only at the discretion of the treating clinician.

Primary treatment outcome was defined as number of days of hospitalization till discharge or death. Secondary outcome measures included differences in certain laboratory parameters on day 4 to assess the effect of drug on severity of disease, number of days where oxygen was used either continuously or intermittently for more than 30 min, number of days to normalization of SaO2 (≥95%), number of patients needing ventilator (invasive or non invasive), number of days from admission to ventilator requirement in these patients and number of days on ventilator and deaths. There was no concealment of allocation during analysis.

Sample size was calculated using a free online sample calculation site (ClinCalc.com) assuming the primary outcome being number of days of hospitalization till discharge or death. A sample size of 16 in each arm was calculated...
assuming that an average patient of moderate to severe COVID-19 infection will stay in the hospital for a mean of 15 ± 5 days (our unpublished observation) and the intervention will be reduce the stay in hospital by at least one third i.e. a mean of 10 days. The alpha error was 0.05 and the power of the study being 80%. Written informed consent was taken from all patients or next of kin in case the patient was not capable of giving consent. The trial was approved from the

| Table 1 – Baseline characteristics at admission/randomization. |
|-------------|-------------|-------------|-------------|
| Sr No | Variable | Control n = 55 | HCQ n = 55 | p value |
| 1 | Age in years (SD) | 57.3 (14.1) | 57.8 (12.6) | 0.72 |
| 2 | Gender (males) (%) | 37 (68.5) | 43 (76.8) | 0.20 |
| 3 | SOFA score at admission (SD) | 2.4 (1.6) | 2.6 (1.7) | 0.56 |
| 4 | Chronic lung disease (%) | 5 (9.1) | 6 (10.9) | 0.75 |
| 5 | Malignancy (%) | 1 (1.9) | 2 (3.6) | 0.56 |
| 6 | Diabetes (%) | 17 (31.5) | 19 (33.9) | 0.68 |
| 7 | Hypertension (%) | 23 (41.8) | 25 (45.5) | 0.70 |
| 8 | Smoking (%) | 11 (20.4) | 19 (33.9) | 0.09 |
| 9 | Coronary artery disease (%) | 8 (14.8) | 9 (16.1) | 0.79 |
| 10 | Body mass index kg/m² (SD) | 26.7 (4.5) | 25.9 (2.7) | 0.45 |
| 11 | SaO2% at admission (SD) | 89.4 (8.2) | 89.4 (9.8) | 0.86 |
| 12 | Total leucocyte count in cmm (TLC) (SD) | 6924 (3159) | 7395 (3494) | 0.38 |
| 13 | Neutrophil lymphocyte ratio (SD) | 7.2 (8.7) | 7.1 (5.6) | 0.29 |
| 14 | Aspartate transaminase (AST) in IU/L (SD) | 51 (40) | 51 (34) | 0.57 |
| 15 | Alanine transaminase (ALT) in IU/L (SD) | 57 (68) | 54 (66) | 0.98 |
| 16 | Serum albumin in g/dL (SD) | 3.2 (0.5) | 3.0 (0.5) | 0.11 |
| 17 | International normalized ratio (INR) (SD) | 0.95 (0.1) | 0.98 (0.2) | 0.12 |
| 18 | Serum lactate dehydrogenase U/L (SD) | 308 (99) | 373 (166) | 0.23 |
| 19 | ESR (SD) mm/hour | 47 (33) | 50 (39) | 0.96 |
| 20 | Serum C-reactive protein mg/L (SD) | 24.0 (12) | 24.4 (10) | 0.66 |
| 21 | Serum D-dimer ng/ml (SD) | 207 (51) | 240 (132) | 0.22 |
| 22 | Serum procalcitonin levels ng/ml (SD) | 0.45 (1.2) | 1.29 (5.8) | 0.92 |
| 23 | Serum creatine phosphokinase U/L | 273 (337) | 235 (382) | 0.68 |
| 24 | Serum ferritin µg/L (SD) | 498 (438) | 632 (719) | 0.70 |
| 25 | Serum troponin I ng/dL (SD) | 39 (146) | 40 (137) | 0.72 |
| 26 | Oxygen at admission (%) | 43 (78.2) | 45 (81.8) | 0.63 |
| 27 | Abnormal radiograph (%) | 48 (87.3) | 46 (83.6) | 0.59 |
| 28 | Zones involved on radiograph (SD) | 2.67 (1.87) | 3.13 (2.30) | 0.38 |

ESR, erythrocyte sedimentation rate.
institute ethics committee. The trial was registered prospectively with the Indian Council of Medical Research (National Institute of Medical Statistics) Clinical Trials Registry India on 07 April 2020 CTRI/2020/04/024479. Details can be found on their website. Permission to recruit first patient was from 13 April 2020. Statistical analysis in the form of Mann-Whitney U test for continuous variables and Chi-square test and Fischer Exact test for categorical variables were used. A p value of <0.05 was considered as significant.

Results

A total of 1658 patients were screened between last week of May (when the pandemic started in this metropolitan city) and 30 September 20 when recruitment was stopped. One hundred and ten consecutive patients who met all the inclusion criteria were recruited in the study. Recruitment continued for around 4 months even though the sample size was exceeded. Fifty five were randomized to HCQ arm and a similar number to the control arm as shown in the consort diagram (Fig. 1). Majority of the patients were men in each arm with the mean age being around 58 years. The baseline characteristics of the two arms is shown in Table 1. They were well matched for severity with no significant difference. The two arms were again compared after four days of admission and randomization for effect of drug on severity of disease (Table 2). There was no significant difference between groups except for the d-Dimer values which were more in the HCQ arm.

Table 3 shows the comparison of the outcome variables. There was no difference in the primary outcome of the mean

| Sr No | Variable                                      | Control n = 55 | HCQ n = 55 | P value |
|-------|-----------------------------------------------|----------------|------------|---------|
| 1     | Days of hospitalization (SD)                  | 13.67 (5.83)   | 13.89 (5.85)| 0.98    |
| 2     | Days on oxygen (SD)                           | 7.98 (5.45)    | 8.49 (6.38) | 0.88    |
| 3     | Days to normalization of SaO2 (SD)            | 7.59 (5.06)    | 6.54 (4.48) | 0.26    |
| 4     | Number needing ventilator (%)                 | 4 (7.27)       | 10 (18.2)  | 0.09    |
| 5     | Days from admission to ventilator (SD)        | 1.5 (2.38)     | 4.90 (4.88) | 0.18    |
| 6     | Days on ventilator (SD)                       | 8.75 (3.09)    | 8.33 (8.60) | 0.37    |
| 7     | Deaths (%)                                    | 2 (3.6)        | 10 (18.2)  | 0.01    |

Table 4 shows the comparison of the outcome variables after excluding remdesivir-treated patients from control group.

| Sr No | Variable                                      | Control n = 26 | HCQ n = 55 | P value |
|-------|-----------------------------------------------|----------------|------------|---------|
| 1     | Days of hospitalization (SD)                  | 12.46 (4.32)   | 13.89 (5.85)| 0.40    |
| 2     | Days on oxygen (SD)                           | 6.45 (3.36)    | 8.49 (6.38) | 0.47    |
| 3     | Days to normalization of SaO2 (SD)            | 5.94 (2.92)    | 6.54 (4.48) | 0.96    |
| 4     | Number needing ventilator (%)                 | 3 (5.45)       | 10 (18.2)  | 0.66    |
| 5     | Days from admission to ventilator (SD)        | 2 (2.64)       | 4.90 (4.88) | 0.37    |
| 6     | Days on ventilator (SD)                       | 7.33 (1.52)    | 8.33 (8.60) | 0.53    |
| 7     | Deaths (%)                                    | 2 (7.7)        | 10 (18.2)  | 0.37    |
| Sr No | Author | Design | Intervention/protocol | Control | Outcome |
|-------|--------|--------|-----------------------|---------|---------|
| 1     | RECOVERY Collaborative group | Open-label RCT | 1561 | 3155 | Death within 28 days: 421; HCQ (27.0%) control (25.0%) (RR: 1.09; 95% CI: 0.97–1.23; p = 0.15) |
| 2     | Tang et al 2020 | Multicentre, open label RCT | 75; 1.2 g/d loading x3 d; 800 mg/d for 2–3 weeks | 75 | Viral cure on day 28: 53/75 vs. 56/75 (not significant); adverse effect: 21/75 vs. 7/80 |
| 4     | Chen et al 2020 | Open label RCT | 15; 400 mg/d x 5 days | 31 | Clinical deterioration: 2vs9; progress to severe illness: 0vs 4 |
| 5     | Geleris et al 2020 | Prospective observational study | 811; 600 mg BD D1; 400 mg OD for 5 days | 562 | Mortality: HCQ 157vs control 75; Intubated: 154 vs26 (not significant) |
| 6     | Rosenberg et al. | Retrospective multicentre cohort | HCQ: 271 Dose not clear | 221 | Mortality: HCQ + AZ 189 (HR: 1.35); HCQ: 54 (HR: 1.08); control: 28 (not significant) |
| 7     | Mahévas et al 2020 | Comparative observational study | 84; 600 mg within 48 h of admission | 89 | Mortality: HCQ 9 vs control 8; ICU admission: 8vs14 (not significant) |
| 8     | Yu et al 2020 | Retrospective observational | 48; 200 mg BD x 7–10 days | 520 | Mortality: 9/48 vs 238/520 (significant in favour of HCQ) |
| 9     | Magagnoli et al 2020 | Retrospective observational | HCQ: 97 HCQ + AZ: 113 | 158 | Mortality: HCQ 27; HCQ + AZ 25; control 18. ICU admission/ventilation: HCQ 12/90; HCQ + AZ 7/101; control 25 (Not significant) |
| 10    | Huang et al 2020 | Retrospective cohort | HCQ + AZ 173 | 173 | No difference in mortality |
| 11    | Peters et al 2020 | Retrospective cohort | 1596 | 353 | adjusted HR of 1.09 (95% CI: 0.81–1.47). No difference HCQ: 30% lower risk of death in hospitalized patients. |
| 12    | CORIST collaboration | Retrospective observational | 2633 | 818 | No significant differences were found in the mean reduction of viral load at D3 |
| 13    | Mitja et al. | Open-label RCT | 136; 800 mg on D1; 400 mg OD till D2-D6 | 157 | No significant differences were found in the mean reduction of viral load at D3 |
| 14    | Ayele Mega T et al 2020 | Meta-analysis | HCQ: 3623; HCQ + AZ: 1020 | 2139 | Virologic cure (OR: 0.78; 95% CI: 0.39–1.56); Risk of mortality (OR: 1.26; 95% CI: 0.66–2.39)(p > 0.05) |
| 15    | Kashour et al 2020 | Meta-analysis | 15,938 | | Short-term mortality: OR 1.05 (95% CI: 0.96–1.15) (p > 0.05) |
| 16    | Yang et al 2020 | Meta-analysis | 4112 | | No changes in mortality rate, clinical progression, viral clearance; subgroup analysis of severe illness mortality OR 0.27, (95% CI 0.13–0.58) |
| 17    | Pathak et al 2020 | Meta-analysis | 1721 | 3091 | OR favourable outcome HCQ 1.11 (95 CI: 0.72–1.69) (p = 0.20) |
number of days of hospitalization till discharge or death between HCQ arm versus control (13.89 days vs 13.67 days; \( p = 0.98 \)). Among the secondary outcomes the proportion of deaths were significantly more in the HCQ arm (18.2% vs 3.6%; \( p = 0.01 \)). The relative risk of death in patients in the HCQ arm was 1.81 (95% CI: 1.13–2.93; \( p = 0.03 \)). There was no significant difference between the two arms in the other secondary outcome including number of days on oxygen, number of days to normalization of SaO2, proportion needing ventilator, number of days from admission to ventilator requirement and number of days on ventilator.

Twenty-nine patients (52.7%) in the control arm and none in the HCQ arm were given remdesivir due to the known interaction of the two drugs. A sub group analysis was done after excluding the remdesivir-treated patients from the control arm (Table 4). Here too, there was no difference in the primary outcome of the number of days of hospitalization till discharge or death. However, now, after adjusted analysis, the relative risk of death in the HCQ arm was not significant (1.28, 95% CI: 0.87–1.88; \( p = 0.37 \)). Other secondary outcomes were similar.

Discussion

Our trial has shown that HCQ, when given to patients with moderate to severe COVID-19 infection who need hospitalization, does not change the number of days of hospitalization to discharge or death. It also does not change the laboratory parameters on day 4 for severity of disease, the number of days the patient needs oxygen or the number needing ventilator. It does not delay the requirement of ventilator or bring down the number of days on ventilator. Overall, there was a significantly increased risk of dying in those patients who took HCQ (RR: 1.81; 95% confidence interval [CI]: 1.13–2.93; \( p = 0.03 \)). When an adjusted analysis was done after removing patients who had taken remdesivir, it did not show any significant difference in the proportion who had died in the two arms (RR: 1.28; 95% CI: 0.87–1.88; \( p = 0.37 \)).

Could the use of remdesivir have provided an undue advantage to control arm and reduced the actual difference between the two groups? It is unlikely that remdesivir would have influenced outcomes as there was no difference in the laboratory parameters assessing disease severity even on day 4 after starting HCQ. Patients received remdesivir around 4 days after admission/randomization. Adjusted analysis also did not show any difference in primary and other secondary outcomes. No patient in the HCQ arm received remdesivir due to the known drug interaction. HCQ reduces the efficacy of remdesivir.

Does the use of HCQ in these patients increase severity and mortality? The adjusted analysis data from our study does not support this statement although there is a non significant trend towards increased severity and death as shown in Table 4.

In the last few months, there has been a deluge of data regarding COVID-19 and HCQ. A PubMed search with the words ‘COVID19’ and ‘HCQ’ showed around 500 such publications, all published in 2020 and in the last few months between February and October 2020. These articles deal with both the safety and efficacy of the drug in treatment and for prophylaxis against COVID-19. The studies pertaining to treatment of COVID-19 with HCQ range from small retrospective observational studies without a control arm to randomized trials to meta-analysis. Some of the relevant studies have been summarized in Table 5. Majority of the randomized trials and the observational studies show that HCQ does not change outcomes. In some, it has shown to increase mortality. The meta-analysis reflect similar results.

In conclusion, in the rapidly changing world of COVID-19 therapeutics, our open-label, parallel group, unblinded randomized control trial suggests that HCQ does not change outcomes in moderate to severe COVID-19 infection. It supports some of the other observational studies and trials conducted in the last few months. We could not comment on the toxicity of HCQ as trial was not designed to assess it. The strength of our trial is that it was randomized and the randomization was good as seen by the well matched baseline characteristics; we recruited more patients than our calculated sample size and this helped us perform the adjusted analysis without losing the strength of the study and our outcomes were both clinical and laboratory based. The chief limitation of our trial is that there was no blinding at randomization or at assessment. Our trial is relevant because it is one of the first few from India. It will help clinicians in not prescribing a drug which does not change outcomes in moderate to severe COVID-19 infection and may be potentially toxic. It will help policy makers in closing the chapter on a repurposed drug which had gained a lot of popularity and spot light at the beginning of the pandemic.

Disclosure of competing interest

All authors have none to declare.

Acknowledgements

The authors acknowledge the valuable contributions of AS Prasad, Rahul Sud, M Harish Kumar and K Shruthi.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mjafi.2021.02.007.

References

1. Yao X, Ye F, Zhang M, 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). Clin Infect Dis. 2020;71(15):732.
2. Revised guidelines on clinical management of COVID – 19 government of India Ministry of Health & family Welfare directorate general of Health Services (EMR division) dated 31
1. Huang HD, Jneid H, Aziz M, et al. Safety and effectiveness of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020 Oct 8. https://doi.org/10.1056/NEJMoa2022926. Epub ahead of print. PMID: 33031652; PMCID: PMC7556338.

2. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of persons with COVID-19 in hospitals with and without standard treatment with (Hydroxy)chloroquine. Clin Microbiol Infect. 2020 Oct 14;S1198-7711(20):30615–30617. https://doi.org/10.1016/j.cmi.2020.10.004. Epub ahead of print. PMID: 33068758; PMCID: PMC7554450.

3. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalised COVID-19 patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020 May 14;369:m1849. https://doi.org/10.1136/bmj.m1849. PMID: 32409561; PMCID: PMC7221473.

4. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020 May 14;369:m1849. https://doi.org/10.1136/bmj.m1849. PMID: 32409561; PMCID: PMC7221473.

5. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2020 May 25;49(2):215–219. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03. PMID: 32391667.

6. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020 Jun 18;382(25):2411–2418. https://doi.org/10.1056/NEJMoas2012410. Epub 2020 May 7. PMID: 32379955; PMCID: PMC7224609.

7. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. J Am Med Assoc. 2020 Jun 23;323(24):2493–2502. https://doi.org/10.1001/jama.2020.8630. PMID: 32392282; PMCID: PMC7215635.

8. Mahevas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ. 2020 May 14;369:m1844. https://doi.org/10.1136/bmj.m1844. Erratum in: BMJ. 2020 Jun 18;369:m2328. PMID: 32409486; PMCID: PMC7221472.

9. Yu B, Li C, Chen P, Zhou N, Wang L. Hydroxychloroquine Application Is Associated with a Decreased Mortality in Critically Ill Patients with COVID-19. MedRxiv; 2020.

10. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. Med (N Y). 2020 Jun 5. https://doi.org/10.1016/j.medj.2020.06.001. Epub ahead of print. PMID: 32838355; PMCID: PMC7274588.

11. Huang HD, Jneid H, Aziz M, et al. Safety and effectiveness of hydroxychloroquine and azithromycin combination therapy for treatment of hospitalized patients with COVID-19: a propensity-matched study. Cardiol Ther. 2020 Dec;9(2):523–534. https://doi.org/10.1007/s40119-020-00201-7. Epub 2020 Oct 14. PMID: 33058086; PMCID: PMC7556606.

12. Peters EJG, Collard D, Van Assen S, et al, CovidPredict Study Group. Outcomes of persons with COVID-19 in hospitals with and without standard treatment with (Hydroxy)chloroquine. J Antimicrob Chemother. 2020 May 25;49(2):215–219. https://doi.org/10.1093/jac/dkaa403. Epub ahead of print. PMID: 32859477; PMCID: PMC7446618.

13. COVID-19 RISK and Treatments (CORIST) Collaboration. Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: findings from the observational multicentre Italian CORIST study. Eur J Intern Med. 2020 Aug 25;S0953-6647(20):30336–30336. https://doi.org/10.1016/j.ejim.2020.08.019. Epub ahead of print. PMID: 32859477; PMCID: PMC7446618.

14. Mitja O, Corbacho-Monné M, Ubals M, et al, BCN PEP-CoV-2 RESEARCH GROUP. Hydroxychloroquine for early treatment of adults with mild covid-19: a randomized-controlled trial. Clin Infect Dis. 2020 Jul 16. https://doi.org/10.1093/cid/ciaa1009. Epub ahead of print. PMID: 32674126; PMCID: PMC7454406.

15. Ayele Mega T, Feyissa TM, DessalegnBosho D, KumelaGoro K, ZelekeNegera G. The outcome of hydroxychloroquine in patients treated for COVID-19: systematic review and meta-analysis, 2020. J Antimicrob Chemother. 2020 Oct 8. https://doi.org/10.1093/jac/dkaa403. Epub ahead of print. PMID: 33031488.

16. Kashour Z, Riaz M, Garbati MA, et al. Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis. J Antimicrob Chemother. 2020 Oct 8. https://doi.org/10.1093/jac/dkaa403. Epub ahead of print. PMID: 33031488.

17. Yang TH, Chou CY, Yang YF, et al. Systematic review and meta-analysis of the effectiveness and safety of hydroxychloroquine in treating COVID-19 patients: a systematic review and meta-analysis. J Chin Med Assoc. 2020 Sep 15. https://doi.org/10.1097/ JCMS.000000000000425. Epub ahead of print. PMID: 32947506.

18. Pathak DSK, Salunke DAA, Thivari DP, et al. No benefit of hydroxychloroquine in COVID-19: results of systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Syndr. 2020 Sep 1;14(6):1673–1680. https://doi.org/10.1016/j.dxsy.2020.08.033. Epub ahead of print. PMID: 32905939; PMCID: PMC7462641.