Hydroxychloroquine/chloroquine and the risk of acute kidney injury in COVID-19 patients: a systematic review and meta-analysis

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ABSTRACT

Objectives: Hydroxychloroquine/chloroquine has been widely used as part of the standard treatment for patients with coronavirus disease 2019 (COVID-19). We conducted a systematic review and meta-analysis to determine whether hydroxychloroquine/chloroquine increases the risk of acute kidney injury (AKI) in COVID-19 patients.

Methods: PubMed and Embase were searched for related publications from inception to Dec 31, 2021, including randomized controlled trials (RCTs) and non-randomized studies of interventions (NRSIs) comparing the risk of AKI and/or increased creatinine in COVID-19 patients receiving hydroxychloroquine/chloroquine and other controls (active treatment and placebo). We conducted separate meta-analyses for RCTs and NRSIs based on fixed-effect model, with odds ratios (ORs) being considered as effect sizes.

Results: We included 21 studies in the analysis, with 12 were RCTs. Based on the RCTs, compared to placebo, the OR was 1.19 (95% confidence interval [CI]: 0.86, 1.64; p = 0.30, n = 4, moderate quality) for AKI and 1.00 (95%CI: 0.64, 1.56; p = 0.99, n = 5, moderate quality) for increased creatinine for patients received hydroxychloroquine/chloroquine treatment; compared to active treatment, the odds was 1.28 (95%CI: 0.65, 2.53; p = 0.47, n = 2, low quality) for AKI and 0.64 (95%CI: 0.13, 3.20; p = 0.59, n = 1, low quality) for increased creatine. Evidence from NRSIs showed slightly increased odds of AKI, with low quality.

Conclusion: Based on current available studies which were graded as low to moderate quality, there is insufficient evidence to conclude that hydroxychloroquine/chloroquine use is associated with increased risk of AKI or raised creatinine.

Abbreviations: AKI: acute kidney injury; COVID-19: Coronavirus Disease 2019; RCT: randomized controlled trials; NRSI: non-randomized studies of interventions; OR: odds ratios; ROBIS-I: Risk Of Bias In Non-randomized Studies – of Interventions

Introduction

The coronavirus disease 2019 (COVID-19) pneumonia is caused by a new type of coronavirus, posing a huge threat to human health. According to the World Health Organization Coronavirus Dashboard, there have been 230,418,451 confirmed cases and 4,724,876 deaths globally, as of September 24, 2021 [1]. The common symptoms of COVID-19 pneumonia include fever, cough, headache, and other influenza-like symptoms [2]. While increasing evidence suggests that many COVID-19 patients have complications in the urinary system, acute kidney injury (AKI) is one of the most severe conditions [3–5]. As estimated by a meta-analysis, about 11% of the COVID-19 patients would develop AKI over 2 to 28 days follow-up and 6.8% needed the renal replacement therapy [6].

AKI is defined as a sudden loss of excretory kidney function that occurs within a few hours or days, presenting as an increase in serum creatinine levels with or without reduced urine output [7]. Many factors can lead to AKI, such as decreased renal perfusion/arterial pressure by any other conditions (e.g., heart failure), damage to tubular cells by nephrotoxic agents, or acute inflammation of blood vessels and glomeruli by systemic illness [8,9]. For COVID-19 patients, it is still unclear if AKI is largely due to hemodynamic changes, nephrotoxic agents or if the virus also leads to direct cytotoxicity [10].
Hydroxychloroquine, a derivative of chloroquine that has both antimalarial and anti-inflammatory activities, has been considered as part of the standard care for COVID-19 patients in some countries, especially during the first pandemic phase [11,12]. Although existing well-conducted meta-analyses have denied the potential benefits of hydroxychloroquine/chloroquine treatment on the prognosis of COVID-19 patients [12–15], millions of patients have already received such treatment. Hydroxychloroquine was found could potentially induce or intensify AKI by increasing lysosomal pH and inhibiting autophagy, because it has been demonstrated that Hydroxychloroquine inhibits autophagic flux by impairing autophagosome-lysosome fusion [16]. However, epidemiological evidence suggested controversy findings that make it unclear whether the development of AKI was associated with the use of hydroxychloroquine/chloroquine.

In this study, we conducted a systematic review and meta-analysis of current studies to explore the relationship between hydroxychloroquine/chloroquine and the risk of AKI.

Methods

The current systematic review was registered in PROSPERO (CRD42021265663) and was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement 2020 [17].

Inclusion criteria

We included original studies that investigated the relationship between hydroxychloroquine/chloroquine treatment and the risk of AKI in COVID-19 patients (both adults and children). The primary intervention was hydroxychloroquine or chloroquine, while the control was any other treatment meant for active treatments, supportive care, or placebo. The primary outcome was AKI reported by the original studies, and the secondary outcome was increased creatinine. For the study design, we considered randomized controlled trials (RCTs), cohort studies, and case-control studies. For simplicity, we referred to the latter two types of studies as non-randomized studies of intervention (NRSIs). For studies with few patients who may have had renal failure before the infection, we only considered new cases of AKI after treatment.

Literature search

We searched PubMed and Embase for studies on the treatment of COVID-19 patients with hydroxychloroquine/chloroquine published from inception to July 10, 2021 (LZ). An updated search on Dec 31, 2021 was conducted during the process of revision. We did not search for unpublished sources because the current largest preprint database for health science (medRxiv) with the topic of COVID-19 has already been indexed in PubMed. We did not restrict the outcome of the search strategy to avoid potential omissions for eligible studies. The following medical subject headings and/or keywords were used for hydroxychloroquine/chloroquine: ‘Hydroxychloroquine’, ‘Oxochloroquine’, ‘Plaquenil’, ‘Chloroquine’, ‘Chlorochin’, ‘Chingamin’, ‘Khingamin’, ‘Nivaquine’, ‘Aralen’, and ‘Arechine’. Moreover, the following medical subject headings and/or keywords were used for COVID-19: ‘COVID-19’, ‘2019-Cov’, ‘2019-nCov’, ‘nCov’, ‘severe acute respiratory syndrome coronavirus 2’, ‘SARS-CoV-2’, ‘sars coronavirus 2’, ‘SARS-2’, ‘SARS2’, ‘2019-novel-corona’, ‘Novel-corona’, ‘novel coronavirus’, ‘New-corona’, ‘Coronavirus’, ‘coronavirus 2’, ‘corona virus’, ‘Betacoronavirus’, and ‘Cov2’. The full search strategy is presented in the Supplementary Appendix.

Literature screen

Two review authors (LZ, ZZ) independently conducted the literature review. We first screened the titles and abstracts of the publications obtained by the search, followed by a review of the full text of the remaining records. Any disagreements were resolved through discussion. For each potential study, we also checked ClinicalTrial.gov for the outcome information.

Data extraction

Two review authors (ZZ, LQ) conducted data extraction using a pre-specified Excel sheet template. The following information was extracted: name of the first author, country where the study was conducted, patient characteristics (including age, comorbidity, diagnostic methods), intervention agent and dosage, control agent and dosage, outcomes, sample size of the study, number of outcomes in each group, follow-up of the study for the outcomes, and type of studies. Any disagreements in the extracted information were resolved through discussion.

Risk of bias

As planned, we used the Cochrane ROB 2.0 tool to assess the RCT’s risk of bias [18]. This tool considers five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement...
of the outcome, and bias in the selection of the reported result. For the cohort and case-control studies, we primarily planned to use the Newcastle-Ottawa Scale checklist [19], but we found that it could not be presented through a risk of bias plot. Therefore, we used the Risk Of Bias In Non-randomized Studies - of Interventions (ROBIS-I), as suggested by the Cochrane handbook, to assess the risk of bias [20]. To reduce subjective judgment, all review authors assessed the risk of bias.

**Statistical analysis**

The meta-analyses were conducted using RevMan 5.3 (Cochrane; London, United Kingdom) and Stata 12.0 (StataCorp LLC; Texas, United States). Given that both the primary and secondary outcomes were binary outcomes, we used the odds ratio (OR) and its 95% confidence interval (CI) to measure the potentially harmful effects of hydroxychloroquine/chloroquine. Furthermore, we used the Mantel-Haenszel method to pool the study-specific effects [21], and studies with different designs (RCTs vs. NRSIs) were pooled separately. Statistical significance was set at $p < .05$. Considering that the events of AKI and increased creatinine could be rare in some of the studies, we neglected the potential heterogeneity among the included studies and used the fixed-effect model to increase the statistical power. This decision was based on the recommendations of the Cochrane Handbook [21]. Considering the potential zero events in some studies, we used risk difference based on the Mantel-Haenszel method as a sensitivity analysis for those with double-zero studies [22].

Heterogeneity was measured using $I^2$. As suggested in the Cochrane handbook [21], we treated $I^2 < 30\%$ as no or slight heterogeneity; otherwise, there was moderate or substantial heterogeneity ($I^2 \geq 30\%$). For meta-analyses with moderate or substantial heterogeneity, the evidence was downgraded and a sensitivity analysis using a random-effect model based on the inverse-variance method was conducted.

Subgroup analysis was performed by type of control to determine if there was a difference in the ORs for active and placebo controls. We primarily planned to use age and dosage of treatment for the subgroup analysis, but half of the included studies did not provide detailed age information (i.e., adults or children), and only a few studies used different doses, making the planned subgroup analyses unimplementable. A further sensitivity analysis was conducted by omitting one study at a time to determine if the results were stable. Egger’s method was used to detect potential publication bias. Finally, the Grading of Recommendations Assessment, Development and Evaluation tool was used to rate the global evidence of each meta-analysis to form the conclusions [23].

**Results**

**Baseline characteristics**

The initial literature search in the two databases resulted in 4,830 records, and we identified 798 duplicates by author’s name, title, and publication year. Therefore, 4,032 publications were screened by title and abstract. We further excluded 3,832 records that did not meet the criteria, and the remaining 200 publications were screened through a review of the full text. After excluding 134 with different outcomes, 33 with different interventions, ten with different populations, and three with different study types, we finally included 20 studies [24–43] for the current systematic review, with a kappa value of 0.85 between the two reviewers (Figure S1, Supplementary Appendix). The updated search in 31 Dec 2021 (10 July, 2021 to 31, Dec 2021) resulted in 648 records, 72 were identified as duplicates, and 1 RCT [44] was identified as new studies that included in current meta-analysis.

Table 1 presents the main characteristics of the included studies. Among the 21 included studies, 14 considered AKI outcomes, and seven analyzed increased creatinine levels. Of the 14 studies on AKI, six were RCTs, six were cohort studies, and two were nested case-control studies. For the seven studies on increased creatinine levels, six were RCTs, and one was a cohort study. For the 21 studies, 13 clearly specified the age range, with 12 focusing on adults and one focusing on children. The daily total dosage of hydroxychloroquine/chloroquine ranged from 200 mg to 1200 mg (available from 18 studies), with 13 studies providing 400 mg, two studies providing 200 mg, one study providing 600 mg, one study providing 800 mg, and one study providing 1200 mg. The follow-up for the safety outcomes ranged from 3 to 42 days, while three studies did not provide such information. Eight studies were conducted in Europe, seven in Asia, and six in America.

**Risk of bias**

Figure 1 presents the risk of bias in the 12 RCTs and nine NRSIs. Among the 12 RCTs, the study by Chen (2020) [39] had a high risk of bias in the randomization process, four studies [28,39,41,42] had a high risk of
### Table 1. Baseline characteristics of included studies.

| Author          | Country | Population | Age (years, IQR) | Intervention (maintain dose) | Comparison (maintain dose) | Outcomes (total) | Sample size (events) | Follow-up for safety | Type of study |
|-----------------|---------|------------|------------------|------------------------------|---------------------------|------------------|----------------------|----------------------|--------------|
| Ader 2021 [24]  | France  | Adults (≥18 years) with a PCR-proven SARS-COV-2 infection; 71.7% male; patients with Stage 4 severe chronic kidney disease or requiring dialysis (i.e., eGFR <30 mL/min) were excluded | 63 (54 to 71) | Hydroxychloroquine (400 mg once daily) plus Standard care | Standard care | AKI: 50 out 579 patients | 143 (14) vs. 148 (9) | 29 days | Randomized controlled trial |
| Brown 2020 [25] | America | Hospitalized patients with symptomatic laboratory-confirmed COVID-19 within 10 days of a positive test; patients with renal failure were excluded | 55 (42 to 65) | Hydroxychloroquine (200 mg twice daily) plus Azithromycin (250 mg daily) | Placebo | AKI: 6 out of 83 patients | 41 (6) vs. 42 (0) | 5 days | Randomized controlled trial |
| Dubee 2021 [26] | France  | Adult (aged ≥18 years) with a diagnosis of COVID-19 confirmed by positive SARS-CoV-2 RT-PCR test on a nasopharyngeal swab; | 77 (58 to 86) | Hydroxychloroquine (200 mg twice daily) | Placebo | AKI: 74 out of 579 patients | 242 (37) vs. 237 (37) | 28 days | Randomized controlled trial |
| Self 2020 [27]  | Iran    | Adults (aged ≥18 years) who were hospitalized for less than 48 hours with laboratory-confirmed SARS-CoV-2 infection and symptoms of respiratory illness for less than 10 days were enrolled | 57.5 (43 to 69) | Hydroxychloroquine sulate (200 mg twice daily) | Placebo | AKI: 1 out of 150 patients | 70 (1) vs. 80 (0) | 28 days | Randomized controlled trial |
| Tang 2020 [28]  | China   | Adult (aged ≥18 years) with a diagnosis of COVID-19 confirmed by RT-PCR; patients with severe conditions including kidney disease and renal impairment were excluded | 46.1 (5D: 14.7) | Hydroxychloroquine (800 mg daily) plus Standard of care | Standard of care | AKI: 1 out of 150 patients | 70 (1) vs. 80 (0) | 28 days | Randomized controlled trial |
| Davoudi-Monfared 2020 [29] | Iran | Adult (aged ≥18 years) patients diagnosed with COVID-19; 3 patients (2 vs. 1) with renal disease secondary to COVID-19 was included. | 61 (50 to 70) | Hydroxychloroquine (200 mg twice daily) plus IFN-1a (44 ug/ml) | Standard of care | AKI: 23 out of 81 patients | 39 (11) vs. 42 (12) | 30 days | Randomized controlled trial |
| Falcão 2021 [30] | Portugal | Adult (aged ≥18 years) with a diagnosis of COVID-19 confirmed by positive SARS-CoV-2 RT-PCR test; 19 CKD patients in Hydroxychloroquine group and 1 in Remdesivir group were included. | 65.5/62 (18~) | Hydroxychloroquine (200 mg twice daily) plus lopinavir-ritonavir (400 and 100 mg, respectively, twice daily) or atazanavir-ritonavir Remdesivir (100 mg once daily) | Standard of care | AKI: 9 out of 149 patients | 101 (8) vs. 48 (1) | 18 to 22 days | Cohort study |
| Grimaldi 2020 [31] | Belgian-French | Adult (aged ≥18 years) with a diagnosis of COVID-19 confirmed by positive PCR test with moderate-to-severe acute respiratory distress syndrome | 63 (18~) | Hydroxychloroquine (no dose information) plus Lopinavir-ritonavir (no dose information) | Placebo | AKI: 261 out of 414 patients | 183 (124) vs. 231 (137) | 28 days | Cohort study |

(continued)
| Author               | Country                  | Population                                                                 | Age (years, IQR) | Intervention (maintain dose)                                                                 | Comparison (maintain dose)                                                                 | Outcomes (total) | Sample size (events) | Follow-up for safety | Type of study          |
|----------------------|--------------------------|-----------------------------------------------------------------------------|------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------------|----------------------|----------------------|-----------------------|
| Lagier 2020 [32]     | Marseille and France     | Adult (aged ≥ 18 years) with PCR-documented SARS-CoV-2 RNA from a nasopharyngeal sample | 45.3 (18–)      | Hydroxychloroquine (200 mg three times daily) and Azithromycin (250 mg once daily)          | Azithromycin (250 mg once daily)                                                           | AKI: 4 out of 3737 patients | 3337 (4) vs. 137 (0) | 3 to 13 days       | Cohort study          |
|                      |                          |                                                                             |                  | Hydroxychloroquine (200 mg three times daily)                                                | Azithromycin (250 mg once daily)                                                          |                  |                      |                      |                       |
|                      |                          |                                                                             |                  |                                                                                               |                                                                                             |                  |                      |                      |                       |
| Schneider 2020 [33]  | Germany                  | Patients with PCR-documented SARS-CoV-2 RNA from a nasopharyngeal or oropharyngeal swab specimen; 5 and 3 with CKD in treatment and control groups; non-ICU sample was used here | 67 in treatment and 70.5 in control | Hydroxychloroquine (200 mg twice daily) plus lopinavir/ritonavir                          | Unclear treatment                                                                           | AKI: 13 out of 28 | 14 (11) vs. 14 (2)   | NA                   | Cohort study          |
| Lecronier 2020 [34]  | France                   | Critical III patients with infection by SARS-CoV-2 defined by positive reverse transcriptase polymerase chain reaction (RT-PCR) | 57 (53 to 68)    | Hydroxychloroquine (200 mg twice daily) plus standard care                                  | Standard care                                                                               | AKI: 40 out of 80 patients | 38 (16) vs. 22 (12) | 7 days               | Cohort study          |
|                      |                          |                                                                             |                  | Hydroxychloroquine (200 mg twice daily) plus lopinavir/ritonavir                            | Lopinavir/ritonavir                                                                         |                  |                      |                      |                       |
|                      |                          |                                                                             |                  |                                                                                               |                                                                                             |                  |                      |                      |                       |
| Basalely 2021 [35]   | America                  | Children (≤ 18 years) who were admitted for treatment of acute COVID-19; Patients who were kidney transplant recipients, patients with end-stage kidney disease (estimated glomerular filtration rate <15 ml/min per 1.73 m² or dialysis) were excluded | 8.2 (1.5 to 13.8) | Hydroxychloroquine (no dose information)                                                    | Without Hydroxychloroquine                                                                  | AKI: 8 out of 97 patients | 8 (3) vs. 88 (14)    | NA                   | Nested case control   |
| Pham 2021 [36]       | America                  | All patients who presented to Weill Cornell Medical Center with confirmed COVID-19 by RT-PCR of nasopharyngeal sample; 2 and 3 with end-stage renal disease at the entry | 63 (43 to 73)    | Hydroxychloroquine (200 mg or 400 mg daily)                                                  | Without Hydroxychloroquine                                                                 | AKI: 18 out of 42 patients | 14 (9) vs. 28 (9)    | 28 days              | Nested case control   |
| Ghosn 2021 [37]      | Abu Dhabi                | Adult critical III patients (age ≥ 18 years) admitted to our ICU with confirmed SARS-CoV-2 infection by RT-PCR of nasopharyngeal sample; patients admitted to ICU with reasons other than acute respiratory were excluded. | 50 (40 to 59)    | Hydroxychloroquine (no dose information)                                                      | Without Hydroxychloroquine                                                                  | AKI: 50 out of 110 patients | 50 (18) vs. 60 (27) | NA                   | Case control          |
|                      |                          |                                                                             |                  |                                                                                               |                                                                                             |                  |                      |                      |                       |
| Outcomes were not primary clearly defined as AKI |                       |                                                                             |                  |                                                                                               |                                                                                             |                  |                      |                      |                       |
| Ulrich 2020 [38]     | America                  | Hospitalized patients with a positive SARS-CoV-2 by RT-PCR with at least one symptom | 66.2 (SD: 16.2) | Hydroxychloroquine (200 mg daily)                                                            | Placebo                                                                                    | Increased creatinine: 7 out of 128 patients | 67 (5) vs. 61 (2)    | 30 days              | Randomized controlled trial |
Table 1. Continued.

| Author          | Country   | Population                                                                 | Age (years, IQR) | Intervention (maintain dose)                                      | Comparison (maintain dose)                      | Outcomes (total)                                                                 | Sample size (events) | Follow-up for safety | Type of study          |
|-----------------|-----------|-----------------------------------------------------------------------------|------------------|------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------|----------------------|-----------------------|-----------------------|
| Chen 2020 [39]  | China     | Treatment naïve adult patients (≥ 18 years) confirmed COVID-19; patients with any renal disease were excluded | 48.6 (18–)       | Hydroxychloroquine (400 mg once daily) plus standard supportive care | Standard supportive care Increased creatinine: 1 out of 30 patients | 15 (0) vs. 15 (1)                                                             | 14 days              | Randomized controlled trial |
| Borba 2020 [40] | Brazil    | Hospitalized patients with clinical suspicion of COVID-19 (ie, history of fever and any respiratory symptom, e.g. cough or rhinorrhea), aged 18 years or older at the time of inclusion; 4 patients with impaired renal functions were excluded. | 51.1 (SD: 13.9)  | Chloroquine diphosphate (600 mg twice daily)                       | Chloroquine diphosphate (450 mg twice daily) | Increased creatinine: 13 out of 27 patients                                   | 18 (8) vs. 9 (5)     | 14 days               | Randomized controlled trial |
| Mitjà 2020 [41] | Spain     | Non-hospitalized adult patients with recently confirmed SARS-CoV-2 infection and less than five days of symptoms, with positive PCR test for SARS-CoV-2 by nasopharyngeal swab; those with moderate or severe condition as well as renal failure were excluded. | 41.6 (SD: 12.5)  | Hydroxychloroquine (400 mg once daily)                            | Without treatment except usual care            | Renal and urinary disorders: 1 out of 351 patients                            | 169 (1) vs. 184 (0)  | 28 days               | Randomized controlled trial |
| Purwati 2021 [42] | Indonesia | Adult (aged ≥ 18 years) with a diagnosis of COVID-19 with mild to moderate symptoms confirmed by PCR swab test; patients with impaired renal functions were excluded. | 36.5 (20 to 55)  | Hydroxychloroquine (200 mg once daily)                            | Azithromycin (500 mg once daily)               | Increased creatinine: 62 out of 751 patients                                   | 121 (11) vs. 119 (9) | 7 days                | Randomized controlled trial |
| Kim 2021 [43]   | Korea     | Patients with PCR-documented SARS-CoV-2 RNA from a nasopharyngeal or oropharyngeal swab specimen, treated with lopinavir-ritonavir or hydroxychloroquine for 7 days or more; 1 and 3 patients with CKD in treatment and control groups | 64.3 (SD: 15.4)  | Hydroxychloroquine (400 mg once daily)                            | Lopinavir-ritonavir (400 and 100 mg, respectively) | Increased creatinine: 9 out of 28 patients                                   | 34 (6) vs. 31 (3)    | 42 days               | Cohort study             |
| Hernandez-Cardenas 2021 [44] | Mexico | Adults aged more than 18 years with COVID-19 confirmed by RT-PCR and lung injury; no patients had kidney disease. | 50 (50: 11 in treatment and 49 (50: 12 in control) in hydroxychloroquine (200 mg every 12 hours) | Placebo | Increased creatinine: 144 out of 214 patients | 106 (69) vs. 108 (75) | 30 days               | Randomized controlled trial |

IQR: interquartile range; SD: standard deviation; CKD: Chronic Kidney Disease; PCR: Polymerase Chain Reaction; RT-PCR: Real time-Polymerase Chain Reaction; ICU: Intensive Care Unit; AKI: acute kidney injury.
bias due to the deviation from the intended intervention, and one study [39] had a high risk of bias in the selection of the reported result. In addition, four studies [24,26,27,38] had a possible bias of deviation from the intended intervention, and five [29,39–42] presented some concerns regarding the bias of missing outcomes. For the nine NRSIs, six studies [30,31,34,35,37,43] showed a critical bias, three [32,33,36] showed moderate bias due to confounding, and four studies [31,34,35,37] showed moderate bias due to the selection of participants. In addition, three [31,32,36] showed critical bias, and three [32,34,43] showed moderate bias due to the measurement of outcomes, and one [43] showed moderate bias due to the selection of the reported result.

**Hydroxychloroquine vs. placebo**

Figure 2 presents the comparison of hydroxychloroquine/chloroquine vs. placebo on the risk of AKI and increased creatinine for hydroxychloroquine/chloroquine compared to placebo based on the evidence of RCTs.

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**Table 1: Risk of bias of included studies (RCTs)**

| Study         | D1 | D2 | D3 | D4 | D5 | Overall |
|---------------|----|----|----|----|----|---------|
| Ader 2021     | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Brown 2020    | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Dubec 2021    | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Scr 2020      | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Tang 2020     | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Davoudi-Montef 2020 | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Licn 2020     | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Chen 2020     | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Horba 2020    | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Mija 2020     | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Punwali 2021  | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Hernandez-Cardenas 2021 | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |

**Table 2: Risk of bias of included studies (NRSIs)**

| Study         | D1 | D2 | D3 | D4 | D5 | Overall |
|---------------|----|----|----|----|----|---------|
| Falteo 2021   | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Grimaldi 2020 | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Lagier 2020   | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Schneider 2020| ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Leucronier 2020 | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Batasely 2021 | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Pham 2021     | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Ghoren 2021   | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |
| Kim 2021      | ✥ | ✥ | ✥ | ✥ | ✥ | ✥       |

**Figure 1.** The risk of bias of included studies.

**Figure 2.** The risk of AKI and increased creatinine for hydroxychloroquine/chloroquine compared to placebo based on the evidence of RCTs.
increased creatinine in RCTs. The meta-analysis showed that, compared to placebo, the OR of AKI with hydroxychloroquine/chloroquine was 1.19 (95% CI: 0.86, 1.64; \( p = .30, n = 4, \) moderate quality), with no evidence of heterogeneity (\( I^2 = 0 \)). Similarly, the OR of increased creatinine was 1.00 (95%CI: 0.64, 1.56; \( p = .99, n = 5, \) moderate quality), with no evidence of heterogeneity (\( I^2 = 0 \)). Based on two NRSIs, the OR for AKI was 0.48 (95%CI: 0.16, 0.46, low quality), Figure S2 (Supplementary Appendix).

**Hydroxychloroquine vs. active treatment**

Two RCTs compared the risk of AKI, and one RCT compared the risk of increased creatinine between hydroxychloroquine/chloroquine and active treatment (Figure 3). Compared to active treatment, the meta-analysis showed that the OR of AKI with hydroxychloroquine/chloroquine was 1.28 (95%CI: 0.65, 2.53; \( p = .47, n = 2, \) low quality), with substantial heterogeneity (\( I^2 = 74\% \)), while the OR of increased creatinine was 0.64 (95%CI: 0.13, 3.2; \( p = .59, n = 1, \) low quality). However, heterogeneity was inestimable as only one study was available. Based on NRSIs, the OR was 1.43 (95%CI: 1.06, 1.94; \( p = .01, n = 8, \) low quality) for AKI with hydroxychloroquine/chloroquine, and 2.00 (95%CI: 0.45, 8.80; \( p = .36, n = 1, \) low quality) for increased creatinine, Figure S3 (Supplementary Appendix).

**Sensitivity analysis and publication bias**

The results of the sensitivity analyses are presented in the Supplementary Appendix file (Figure S4 to S7), which showed that the effects remained stable in the random-effect model based on the evidence from RCTs. However, for evidence of NRSIs, the removal of the studies by Grimaldi [31] or Schneider [33] caused the pooled OR to no longer be significant (\( p > .05 \)) comparing hydroxychloroquine/chloroquine and active treatment. However, this did not alter the direction of the effects.

Considering the limited number of studies on the two outcomes in the meta-analyses, we combined them to detect the potential publication bias, with our results suggesting absent bias (Egger’s \( p = .56 \) for meta-analysis based on RCTs for placebo; Egger’s \( p = .86 \) for meta-analysis based on NRSIs for active treatment).

**Discussion**

We conducted a systematic review and meta-analysis to investigate the risk of AKI and increased creatinine levels in COVID-19 patients treated with hydroxychloroquine/chloroquine. To the best of our knowledge, this was the first systematic review to investigate the harmful effects of hydroxychloroquine/chloroquine in COVID-19 patients. Our results suggest that there is currently no strong evidence that hydroxychloroquine/chloroquine increases the risk of AKI in COVID-19 patients.

In our meta-analysis, the potential for increased risk of AKI was detected by evidence from cohort and case-control studies. However, the quality of the evidence was low, possibly due to the confounding factor that the majority of the NRSIs had a critical risk of bias from potential confounders. In addition, the unstable results in the post-hoc sensitivity analysis for the meta-analyses of NRSIs suggested some evidence of publication bias.
We noticed that the sample size of Schneider’s study was small, while the effect was extremely large. Further, the study had a substantial impact on the pooled effects, which is clear evidence of publication bias. However, Egger’s test failed to confirm this.

Our study’s direct evidence suggests that the routine administration of hydroxychloroquine/chloroquine is not associated with nephrotoxicity in COVID-19 patients. Meanwhile, the indirect evidence suggests that other active treatments may not also result in nephrotoxicity in COVID-19 patients. This further indicates that the AKI cases reported in COVID-19 patients were more likely due to factors other than drug toxicity. Hirsch et al. [45] found that patients who required mechanical ventilation had an almost four times higher risk of developing AKI than non-ventilated patients. Chen et al. found that in hospitalized COVID-19 patients, a higher level of serum phosphorus was associated with an increased risk of AKI [46]. Further research on the molecular biology mechanism is helpful in exploring the potential relationship between COVID-19 infection and AKI.

The current study had some strengths. First, the current study used a systematic review approach to summarize all available studies to ensure more representative and credible results. Second, we also maintained a standard and strict process during the conduct of the systematic review and meta-analysis to guarantee the quality of the current study. Furthermore, the quality of the included RCTs and the homogenous effects ensure a moderate quality of evidence, making the findings conclusive. However, this study had some limitations. First, although we included both RCTs and NRSIs, the quality of the evidence from NRSIs was proved to be low, contributing little contribution to the conclusion. Furthermore, the analysis of NRSIs takes a large amount of time, which largely prolonged the conduct of the current systematic review. Second, there were only four or five RCTs for each outcome, and most of the RCTs were based on an open-label design, which may have led to some bias in the results. Therefore, we downgraded the evidence as moderate. Third, some RCTs reported limited information on the safety outcomes, excluding renal system adverse events, and therefore were not included in the current study. However, such RCTs may have collected the information, but the authors failed to report it, leading to a potential loss of evidence. These limitations should be addressed in updated meta-analyses.

In conclusion, based on currently available studies which were graded as low to moderate quality, there is insufficient evidence to conclude that hydroxychloroquine/chloroquine use is associated with increased risk of AKI or raised creatinine.

**Disclosure statement**

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**References**

[1] The WHO Coronavirus Dashboard; 2021 [cited 2021 Sept 24]. Available from: https://covid19.who.int/

[2] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–513.

[3] Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829–838.

[4] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–1062.

[5] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-Infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–1069.

[6] Kunutsor SK, Laukkanen JA. Renal complications in COVID-19: a systematic review and meta-analysis. Ann Med. 2020;52(7):345–353.

[7] Kellum JA, Romagnani P, Ashuntantang G, et al. Acute kidney injury. Nat Rev Dis Primers. 2021;7(1):52.

[8] Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev. 2016;37(2):85–98.

[9] Rossaint J, Zarbock A. Acute kidney injury: definition, diagnosis and epidemiology. Minerva Urol Nefrol. 2016;68(1):49–57.

[10] de Almeida DC, Franco MDCP, Dos Santos DRP, et al. Acute kidney injury: incidence, risk factors, and outcomes in severe COVID-19 patients. PLoS One. 2021;16(5):e0251048.

[11] Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov. 2020;6:16.

[12] Sinha N, Balayla G. Hydroxychloroquine and COVID-19. Postgrad Med J. 2020;96(1139):550–555.

[13] Singh B, Ryan H, Kredo T, et al. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database Syst Rev. 2021;2(2):CD013587.

[14] Elavarasi A, Prasad M, Seth T, et al. Chloroquine and hydroxychloroquine for the treatment of COVID-19: a
systematic review and meta-analysis. J Gen Intern Med. 2020;35(11):3308–3314.

[15] Kim MS, An MH, Kim WJ, et al. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: a systematic review and network meta-analysis. PLoS Med. 2020;17(12):e1003501.

[16] Mauthe M, Orhon I, Rocchi C, et al. Chloroquine inhibits its autophagic flux by decreasing autophagosome-lysosome fusion. Autophagy. 2018;14(8):1435–1455.

[17] Page MJ, McKenzie JE, Leither LM, et al. Effect of hydroxychloroquine on autoantibody responses and cytokine production in patients with COVID-19. Clin Infect Dis. 2021;73(11):e4081.

[18] Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:i4898.

[19] Wells GA, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses [cited 2021 Sept 2]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[20] Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ. 2016;355:i4919.

[21] Deeks JJ, Higgins JTP, Altman DG, editors. Chapter 10: analysing data and undertaking Meta-analyses. In: Higgins JTP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions version 6.2 [updated February 2021]. Cochrane, 2021. Available from: www.training.cochrane.org/handbook

[22] Xu C, Furuya-Kanamori L, Zorzel L, et al. A proposed framework to guide evidence synthesis practice for meta-analysis with zero-events studies. J Clin Epidemiol. 2021;135:70–78.

[23] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–926.

[24] Ader F, Peiffer-Smадja N, Poissy J, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19. Clin Microbiol Infect. 2021;27(12):1826–1837.

[25] Brown SM, Peltan I, Kumar N, et al. Hydroxychloroquine vs. Azithromycin for hospitalized patients with COVID-19 (HAHPS): results of a randomized. Annals Ats. 2021;18(4):590–597.

[26] Dubéé V, Roy PM, Vielle B, et al. Hydroxychloroquine in mild-to-moderate coronavirus disease 2019: a placebo-controlled double blind trial. Clin Microbiol Infect. 2021;27(8):1124–1130.

[27] Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. JAMA. 2020;324(21):2165–2176.

[28] Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: an open label, randomised controlled trial. BMJ. 2020;369:m1849.

[29] Davoudi-Monfareed E, Rahmani H, Khalili H, et al. A randomized clinical trial of the efficacy and safety of interferon β-1a in treatment of severe COVID-19. Antimicrob Agents Chemother. 2020;64(9):e01061–20.

[30] Falcão F, Viegas E, Carmo I, et al. A prospective, observational study to evaluate adverse drug reactions in patients with COVID-19 treated with remdesivir or hydroxychloroquine: a preliminary report. Eur J Hosp Pharm. 2021;28(5):248–253.

[31] Grimaldi D, Aissaoui N, Blonz G, et al. Characteristics and outcomes of acute respiratory distress syndrome related to COVID-19 in Belgian and French intensive care units according to antiviral strategies: the COVADIS multicentre observational study. Ann Intensive Care. 2020;10(1):131.

[32] Lagier JC, Million M, Gautret P, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a retrospective analysis. Travel Med Infect Dis. 2020;36:101791.

[33] Schneider J, Jaenigen B, Wagner D, et al. Therapy with lopinavir/ritonavir and hydroxychloroquine is associated with acute kidney injury in COVID-19 patients. PLoS One. 2021;16(5):e0249760.

[34] Lecronier M, Beurton A, Burrel S, et al. Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis. Crit Care. 2020;24(1):418.

[35] Basalely A, Gurusinge S, Schneider J, et al. Acute kidney injury in pediatric patients hospitalized with acute COVID-19 and multisystem inflammatory syndrome in children associated with COVID-19. Kidney Int. 2021;100(1):138–145.

[36] Pham K, Torres H, Satlin MJ, et al. Failure of chronic hydroxychloroquine in preventing severe complications of COVID-19 in patients with rheumatic diseases. Rheumatol Adv Pract. 2021;5(1):rkab014.

[37] Ghosn M, Attallah N, Badr M, et al. Severe acute kidney injury in critically ill patients with COVID-19 admitted to ICU: incidence, risk factors, and outcomes. JCM. 2021;10(6):1217.

[38] Ulrich RJ, Troxel AB, Carmody E, et al. Treating COVID-19 with hydroxychloroquine (TEACH): a multicenter, double-blind randomized controlled trial in hospitalized patients. Open Forum Infect Dis. 2020;7(10):ofaa446.

[39] 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;49(2):215–219.

[40] Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open. 2020;3(4):e208857.

[41] Mitjá O, Corbacho-Monné M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild covid-19: a randomized-controlled trial. Clin Infect Dis. 2021;73(11):e4073–e4081.

[42] Purwati, Budiono, Rachman BE, et al. A randomized, double-blind, multicenter clinical study comparing the efficacy and safety of a drug combination of lopinavir/ritonavir-azithromycin, lopinavir/ritonavir-
doxycycline, and azithromycin-hydroxychloroquine for patients diagnosed with mild to moderate COVID-19 infections. Biochem Res Int. 2021;2021:6685921.

[43] Kim JW, Kim EJ, Kwon HH, et al. Lopinavir-ritonavir versus hydroxychloroquine for viral clearance and clinical improvement in patients with mild to moderate coronavirus disease 2019. Korean J Intern Med. 2021;36(Suppl 1):S253–S263.

[44] Hernandez-Cardenas C, Thirion-Romero I, Rodriguez-Llamazares I, et al. Hydroxychloroquine for the treatment of severe respiratory infection by COVID-19: a randomized controlled trial. PLoS One. 2021;16(9):e0257238.

[45] Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209–218.

[46] Chen Z, Gao C, Yu H, et al. Hypophosphatemia is an independent risk factor for AKI among hospitalized patients with COVID-19 infection. Ren Fail. 2021;43(1):1329–1337.