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

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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 2020.⁵ There is a wide array of clinical symptoms of COVID-19 (coronavirus disease-2019), most common being fever and cough.⁶ Various other atypical symptoms have also been observed, for example, the presence of neurological symptoms in COVID-19–positive patients.⁷

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.⁸ The drug also interferes with the binding of SARS-CoV-2 to these receptors. Hydroxychloroquine: A review of its safety and efficacy in COVID-19. J Family Med Prim Care 2021;10:1124-33.
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. 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. 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
| Author(s) | Country | Study population | Hydroxychloroquine 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 supplementation. | 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 supplementation. | 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. | Nausea 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 administration. 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. Methylprednisolone | 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: azithromycin 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 administration 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. Methylprednisolone 5. Mechanical ventilation. | Worsening clinical symptoms. | Patient was discharged by day 13. | Hepatotoxicity |

Contd...
### Table 1: Contd...

| Author          | Country of study | Study population | Hydroxychloroquine dosage + day of administration | Other drugs/interventions | Condition prior to drug administration | Outcome | Adverse Effects |
|-----------------|------------------|------------------|--------------------------------------------------|---------------------------|----------------------------------------|---------|----------------|
| Mathian et al.  | France           | 17 patients with Systemic Lupus Erythematosus. | In 5 cases: 200 mg In 9 cases: 400 mg In 3 cases: > 400 mg | 1. Prednisone. 2. Tocilizumab 3. Oxygen supplementation. 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 transplantation | Not mentioned. | 1. Antibiotics: azithromycin, ceftriaxone, cephepime, 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. Mechanical ventilation | 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 transplantation | 400 mg, once a day on day 1. | 1. Antibiotics: azithromycin. 2. Antivirals: lopinavir/ ritonavir. 3. Prednisolone. 4. Oxygen supplementation. | 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 Nausea in 1 patient |
| 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. | |
| 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. Dimenhydrinate. 2. Naproxen 3. Oxygen therapy None. | Fever, dry cough, dyspnoea and fatigue for past 4 days | Patient was 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. | | Fever, mild productive cough, body ache, myalgia, shortness of breath and fatigue. | Symptoms resolved over 2 days of hospitalisation. | Not mentioned. |
**Table 1: Contd...**

| Author            | Country of study | Study population | Hydroxychloroquine 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

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**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. Assessment of cohort studies was done using the Newcastle–Ottawa scale.

**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. 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 | 18-85 years | 661 (48.96%) | 689 (51.04%) | 0.96:1 |
|--------------------------------|-------------|--------------|--------------|--------|

| Comorbidities | 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. 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. Wang et al. found the drug's immune-modulating action to help augment its antiviral effect in vitro. 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. 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     | Clinical and/or radiological improvement | Under observation | Worsening symptoms and/or shifted to ICU | Discharged | Mortality (n) |
|-------------|----------------------------------------|-------------------|-----------------------------------------|-----------|---------------|
| Righi et al. | 1                                      | 1                 | 1                                       | 1         | 1             |
| Gautret et al. | 65                                     | 13                | 3                                       | 65        | 1             |
| Spezzani et al. | 1                                      | 1                 | 1                                       | 2         |               |
| Bartiromo et al. | 1                                      | 1                 | 1                                       |           |               |
| Fontana et al. | 1                                      | 1                 | 1                                       |           |               |
| Falcao et al. | 1                                      | 1                 | 1                                       |           |               |
| Song et al. | 1                                      | 1                 | 1                                       |           |               |
| Hillaker et al. | 1                                      | 1                 | 1                                       |           |               |
| Mathian et al. | 7                                      | 7                 | 7                                       | 2         |               |
| Nair et al. | 7                                      | 7                 | 5                                       | 7         | 3             |
| Mercuro et al. | 45                                     | 45                | 5                                       | 41        | 4             |
| Kim et al. | 2                                      | 2                 | 2                                       |           |               |
| Million et al. | 1048                                   | 1048              | 5                                       | 1048      | 8             |
| Gautret et al. | 3                                      | 3                 |                                          | 3         | 1             |
| Ferrey et al. | 1                                      | 1                 | 1                                       |           |               |
| Mitra et al. | 1                                      | 1                 | 1                                       |           |               |
| Jafari et al. | 1                                      | 1                 | 1                                       |           |               |
| Dousa et al. | 1                                      | 1                 | 1                                       |           |               |
| Morlacchi et al. | 3                                      | 3                 | 3                                       | 3         | 1             |
| Mohan et al. | 8                                      | 6                 | 8                                       |           | 2             |

ICU: intensive care unit
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 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                                                 | N/A                                                                              | Yes                         | Yes                            | N/A                                                                              | Yes                                                                                | Yes                                             | Yes                                             | Good                             |
| Spezzani et al.            | Yes                                                 | Not described                                                                   | Yes                         | Yes                            | Yes                                                                              | Yes                                                                                | Yes                                             | Not described                     | Fair                             |
| Bartiramo et al.           | Yes                                                 | Not described                                                                   | Yes                         | N/A                            | Yes                                                                              | Not described                       | N/A                                              | Yes                                             | Good                             |
| Fontana et al.             | Yes                                                 | N/A                                                                              | Yes                         | Yes                            | Yes                                                                              | N/A                                                                                | Yes                                             | Yes                                             | Good                             |
| Falcão et al.              | Yes                                                 | N/A                                                                              | Yes                         | Yes                            | Yes                                                                              | Not described                       | N/A                                              | Yes                                             | Good                             |
| Song et al.                | Yes                                                 | N/A                                                                              | Yes                         | Yes                            | Yes                                                                              | Not described                       | N/A                                              | Yes                                             | Good                             |
| Hillaker et al.            | Yes                                                 | N/A                                                                              | Yes                         | Yes                            | Yes                                                                              | Not described                       | Yes                                              | No                                              | Good                             |
| Mathian et al.             | Yes                                                 | Yes                                                                              | Yes                         | Yes                            | Yes                                                                              | Not described                       | Yes                                              | No                                              | Good                             |
| Nair et al.                | Yes                                                 | Not described                                                                   | Yes                         | Yes                            | Yes                                                                              | Not described                       | Yes                                              | No                                              | Fair                             |
| Bessière et al.            | Yes                                                 | Yes                                                                              | Yes                         | Yes                            | Yes                                                                              | Not described                       | Yes                                              | No                                              | Fair                             |
| Kim et al.                 | Yes                                                 | Not described                                                                   | Yes                         | Yes                            | Yes                                                                              | Not described                       | Yes                                              | No                                              | Fair                             |
| Million et al.             | Yes                                                 | Not described                                                                   | Yes                         | Yes                            | Yes                                                                              | Not described                       | Yes                                              | No                                              | Fair                             |
| Ferrey et al.              | Yes                                                 | N/A                                                                              | Yes                         | Yes                            | Yes                                                                              | N/A                                                                                | Yes                                             | Yes                                             | Good                             |
| Mitra et al.               | Yes                                                 | N/A                                                                              | Yes                         | Yes                            | Yes                                                                              | N/A                                                                                | Yes                                             | Yes                                             | Good                             |
| Jafari et al.              | Yes                                                 | N/A                                                                              | Yes                         | Yes                            | Yes                                                                              | Not described                       | N/A                                              | Yes                                             | Good                             |
| Dousa et al.               | Yes                                                 | N/A                                                                              | Yes                         | Yes                            | Yes                                                                              | Not described                       | N/A                                              | Yes                                             | Good                             |
| Morlacchi et al.           | Yes                                                 | Not described                                                                   | Yes                         | Yes                            | Yes                                                                              | Not described                       | Yes                                              | No                                              | Fair                             |
| Mohan et al.               | Yes                                                 | Not described                                                                   | Yes                         | Yes                            | Yes                                                                              | Not described                       | Yes                                              | No                                              | Fair                             |

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 definition and fully described | Assessment of outcome | Was the 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         |
| Mercurio 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. 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. 23 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 Allamach 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).[4,15,20,22,41] 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.[43] 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.[44] 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.[45] 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.[46]

**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.

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**Conflicts of interest**

There are no conflicts of interest.

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