Review Article

Hydroxychloroquine: A review of its safety and efficacy in COVID-19

Rutu H. Karia[1], Sanjana Nagraj[2], Ishita Gupta[3], Amit Barua[4], Nirmaljot Kaur[5], Harmandeep Singh[5]

[1]Anna Medical College and Research Centre, Mauritius, [2]Internal Medicine, Jacobi Medical Centre/Albert Einstein College of Medicine, New York, USA, [3]Dr. Rajendra Prasad Government Medical College, Tanda, Himachal Pradesh, India, [4]Institute of Applied Health Sciences, Chattogram, Bangladesh, [5]Sri Guru Ramdas Institute of Medical Sciences and Research, Amritsar, Punjab, India

Abstract

SARS-CoV-2 is a novel virus that has infected millions of people across the world. Given the compelling need to develop a therapeutic strategy, hydroxychloroquine has been advocated as an effective drug for the infection. However, multiple clinical trials conducted using hydroxychloroquine have yielded contrasting results. An electronic search using the primary databases from WHO, PubMed and Google Scholar was performed that yielded 21 studies eligible for inclusion. Among a total of 1,350 patients who received hydroxychloroquine, 689 (51.04%) were females. The most commonly reported comorbidities include hypertension (15.18%), diabetes mellitus (8.44%) and pulmonary disease (8.96%). Of the hydroxychloroquine-treated patients, 70% were virologically cured compared to 12.5% of the control group (p = 0.001). A good clinical outcome with virological cure was reported in 973 patients (91%) within 10 days out of 1,061 hydroxychloroquine-treated patients. A total of 29 (65%) renal transplant recipients achieved complete recovery following hydroxychloroquine administration. A total of 37 (2.7%) patients reported QT prolongation. Hydroxychloroquine was found to reduce mortality in healthy, SARS-Cov-2 positive patients and improve clinical recovery in renal transplant recipients. However, a definitive conclusion regarding its effect on viral clearance can only be reached by conducting more clinical trials involving bigger and diverse samples.

Keywords: Chloroquine, efficacy, hydroxychloroquine, safety, treatments of COVID-19

Introduction

Since the emergence of SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) in Wuhan, China in December 2019, more than 68 million confirmed cases and over 1 million deaths have been reported to date. The WHO declared it as a pandemic on 11th March 2020.[1] There is a wide array of clinical symptoms of COVID-19 (coronavirus disease-2019), most common being fever and cough.[2] Various other atypical symptoms have also been observed, for example, the presence of neurological symptoms in COVID-19–positive patients.[3]

With more than 100 countries affected, and a year since the first reported case, no effective and blanket therapeutic intervention or prophylactic measure has entered clinical practice. Although a number of drugs such as hydroxychloroquine (HCQ), remdesivir, lopinavir-ritonavir, and ivermectin provided promising *in vitro* results, none have achieved replicable therapeutic efficacy *in vivo*.

HCQ is believed to prevent the entry of the virus into the host cell by inhibiting the terminal glycosylation of angiotensin-converting enzyme-2 (ACE-2) receptors on the host cell membrane.[4] The drug also interferes with the binding of

Address for correspondence: Dr. Rutu H. Karia, "Shreeji", 1, Dwarka, Nasik, Maharashtra, India.
E-mail: rutu.karia@gmail.com

Received: 22-09-2020 **Revised:** 06-12-2020
Accepted: 21-12-2020 **Published:** 08-04-2021

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1961_20

How to cite this article: Karia RH, Nagraj S, Gupta I, Barua A, Kaur N, Singh H. Hydroxychloroquine: A review of its safety and efficacy in COVID-19. J Family Med Prim Care 2021;10:1124-33.

the viral spike protein to the host cell surface gangliosides.[5] Another proposed mechanism of action is the prevention of membrane fusion and viral replication by increasing the pH of the endosomes/lysosomes. Jia Liu *et al.* have reported a higher antiviral activity of HCQ against SARS-CoV-2 in monkey Vero E6 cells compared to chloroquine.[6,7] Despite promising *in vitro* results, the usage of HCQ in treating SARS-CoV-2 infection is uncertain. A wide range of adverse drug effects has also been reported. Our study is aimed at guiding researchers to come to a common consensus regarding the use of HCQ in the treatment of SARS-CoV-2 patients.

Methodology

Search method and strategy

An electronic literature search was conducted during the months of June and July, 2020 for articles on HCQ as a treatment option for COVID-19. Primary databases used for the search were WHO, PubMed and Google Scholar. The detailed search strategy is summarised in Figure 1.[8] The keywords used for the search strategy were hydroxychloroquine, coronavirus, COVID-19 and their combinations.

Data screening and eligibility

Articles were screened for eligibility based on the following criteria:

Inclusion criteria

1. Reported the use of HCQ to treat RT-PCR positive COVID-19 patients
2. Patient age >18 years
3. Full text and peer-reviewed articles
4. Articles in English.

Exclusion criteria

1. Pregnant patients
2. They represented review articles, commentaries, news reports or studies published as abstracts only.

Out of 716 published studies, 21 studies met the eligibility criteria and were included in the final review [Table 1]. Each article was reviewed by two authors independently. The disagreements were discussed and resolved by reaching a common consensus.

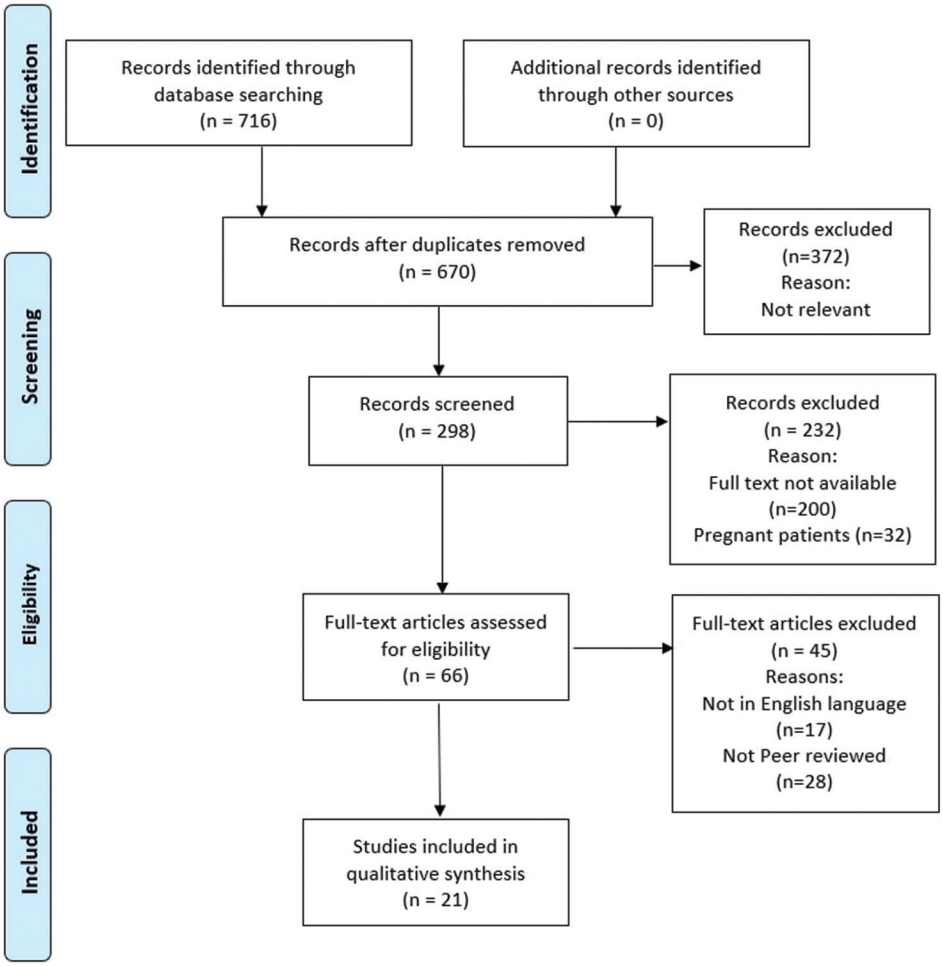

Figure 1: Details of Search Strategy

Table 1: Summary of the included studies

Author	Country of study	Study population	Hydroxychloro-quine dosage + day of administration	Other drugs/ interventions	Condition prior to drug administration	Outcome	Adverse Effects
Righi *et al.*	Italy	56-year-old male with spinal cord injury	200 mg, twice a day	1. Antibiotics: Piperacillin/ tazobactam. 2. Antiviral: lopinavir/ ritonavir. 3. Oxygen supplement-ation.	Worsening of Chest X-ray findings and persistence of fever despite 48 hours of antibiotic therapy.	Fever ceased after 2 days of therapy. Low-dose oxygen was not required further. Patient was discharged.	Not mentioned.
Gautret *et al.*	France	A cohort of 80 mildly infected cases.	200 mg, thrice a day.	1. Antibiotics: azithromycin. 2. Ceftriaxone in cases with NEWS score>5. 3. Oxygen supplement-ation.	All patients had mild symptoms.	65 patients recovered and were discharged. 1 patient died. 1 patient was still in intensive care unit. 13 patients were in the infectious disease ward.	1 case: Nausea, vomiting 4 cases: Diarrhoea 1 case: Blurring of vision
Spezzani *et al.*	Italy	Case 1: Breast cancer Case 2: controlled hypertension.	200 mg, twice a day.	1. Antibiotics: levofloxacin, piperacillin and tazobactam. 2. Antiviral: Darunavir/ cobicistat 3. Filgrastim	Case 1: mild symptoms with chest X-ray showing evidence of pneumonia Case 2: worsening symptoms Chest X-ray showing evidence of pneumonia.	Case 1: improvement in imaging findings within 6 days of HCQ administrat-ion. Case 2: ICU was required. Improved later. Both the patients were discharged.	Not mentioned
Bartiromo *et al.*	Italy	36-year-old woman with a transplanted kidney. (due to Senior-Loken syndrome)	200 mg, twice a day, administered on day 1	1. Antibiotics: ceftriaxone 2. Antiviral: lopinavir/ ritonavir, later replaced by Darunavir/ cobicistat. 3. Tacrolimus 4. Methyl-prednisolone	Patient had fatigue, dry cough and coryza. Patient did not have a fever.	By day 9, the patient recovered and was discharged.	Not mentioned.
Fontana *et al.*	Italy	61-year-old man with transplanted kidney. (due to chronic interstitial nephritis)	200 mg, twice a day, administered on day 9.	1. Low-dose oxygen through nasal cannula. 2. Tocilizumab 3. Antibiotics: azithromy-cin and meropenem 4. Immuno- globulin. (IV)	Persistence of fever despite antibiotic therapy.	Patient was discharged on day 22.	Not mentioned.
Falcão *et al.*	Brazil	29-year-old female who just gave birth at term, via caesarean section.	400 mg, twice daily on day 3.	1. Antibiotics: azithromycin, piperacillin, tazobactam. 2. Mechanical ventilation and supportive measures.	Worsening dyspnoea and imaging findings.	Patient was still in the ICU.	Hepatotoxicity upon adminis-tration of HCQ. (10-fold rise in transaminases)
Song *et al.*	South Korea	61-year-old female with Rheumatoid arthritis.	200 mg daily.	1. Lopinavir/ Ritonavir 2. Meloxicam 3. Famotidine	Dry cough, scanty sputum, sore throat. No severe respiratory symptoms like dyspnoea seen.	Patient was discharged by day 10.	Not mentioned.
Hillaker *et al.*	United States	40-year-old male.	400 mg twice daily for 1 day, followed by 200 mg twice daily for 4 days.	1. Antibiotics: cefepime, azithromycin 2. Oxygen by nasal cannula. 3. Remdesivir 4. Methyl-prednisolone 5. Mechanical ventilation.	Worsening clinical symptoms.	Patient was discharged by day 13.	Hepatotoxicity

Contd...

Table 1: Contd...

Author	Country of study	Study population	Hydroxychloro-quine dosage + day of administration	Other drugs/ interventions	Condition prior to drug administration	Outcome	Adverse Effects
Mathian *et al.*	France	17 patients with Systemic Lupus Erythem- atosus.	In 5 cases: 200 mg In 9 cases: 400 mg In 3 cases: > 400 mg	1. Prednisone 2. Ttocilizumab 3. Oxygen supplementa-tion. 4. Mechanical Ventilation 5. ECMO	ARDS, complications due to respiratory failure.	2 cases died. 7 cases were discharged. 7 cases were still in the hospital.	Not mentioned.
Nair *et al.*	United States	10 cases with kidney transplanta-tion	Not mentioned	1. Antibiotics: azithromycin, ceftriaxone, cefepime, piperacillin/ tazobactam. 2. Prednisone	Worsening clinical symptoms.	3 cases died. 7 cases were discharged.	5 cases: Acute kidney injury.
Bessière *et al.*	France	A Cohort of 40 patients.	200 mg, twice a day for 10 days	1. Antibiotics: azithromycin 2. Invasive mechanical ventilation 3. vasoactive drugs.	Not mentioned.	Not mentioned.	14 cases: Increased QT interval.
Mercuro *et al.*	United States	A cohort of 90 patients	Not mentioned.	1. Antibiotics: azithromycin 2. Mechanical ventilation	Not mentioned.	41 cases were discharged. 45 cases were still in the hospital. 4 cases died.	21 cases: Increased QT interval. 10 cases: Nausea
Kim *et al.*	South Korea	2 cases with kidney transplanta- tion	400 mg, once a day on day 1.	1. Antibiotics: azithromycin. 2. Antivirals: lopinavir/ ritonavir, 3. Prednisol-one. 4. Oxygen supplementa- tion.	Case 1: fever and diarrhoea redeveloped on day 7. HCQ was added. Case 2: fever, cough with newly formed ground glass opacities on imaging studies	Both the cases had successfully recovered and discharged.	Probable drug interaction with Tacrolimus, which is used in patients with solid organ transplants. 1 case: fever and diarrhoea.
Million *et al.*	France	Retrospective study of 1061 patients.	200 mg, thrice daily for 10 days.	1. Antibiotics: azithromycin	Not mentioned	1048 cases were discharged at the end of the study. 5 cases were still hospitalised due to worsening symptoms. 8 cases died.	2 cases: rash 12 cases: Diarrhoea 3 cases: abdominal pain 3 cases: headache 2 cases: nausea 2 cases: blurring of vision
Gautret *et al.*	France	36 cases. Out of 36 cases, 20 cases were given HCQ, while 16 cases were controls.	Not mentioned	1. Antibiotics: azithromycin	Not mentioned	3 patients transferred to ICU. 1 patient died.	Nausea in 1 patient
Ferrey *et al.*	United States	56-year-old male with ESRD (due to biopsy - proven IgA nephropathy)	Started on day 6. Dose not mentioned.	1. Antibiotics: azithromycin, ceftriaxone, vancomycin, piperacillin/ tazobactam. 2. Tocilizumab 3. Intubation	Worsening symptoms of ARDS.	Patient remains in critical condition.	Not mentioned
Mitra *et al.*	United States	66-year-old female with Rheumatoid arthritis, pulmonary fibrosis and asthma.	Started on day 5.	1. Antibiotics: doxycycline, levofloxacin, azithromycin	Worsening clinical symptoms and imaging findings.	Patient died due to progressive metabolic acidosis and multi- organ failure.	QT interval prolongation.
Jafari *et al.*	Iran	50-year-old female	Started on day 1.	1. Dimenhydri- nate. 2. Naproxen 3. Oxygen therapy	fever, dry cough, dyspnoea and fatigue for past 4 days	Patient was discharged.	Not mentioned
Dousa *et al.*	United States	39-year-old female with Rheumatoid arthritis and history of mitral valve repair.	Already on HCQ for rheumatoid arthritis. 200 mg daily.	None.	fever, mild productive cough, body ache, myalgia, shortness of breath and fatigue.	Symptoms resolved over 2 days of hospitalisation. Patient was discharged.	Not mentioned.

Contd...

Table 1: Contd...

Author	Country of study	Study population	Hydroxychloro-quine dosage + day of administration	Other drugs/ interventions	Condition prior to drug administration	Outcome	Adverse Effects
Morlacchi *et al.*	Italy	case 1: 48-year- old male with cystic fibrosis. case 2: 57-year -old female case 3: 70-year -old male with pulmonary fibrosis case 4: 69-year -old female	case 1: given on day 1. case 2: given on day 1. case 3: given on day 16. case 4: given on day 1.	1. Antibiotics: Levofloxacin, piperacillin/ tazobactam, doxycycline, meropenem. 2. Antifungal (in case 2 only) 3. Oxygen therapy	case 1: worsening symptoms and kidney function. case 2: worsening hypoxemia. case 3: worsening imaging findings case 4: on CPAP support and severe malaise.	3 cases: discharged. 1 case: died.	Not mentioned.
Mohan *et al.*	United States	A case series of 15 kidney transplant patients	Not mentioned.	1. Antibiotics: azithromycin 2. Tocilizumab 3. Tacrolimus 4. Steroids 5. Mycopheno- late mofetil	Not mentioned.	Deaths: 2 Discharged: 8 Still in the hospital: 6	Not mentioned.

HCQ: hydroxychloroquine; ICU: intensive care unit; CPAP: continuous positive airway pressure; ARDS: acute respiratory distress syndrome; ESRD: end-stage renal disease; ECMO: extra-corporeal membrane oxygenation[11-31]

Data collection and analysis

Data were extracted under the following categories when available:

1. Study design
2. Study country
3. Patient demographics
4. Median days of hospital days
5. Pharmacological and supportive management
6. Adverse effects

The primary and secondary outcomes assessed were:

1. Patients showing clinical/radiological improvement
2. Patients under observation
3. Patients worsening of symptoms/shifted to ICU
4. Patients discharged
5. Number of deaths

Our review included studies from various countries across the globe. A summary of the included studies is outlined in Table 1.

The data were tabulated using Microsoft Excel. Referencing was done using the standard software Zotero, as per guidelines.

Our study did not require ethical approval as data were obtained from already available databases, and patients were not directly involved.

Risk of bias assessment

Two authors independently assessed the risk of bias for each of the included studies (RK and IG). The disagreements were resolved by reaching a consensus. Assessment of the case reports and/or case series was done using the NIH Quality Assessment Tool for Case Series Studies.[9] Assessment of cohort studies was done using the Newcastle–Ottawa scale.[10]

Results

The search strategy described above retrieved a total of 716 published articles. Among these, 21 studies were identified to qualify for inclusion, as described in Figure 1. A summary of the baseline clinical conditions, outcomes and adverse effects reported in patients in the included studies is detailed in Table 1.

In this study, we investigated data from 1,367 COVID-19 patients, of which 1,350 received HCQ. Data have been reported for these 1,350 patients in our systematic review. In most of the patients, the administered dosage of HCQ was 200 mg per oral twice or thrice a day. In addition to this, very few cases received 400 mg of HCQ on day 1, followed by 200 mg of HCQ on the preceding days. Of note, out of the total number of patients who received HCQ, a majority of them had worsening symptoms/ radiological findings before drug administration. The patients also received other medications like antibiotics, antivirals, steroids and immunoglobulin and supportive management like oxygen therapy.

Five studies were conducted only on kidney transplant recipients with a pooled total of 29 patients.[14,15,20,23,31] 65% of the kidney transplant patients from these studies were successfully discharged. In our pooled analysis of 1,350 patients, 37 developed QT prolongation. Almost all of these 37 patients were also on other QT-prolonging drugs such as azithromycin and/or levofloxacin. Other commonly reported adverse effects were diarrhoea, nausea, rash, headache, blurry vision and hepatotoxicity.

The epidemiologic characteristics and comorbidities in the included patients are detailed in Table 2. Sex distribution was reported in the included studies with the number of females being 689 (51.04%) and the number of males was 661 (48.96%). Hypertension (15.18%), was the most frequently reported

comorbidity, followed by pulmonary disease (8.96%) and diabetes mellitus (8.44%).

The outcomes are reported in Table 3. We primarily reviewed the "clinical and/or radiological improvement", "under observation" and "worsening symptoms and/or shifted to intensive care unit (ICU)" post-HCQ administration and mortality rate. Of note, 1,148 (85%) out of 1,350 patients clinically and/or radiologically improved after the administration of HCQ.

Table 2: Epidemiological characteristics and comorbidities (*n*=1350)

Epidemiological characteristics		
Age Range	18-85 years	
No. of Males	661 (48.96%)	
No. of Females	689 (51.04%)	
Male to Female Ratio	0.96:1	
Comorbidities		
Variables	**No. of Patients**	**Percentage**
Hypertension	205	15.18
Diabetes Mellitus	114	8.44
Pulmonary disease	121	8.96
Cardiovascular disease	63	4.67
Renal disease	14	1.03
Neurological disease	5	0.37
Malignancy	34	2.52
Autoimmune disease	25	1.85
Organ Transplant	18	1.33
Others	67	4.96

Others: Obesity, Varicose veins, Senior Loken syndrome (SLS), Dyslipidemia, Osteoporosis and Cystic fibrosis

Quality assessment of included studies

Quality assessments of case reports/case series and for Cohort studies were done. The analyses are summarized in [Table 4] and [Table 5], respectively.

Discussion

Challenges associated with curtailing the community spread of the virus such as multiple modes of transmission and sources of virus shedding have made it imperative to find a promising drug that can combat the pandemic early in its course.[32,33] HCQ, a well-known disease-modifying anti-rheumatic drug, is used to treat auto-immune diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis, juvenile idiopathic arthritis and tropical infections such as malaria. Recently, the drug's antiviral properties are being applied as an attempt to mitigate the SARS-CoV-2 pandemic. By concentrating in different tissues, including the lungs, HCQ interferes with the glycosylation of ACE-2 cellular receptors of SARS-CoV-2.[4] Wang *et al.* found the drug's immune-modulating action to help augment its antiviral effect *in vitro*.[34] Thus, further studies detailing the antiviral property of HCQ, a derivative of chloroquine, in patients infected with the SARS-CoV-2 is needed.

In a study by Gautret *et al.*, a significant decrease in the nasopharyngeal viral load in patients on HCQ and azithromycin therapy was observed, with 83% of patients testing negative by Day 7 and 93% by Day 8.[15] Million *et al.* reported a good clinical outcome and virological cure in 973 patients (91.7%) within 10 days out of a total of 1,061 patients who were administered HCQ 200 mg three times a day for 10 days and azithromycin

Table 3: Outcomes reported in the included studies

Studies	Outcomes				
	Clinical and/or radiological improvement	**Under observation**	**Worsening symptoms and/or shifted to ICU**	**Discharged**	**Mortality (*n*)**
Righi *et al.*	1			1	
Gautret *et al.*	65	13	3	65	1
Spezzani et al.	1		1	2	
Bartiromo *et al.*	1			1	
Fontana *et al.*	1			1	
Falcão *et al.*			1		
Song *et al.*	1			1	
Hillaker *et al.*	1			1	
Mathian *et al.*	7	7		7	2
Nair *et al.*	7		5	7	3
Mercuro *et al.*		45		41	4
Kim *et al.*	2			2	
Million *et al.*	1048		5	1048	8
Gautret *et al.*			3		1
Ferrey *et al.*			1		
Mitra *et al.*					1
Jafari *et al.*	1			1	
Dousa *et al.*	1			1	
Morlacchi *et al.*	3			3	1
Mohan *et al.*	8	6		8	2

ICU: intensive care unit.[11-20,22-31]

Table 4: NIH Quality Assessment Tool for Case Series/Case reports

Study	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the cases consecutive?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable and implemented consistently across all study participants?	Was the length of follow-up adequate?	Were the statistical methods well described?	Were the results well described?	Quality rating (Good, Fair and Poor)
Righi *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Not described	N/A	Yes	Good
Spezzani *et al.*	Yes	Yes	Not described	Yes	Yes	Yes	Yes	Not described	Yes	Fair
Bartiromo *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes	Good
Fontana *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes	Good
Falcão *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Not described	N/A	Yes	Good
Song *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Not described	N/A	Yes	Good
Hillaker *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes	Good
Mathian *et al.*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not described	Yes	Good
Nair *et al.*	Yes	Yes	Not described	Yes	Yes	Yes	Yes	Not described	Yes	Fair
Bessière *et al.*	Yes	Yes	Yes	Yes	Yes	Yes	Not described	Not described	Yes	Fair
Kim *et al.*	Yes	Yes	Not described	Yes	Yes	Yes	Yes	Not described	Yes	Fair
Million *et al.*	Yes	Yes	Not described	Yes	Yes	Yes	Yes	Yes	Yes	Good
Ferrey *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes	Good
Mitra *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Yes	N/A	Yes	Good
Jafari *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Not described	N/A	Yes	Good
Dousa *et al.*	Yes	Yes	N/A	N/A	Yes	Yes	Not described	N/A	Yes	Good
Morlacchi *et al.*	Yes	Yes	Not described	Yes	Yes	Yes	Yes	Not described	Yes	Fair
Mohan *et al.*	Yes	Yes	Not described	Yes	Yes	Yes	Yes	Not described	Yes	Fair

N/A: not applicable.[11,13-21,23,24,26-31]

Table 5: Quality assessment for cohort studies as per (NewCastle-Ottawa quality assessment scale)

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Risk of Bias
Gautret *et al.*	Somewhat representative of patients	Drawn from the same community as the exposed cohort	Prescription, medical records	Yes	Unadjusted	Clinical and microbiological effect	Yes	Adequate follow up: >90% of subjects accounted for.	Good
Gautret *et al.*	Somewhat representative of patients	Drawn from the same community as the exposed cohort	Prescription, medical records	Yes	Unadjusted	Clinical and microbiological effect	Yes	Adequate follow up: >90% of subjects accounted for.	Good
Mercuro *et al.*	Somewhat representative of patients	Drawn from the same community as the exposed cohort	Prescription, medical records	Yes	Unadjusted	Clinical	Yes	Adequate follow up: >90% of subjects accounted for.	Good

References[12,22,25]

for 5 days.[24] 97.6% of these patients did not report any drug-related adverse effect. Although a low serum HCQ level was associated with poor clinical outcome initially, upon multivariate analysis, the association did not reach statistical significance.

In a comparative study conducted by Gautret *et al.*, a control group was included as a basis for comparison with the group receiving HCQ.[25] The study reported a significant reduction in the conversion rate (negative PCR results in nasopharyngeal samples)

between the HCQ group and the control group (p = 0.001). In the same study, the probability of achieving a virological cure with a HCQ plus azithromycin combination compared to HCQ alone was significantly higher. At day 6 post-inclusion, 100% of patients treated with HCQ plus azithromycin achieved virological cure compared to 57.1% patients treated with HCQ only, and only 12.5% patients in the control group (p < 0.001).

A reduction in the mortality rate was noted among the included studies. More number of patients showed improvements in their clinical and radiological findings after the administration of HCQ alone or in combination with azithromycin. Similar results pertaining to reduced mortality were noted in a study by Arshad *et al.* and Ayerbe *et al.*[35,36] Independent mortality factors in our study mainly included age ≥55 years and pre-existing co-morbidities like SLE. These findings were similar to those observed by Rio and Malani.[37] However, Rosenberg *et al.*, Annie *et al.* and Allameh *et al.* observed no significant differences in in-hospital mortality between patients treated with HCQ with or without azithromycin and patients who received neither drugs.[38-40] Lee *et al.* studied several observational studies and two huge randomised control trials and suggested that HCQ does not offer efficacy against hospitalised COVID-19 patients.[41]

Several studies (Mohan *et al.*, Bartiromo *et al.*, Fontana *et al.*, Nair *et al.*, and Kim *et al.*) in our pooled analysis focused on the effects of HCQ on immunocompromised patients (134/1350).[14,15,20,23,31] These patients were on different immunosuppressants when they were diagnosed with COVID-19. In many of the studies, the dosage of these immunosuppressants was reduced or the drug was temporarily withheld. 65% of the kidney transplant patients from these studies were successfully discharged.

The main drawback with HCQ administration is cardiovascular toxicity. The WHO pharmacovigilance database (VigiBase) contains reports of 83 episodes of torsades de pointes or other types of ventricular tachycardia that were associated with HCQ. Over a 52-year period, seven out of the 83 cases were found to be fatal.[42] The US Food and Drug Administration (FDA) had identified four cases of torsades de pointes and 14 cases of ventricular arrhythmia in chloroquine- or HCQ-treated COVID-19 patients.[42] In our study of 1,350 patients, several patients experienced adverse effects during their course of HCQ treatment. The most common side effect was the prolongation of the QT interval (2.7%). Almost all of these patients were also on other QT-prolonging drugs such as azithromycin and/or levofloxacin. Other side effects observed were diarrhoea (1.25%), nausea/vomiting (1.18%) and acute kidney injury (0.37%). Mercuro *et al.* emphasized that treatment with HCQ alone was associated with a high risk of QTc prolongation, and concurrent treatment with azithromycin was associated with greater changes in QTc.[24] Another study conducted by Bessière *et al.* on 40 patients treated with HCQ observed that seven (17.5%) patients had an increase in QTc of 500 milliseconds or greater.[23] A report by the Centres for Disease Control and Prevention (CDC) suggested that because of the long-half-life of HCQ (>40 days), patients could continue to be at risk for adverse cardiac events and drug interactions even after the completion of the course of therapy.[43]

Strengths

Our study findings have added to the existing literature on the efficacy and adverse effect profiles of HCQ use in COVID-19. One of the major strengths of our study is the robust analysis of patients treated with HCQ from different countries across the world including the USA, Italy, France, Spain, China, Brazil, South Korea, United Arab Emirates and Iran.

Limitations

We acknowledge the limitations of our study. We understand that the review methodology could have missed a relevant article and that variability in the quality of the included studies exists. Also, the sample size in most of the included studies is relatively small. We believe that a detailed study of HCQ use in a larger sample of COVID-19 patients would provide further insights into its efficacy and safety.

Conclusion

Although our study shows that HCQ is beneficial in reducing the mortality rate of COVID-19 patients and improving outcomes in renal transplant recipients, its effect on the clearance of virus is questionable. In the setting of polypharmacy and comorbid conditions, such as pre-existing heart conditions, performing an electrocardiogram, especially in those receiving other QT-prolonging medications is recommended as QT prolongation was a commonly reported adverse effect. All in all, varied views on the efficacy and safety of HCQ use was found through this extensive literature study. This study may help primary care physicians to familiarise themselves with the side-effects of HCQ and avoid the use of this drug as prophylaxis for COVID-19. The best step for physicians would be to refer patients where they can be carefully monitored. It is not recommended to prescribe HCQ as routine prophylaxis for COVID-19 infection in the primary care setting. Prudent clinical decision-making by family physicians will help triage those patients who need clinical monitoring in an inpatient setting. Also, the judicious use of HCQ will curtail the shortage in supply for conditions like autoimmune diseases where its utility is established. Large randomised controlled trials are required to elucidate the role of HCQ in the treatment of COVID-19.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organisation [Internet]. WHO. Available from:

www.who.int. [Last accessed on 2020 Aug 22].

2. Kaur N, Gupta I, Singh H, Karia R, Ashraf A, Habib A, *et al.* Epidemiological and clinical characteristics of 6635 COVID-19 patients: A pooled analysis. SN Compr Clin Med 2020:1-5. doi: 10.1007/s42399-020-00393-y.
3. Gupta I, Reddy MK, Hussain MM, Murthy PM, Robert CA. Atypical neurological manifestations of COVID-19. Cureus 2020;12:e8518.
4. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, *et al.* Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69.
5. Fantini J, Di Scala C, Chahinian H, Yahi N. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J Antimicrob Agents 2020;55:105960.
6. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, *et al.* Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020;6:16.
7. 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). Clin Infect Dis 2020;71:732-9.
8. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.
9. Quality Assessment Tool for Case Series studies [Internet]. National Heart, Lung, and Blood Institute. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. [Last accessed 2020 Aug 22].
10. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
11. Righi G, Del Popolo G. COVID-19 tsunami: The first case of a spinal cord injury patient in Italy. Spinal Cord Ser Cases 2020;6:22.
12. Gautret P, Lagier J-C, Parola P, Meddeb L, Sevestre J, Mailhe M, *et al.* Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis 2020;34:101663.
13. Spezzani V, Piunno A, Iselin H-U. Benign COVID-19 in an immunocompromised cancer patient-the case of a married couple. Swiss Med Wkly 2020;150:w20246.
14. Bartiromo M, Borchi B, Botta A, Bagalà A, Lugli G, Tilli M, *et al.* Threatening drug-drug interaction in a kidney transplant patient with Coronavirus Disease 2019 (COVID-19). Transpl Infect Dis 2020;22:e13286.
15. Fontana F, Alfano G, Mori G, Amurri A, Tei L, Ballestri M, *et al.* COVID-19 pneumonia in a kidney transplant recipient successfully treated with tocilizumab and hydroxychloroquine. Am J Transplant 2020;20:1902-6.
16. Falcão MB, de Góes Cavalcanti LP, Filgueiras Filho NM, de Brito CAA. Case Report: Hepatotoxicity associated with the use of hydroxychloroquine in a patient with COVID-19. Am J Trop Med Hyg 2020;102:1214-6.
17. Song J, Kang S, Choi SW, Seo KW, Lee S, So MW, *et al.* Coronavirus disease 19 (COVID-19) complicated with pneumonia in a patient with rheumatoid arthritis receiving conventional disease-modifying antirheumatic drugs. Rheumatol Int 2020;40:991-5.
18. Hillaker E, Belfer JJ, Bondici A, Murad H, Dumkow LE. Delayed initiation of remdesivir in a COVID-19-positive patient. Pharmacotherapy 2020;40:592-8.
19. Mathian A, Mahevas M, Rohmer J, Roumier M, Cohen-Aubart F, Amador-Borrero B, *et al.* Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. Ann Rheum Dis 2020;79:837-9.
20. Nair V, Jandovitz N, Hirsch JS, Nair G, Abate M, Bhaskaran M, *et al.* COVID-19 in kidney transplant recipients. Am J Transplant 2020;20:1819-25.
21. Bessière F, Roccia H, Delinière A, Charrière R, Chevalier P, Argaud L, *et al.* Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. JAMA Cardiol 2020;5:1067-9.
22. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, *et al.* Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:1036-41.
23. Kim Y, Kwon O, Paek JH, Park WY, Jin K, Hyun M, *et al.* Two distinct cases with COVID-19 in kidney transplant recipients. Am J Transplant 2020;20:2269-75.
24. Million M, Lagier J-C, Gautret P, Colson P, Fournier P-E, Amrane S, *et al.* Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis 2020;35:101738.
25. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56:105949.
26. Ferrey AJ, Choi G, Hanna RM, Chang Y, Tantisattamo E, Ivaturi K, *et al.* A case of novel coronavirus disease 19 in a chronic hemodialysis patient presenting with gastroenteritis and developing severe pulmonary disease. Am J Nephrol 2020;51:337-42.
27. Mitra RL, Greenstein SA, Epstein LM. An algorithm for managing QT prolongation in coronavirus disease 2019 (COVID-19) patients treated with either chloroquine or hydroxychloroquine in conjunction with azithromycin: Possible benefits of intravenous lidocaine. HeartRhythm Case Rep 2020;6:244-8.
28. Jafari R, Cegolon L, Jafari A, Kashaki M, Otoukesh B, Ghahderijani BH, *et al.* Large saddle pulmonary embolism in a woman infected by COVID-19 pneumonia. Eur Heart J 2020;41:2133.
29. Dousa KM, Malavade SS, Furin J, Gripshover B, Hatszegi M, Hojat L, *et al.* SARS-CoV-2 infection in a patient on chronic hydroxychloroquine therapy: Implications for prophylaxis. IDCases 2020;20:e00778.
30. Morlacchi LC, Rossetti V, Gigli L, Amati F, Rosso L, Aliberti S, *et al.* COVID-19 in lung transplant recipients: A case series from Milan, Italy. Transpl Infect Dis 2020:e13356. doi: 10.1111/tid. 13356.
31. Columbia University Kidney Transplant Program. Early

description of coronavirus 2019 disease in kidney transplant recipients in New York. J Am Soc Nephrol 2020;31:1150-6.

32. Karia R, Nagraj S. A review of viral shedding in resolved and convalescent COVID-19 patients. SN Compr Clin Med 2020:1-10. doi: 10.1007/s42399-020-00499-3.
33. Karia R, Gupta I, Khandait H, Yadav A, Yadav A. COVID-19 and its modes of transmission. SN Compr Clin Med 2020:1-4. doi: 10.1007/s42399-020-00498-4.
34. 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 Res 2020;30:269-71.
35. Arshad S, Kilgore P, Chaudhry ZS, Jacobsen G, Wang DD, Huitsing K, *et al*. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis 2020;97:396-403.
36. Ayerbe L, Risco-Risco C, Ayis S. The association of treatment with hydroxychloroquine and hospital mortality in COVID-19 patients. Intern Emerg Med 2020;15:1501-6.
37. Del Rio C, Malani PN. COVID-19—new insights on a rapidly changing epidemic. JAMA 2020;323:1339-40.
38. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, *et al*. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. JAMA 2020;323:2493-502.
39. Annie FH, Sirbu C, Frazier KR, Broce M, Lucas BD. Hydroxychloroquine in hospitalized COVID-19 patients: Real world experience assessing mortality. Pharmacotherapy 2020;40:1072-81.
40. Allameh SF, Nemati S, Ghalehtaki R, Mohammadnejad E, Aghili SM, Khajavirad N, *et al*. Clinical characteristics and outcomes of 905 COVID-19 Patients Admitted to Imam Khomeini Hospital Complex in the capital city of Tehran, Iran. Arch Iran Med 2020;23:766-75.
41. Lee Z, Rayner CR, Forrest JI, Nachega JB, Senchaudhuri E, Mills EJ. The rise and fall of hydroxychloroquine for the treatment and prevention of COVID-19. The American journal of tropical medicine and hygiene. 2020 Nov 24:tpmd201320. DOI: https://doi.org/10.4269/ajtmh.20-1320.
42. White NJ, Watson JA, Hoglund RM, Chan XHS, Cheah PY, Tarning J. COVID-19 prevention and treatment: A critical analysis of chloroquine and hydroxychloroquine clinical pharmacology. PLoS Med 2020;17:e1003252.
43. Hydroxychloroquine and Chloroquine Prescribing Patterns by Provider Specialty Following Initial Reports of Potential Benefit for COVID-19 Treatment — United States, January-June 2020 [Internet]. Centres for Disease Control and Prevention. Morbidity and Mortality Weekly Report (MMWR). Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6935a4.htm?s_cid=mm6935a4_w. [Last accessed on 2020 Aug 22].