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Systematic Review

Efficacy and safety of chloroquine and hydroxychloroquine for the treatment of COVID-19 infection: An umbrella review

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Abstract

Introduction: *Among all therapeutic approaches for COVID-19, most controversies have been raised about the efficacy and safety hydroxychloroquine (HCQ) and chloroquine. We conducted an umbrella review to assess any potential benefits of hydroxychloroquine and chloroquine in treating COVID-19.*

Methods: *We searched the Cochrane Database of Systematic Reviews, PubMed and covid-evidence.org from December 2019 until July 2022. Time to viral clearance, need for mechanical ventilation and mortality were assessed as main efficacy outcomes. The analysis was performed using R package version 4.1.2.*

Result : *Hydroxychloroquine had no benefit in decreasing time to viral clearance at days 7 (RR 0.81; 95% CI 0.63, 1.03) and 14 (RR 1.00; 95% CI 0.90, 1.139). Chloroquine has no statistically significant effect in decreasing the time of viral negativity at days 7 (RR 1.20; 95%CI 0.64, 2.25) and 14 (RR 1.08; 95%CI 0.85, 1.36). There is no difference in the need for mechanical ventilation among hydroxychloroquine plus azithromycin versus standard of care groups. Hydroxychloroquine marginally increased the mortality rate compared to placebo but not statistically significant (RR 1.09; P-value 0.05). Adding azithromycin to hydroxychloroquine had no statistically significant effect of decreasing mortality (RR 0.52; 95%CI 0.13, 2.07). Treatments with hydroxychloroquine increased the risk of adverse effects (RR 2.71; 95%CI 1.66, 4.43; p-value <0.0001). Adding azithromycin to hydroxychloroquine increased the adverse events (RR 1.74; 95% CI 1.27, 2.38).*

Conclusion: *Though access to antivirals is an important challenge in developing countries, the decision to suspend hydroxychloroquine and chloroquine in treating COVID-19 appears right.*

.***Keywords****: Review; COVID-19; Hydroxychloroquine; Chloroquine; Efficacy; Safety; Mortality*
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Introduction

In late December 2019, the novel coronavirus disease (COVID-19) was reported in the city of Wuhan, China and has since spread around the globe. The causative agent is β-coronavirus or SARS COV -(1, 2). The pandemic has infected more than 579 million people with 6 million deaths, as of 19thJuly, 2022(3). Due to the extraordinary impact of the pandemic on public health and society in many countries, there is high demand for effective treatments for COVID-19. The attempts to discover new drugs and repurpose previous medications for the treatment of COVID-19 have not been entirely satisfactory, and no preventive drugs have emerged except for the recent vaccines(4). The safety and efficacy of the antimalarial drugs, hydroxychloroquine and chloroquine, along with azithromycin, were among the top agents tested against COVID-19 (5-9). Chloroquine and hydroxychloroquine have been used widely for the

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treatment and prevention of malaria, and autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (10-17). They have demonstrated antiviral effect through inhibiting the virus replication (18-23).

If found effective against COVID-19, the availability of these drugs at low cost would ensure equitable access to treatment, especially in low-and middle-income countries(24).Azithromycin is a safe and well -tolerated antibiotic approved in adults and children aged, 6 months and older (25). Azithromycin has demonstrated in vitro antiviral activity against Zika, Ebola, influenza H1N1 virus, enterovirus and rhinovirus (26, 27). In addition, it has antiviral effect against SARS COV by interfering the binding of the-SARS-CoV-2spike protein and host receptor angiotensin-converting enzyme-2 (ACE2) protein (12, 28).

Despite the uncertain evidence on hydroxychloroquine or chloroquine, some governments have recommended using hydroxychloroquine as prophylaxis and as a first line treatment for COVID-19 patients (29, 30).However, concerns regarding adverse effects have led tothe removal of hydroxychloroquine or chloroquine from several country guidelines.

There have been mixed results from systematic reviews and meta-analyses on the effect of chloroquine and hydroxychloroquine with or without azithromycin on various COVID-19 outcomes (31-35). For example, a review of hydroxychloroquine safety and efficacy in COVID-19 found it to reduce mortality in SARS-Cov-2 positive patients and improve clinical recovery in renal transplant recipients(31)whereas other reviews and meta-analyses reported that chloroquine and hydroxychloroquine had negative effects on COVID-19 hospitalized patients(33), and does not improve clinical outcomes in COVID-19 patients (34). An umbrella review that was carried out in 2020 and included three systematic reviews reported that hydroxychloroquine or chloroquine alone or in combination with azithromycin have no benefit for patients with COVID-19. Additionally, the review reported these medications could result in both statistically and clinically elevated risks of arrhythmias(36) This review was of narrow scope and did not report the broad range of benefits and safely issues related to these medications. Therefore, in the current review, we aimed to update the evidence by extending the review period and including broader efficacy and safety outcomes. We hoped that this would provide more robust evidence on evidence on the overall efficacy and safety of hydroxychloroquine or chloroquine in patients infected with COVID-19 for both policy makers and practitioners

Methods

Study design: This umbrella review was conducted guided by the preferred reporting items for overviews of reviews (PRIOR) statement that has 27 main items covering all steps and considerations involved in planning and conducting an overview of reviews of healthcare interventions (37) (see supplementary file-4), and methodological guidance on the conduct and reporting of an umbrella review approach (38),. The protocol of this review was registered on PROSPERO (CRD42021233069).We augmented the prior guideline with the PRISMA (Preferred Reporting Items for Systematic Reviews and meta-analyses) flow chart(39).

Search strategy and Selection of studies:

We searched Cochrane Database of Systematic Reviews (CDSR) (The Cochrane Library), Pub Med and covid-evidence.org from December 2019 to July 2022 to identify potentially eligible reviews that were published in the English language. We conducted the search using MeSH terms, free text words and word variants as Chloroquine; Hydroxychloroquine; Hydroxychloroquine sulfate; COVID-19; Coronavirus infection SARSCov-2 (**see Table 1**). All the retrieved papers were transferred to ENDNOTE version x7 and duplicates were removed.

Table 1: Search terms used in our umbrella review in the Pub Med database

	Search terms used
1	(("Hydroxychloroquine"[Mesh]) OR ("Chloroquine"[Mesh] OR "chloroquinediphosphate")
2	(("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh] OR "SARS-CoV-2 variants" OR "COVID-19 serotherapy"
3	(("Systematic Review" [Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR "Meta-Analysis as Topic"[Mesh]) OR "Review"

Eligibility criteria

- Eligible articles were assessed against the following inclusion criteria:
- **Population:** participants with any clinical stage of confirmed COVID-19, all age and both sexes.
- **Intervention:** Hydroxychloroquine/ chloroquine with or without Azithromycin.
- **Comparison:** Standard of care or placebo.
- **Outcome: primary outcomes (**mortality, viral clearance and adverse events) and **secondary outcome** (disease progression).

Study design: Only systematic review and meta-analysis of randomized clinical trials were included..

Data extraction
Data extraction was performed by two independent reviewers. The data collection format was adopted from the Cochrane data extraction tool. Any discrepancies were reconciled through discussion and excluded articles and reasons for exclusion were documented. The information extracted from the reviews included: author name, year of publication, number of studies included in the review, total number of participants, setting of the studies, types of participates, the intervention and comparator groups, and outcomes of the studies included were extracted.

Methodological quality assessment
Two reviewers independently evaluated the methodological quality of the included studies using A Measurement Tool to Assess systematic Reviews2(AMSTAR 2) tool(40). Any discrepancy between the reviewers was resolved through discussion. AMSTAR 2 has 16 items (7 critical checklists and 9 noncritical checklists) for assessing systematic reviews and meta-analyses. The items are evaluated either with "yes" or "no" (items 1, 3, 5, 6, 10, 13,14, and 16); with "yes", "partial yes", or "no" (items 2, 4, 7, 8, and 9); or with "yes", "no", or "no meta-analysis conducted" (items 11, 12, and 15). Each of the 16 items a score of 0 (answer "no"), 1 (answer "yes") or 0.5 (answer "partial yes"). The rating criteria of AMSTAR 2 were divided into four levels: the presence of, 0–1 non-critical weakness is defined as high quality; more than, 1 non-critical weakness is defined as moderate quality; 1 critical flaw with or without non-critical weaknesses is defined as low quality; and the presence of more than, 1 critical flaw with or without non-critical weaknesses is defined as critically low quality. The evaluation was completed using the online version available on the AMSTAR website (https://amstar.ca/Amstar_Checklist.php)(40) and finally classified as high, moderate, low, or critically low quality.

Data Synthesis and Analysis
We summarized meta-level description and synthesis of the findings from the included reviews. We categorized into quantitative, qualitative and/or mixed-synthesis groups based on information about the design of primary studies provided in the reviews in tabular form. A narrative was structured around the type of evidence, selected population characteristics and type of outcome. After two reviewers extracted the outcomes on the efficacy and safety, the risk ratio (RR) with 95% confidence intervals (CIs) was calculated.

One of the articles reported hydroxychloroquine and hydroxychloroquine with azithromycin specific adverse effects. For this reason, we described findings of this paper separately(41). We evaluated the heterogeneity of the primary studies using statistical test I^2 considering as significant heterogeneity if I^2 value is greater than 50% by using both fixed-effects model and a random-effects model. The analysis was performed using R package

Assessment of the certainty of evidence
We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the level of evidence for all outcomes separately by employing GRADEpro GDT software (GRADEpro GDT).

Results

Literature search and selection process
A total of 184 articles were identified from the primary search. Of these, two were duplicates and excluded. Of the remaining 182, articles, 164 were excluded during title and abstract screening because they were not reviews or related to COVID-19. Eighteen full-text articles were reviewed with 12 papers excluded because they included individual studies with mixed design or non-RCT methodology. A total of six reviews with 76 RCTs were included in this umbrella review **(Figure 1).**

Study characteristics
Out of six included reviews, three of them reported the effect of hydroxychloroquine or chloroquine on the viral clearance rate(42-44), three reviews reported on the effect of hydroxychloroquine/ chloroquine and hydroxychloroquine with azithromycin on rate of mortality (42, 44, 45), two reviews reported the effect of hydroxychloroquine with and without azithromycin on disease progression(42, 44) and four reviews reported on adverse events of hydroxychloroquine with or without azithromycin(41, 42, 44, 46)**(see Table 2***)*.Some primary studies were included in more than one review: Two primary studies were included in two reviews, five in three reviews, one in four reviews, four in five reviews, and two in six reviews. The remaining 19, studies did not overlap. (See supplementary file-1**)**

Figure 1: PRISMA Flow chart of search strategy and selection study characteristics

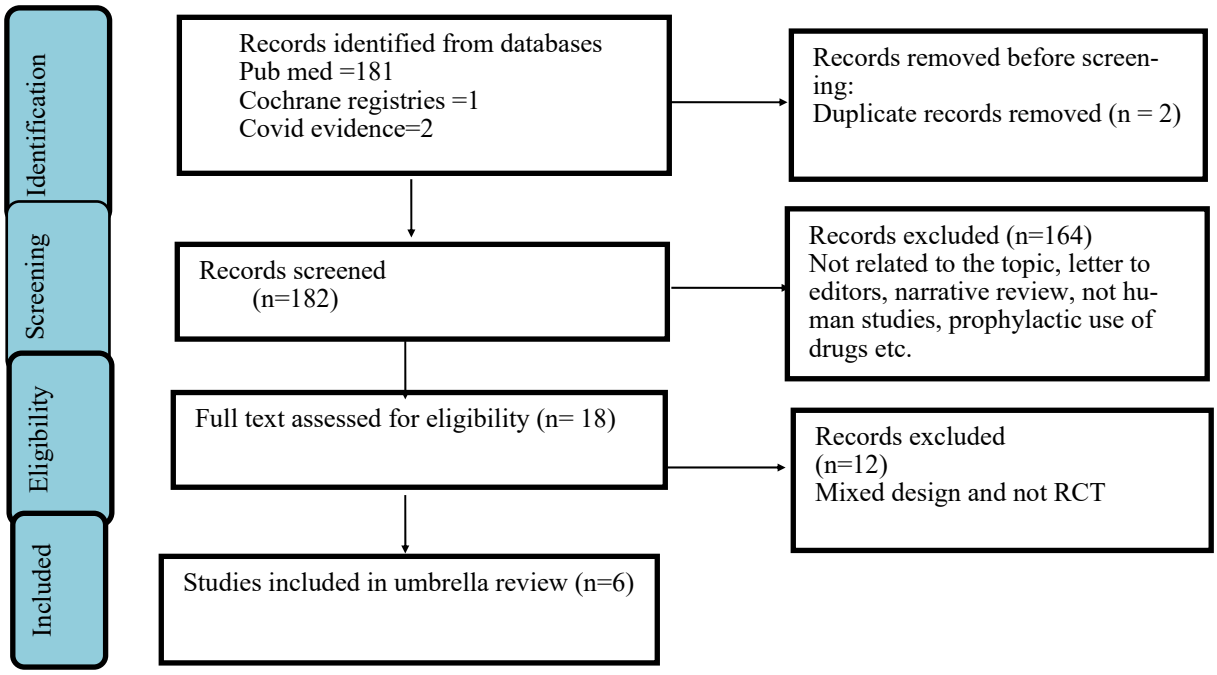

Table 2: characteristics of the included systematic review and meta-analysis studies

Author, year	Total Studies	Total Participants	Intervention drug	Comparator drug	Study Country	Outcomes	Study Quality
Bignardi et al, 2021	12	7,629	HCQ/CQ	not HCQ/CQ	Egypt,USA, Canada, Brazil, China, Taiwan, UK, Norway	Time to viral cure, time of clinical recovery,mortality, dverse events	Critically low
Lacerda et al, 2021	28	10,319	HCQ or CQ	placebo/no treatment	International multicenter	Mortality	Low
Maraolo- et al, 2021	5	2291	HCQ/CQ	Placebo/Standard of care	China, Canada, United states, Spain, Brazil	Adverse events	Critically low
Pathak et al, 2020	7	4984	HCQ/CQ	Standard of care, Lopinavir/ritonavir (400/100 mg) and SOC	China, Brazil, Spain	Clinical improvements and viral clearance	Critically low
Singh et al, 2021	14	11915	HCQ/CQ alone or with other treatment any routeof administration and dose	No treatment, supportive treatment, or other experimental antiviral treatment other than CQ or HCQ).	Brazil, Egypt, Iran, UK, USA, Canada, Spain, Taiwan	Clinical recovery, mechanical ventilation, length of hospital admission, adverse events	High
Izcovich et al 2022	10	3663	HCQ	placebo or standard care	USA,Canada, Brazil, China, Taiwan,UK, Norway	adverse effects	Critically low

Quality of included reviews

Of the six reviews, four reviews have critically low quality, one review has low quality and one review have high quality appraisal (supplementary file-2). The low quality resulted from the weakness in the study design of the reviews. Two of the studies lacked explicit statement that the review methods were established prior to the conduct of the review(42, 43), five reviews did not report list with reason for excluding studies(41-43, 45, 46); no assessments for potential impacts of risk of bias in individual studies on the result of meta-analysis in two of the studies(42, 43), and did not account for the risk of bias in individual studies when interpreting or discussing the result of the review(42, 43). Publication bias was also not reported in three reviews(43, 46). (See supplementary file-2). All articles were evaluated for certainty of evidence at primary data level using online GRADEpro software and the result is elaborated for each primary outcome separately (See supplementaryfile-3).

Mortality rate

A total of three reviews investigated and reported the pooled estimate of mortality.

Two of these reviews compared hydroxychloroquine or chloroquine with or without azithromycine to standard care. The pooled effect from two reviews with thirty-seven RCTs showed that the risk of mortality marginally increased for hydroxychloroquine compared to standard care, but the difference was not statistically significant (RR1.09; 95%CI 1.00, 1.19; I^2 = 0%; 37 RCTs; 13,394 patients; Moderate certainty of the evidence) **(see Figure 2).**The pooled estimate also showed no benefit of chloroquine treatment in decreasing the risk of mortality compared to standard care(OR 1.77; 95% CI0.15, 21.13; p-value 0.21; I^2 = 0%; 4RCTs; 307 patients; Very low certainty of evidence).

The third review showed that hydroxychloroquine plus azithromycin had no statistically significant benefit in decreasing the risk of mortality compared to standard care for COVID-19 patients (RR0.52; 95% CI 0.13, 2.07; 1RCT; 444 patients; Low Certainty of evidence).

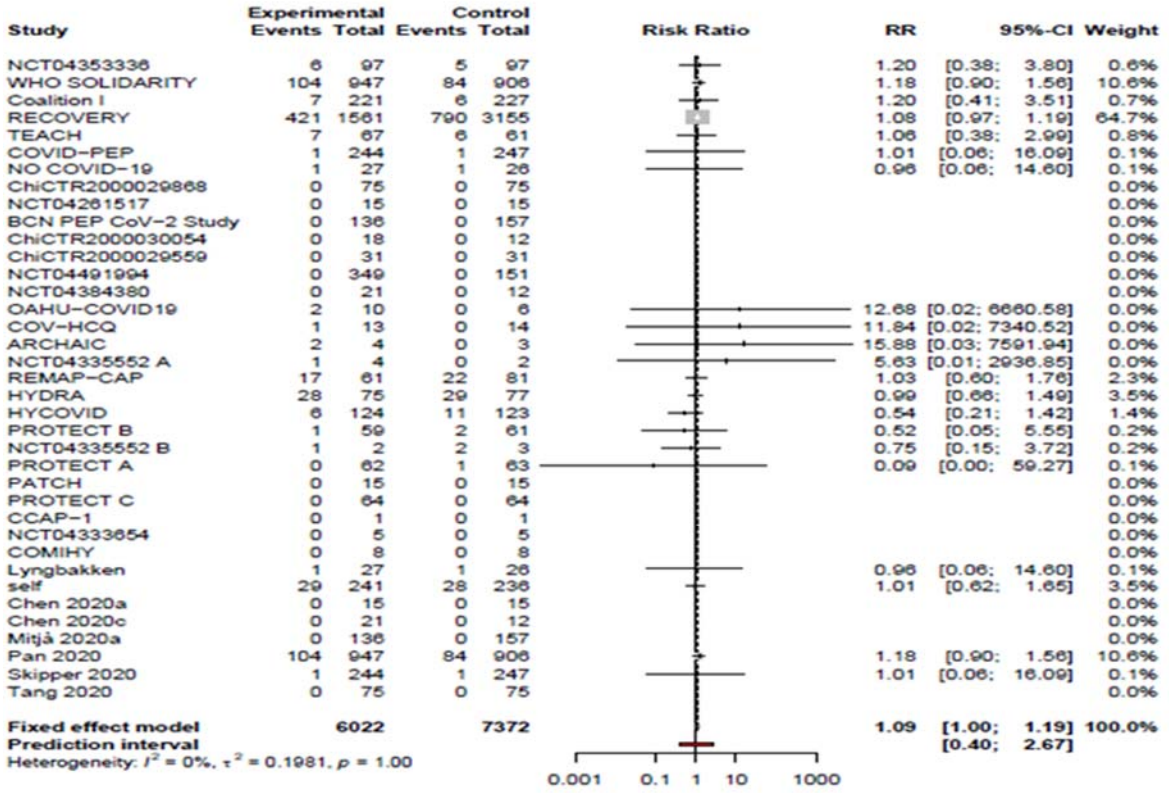

Figure 2: Forest plot of hydroxychloroquine alone versus standard of care in mortality

Viral clearance

The effect of hydroxychloroquine or chloroquine on time to viral clearance was reported in two of the six reviews (42, 44). In both reviews, time to viral clearance was measure time to negative PCR for SARS-CoV-2 on respiratory samples.Meta-analysis done from these two reviews with three overlapping RCTs showed that hydroxychloroquine alone had no statistically significant difference in viral clearance at day 7 (RR 0.81; 95% CI 0.63, 1.03; P value = 0.08; I^2 = 0%; 2RCTs; 180 participants; Very low certainty of evidence) and at day 14 (RR 1.00; 95% CI 0.90, 1.13; P = 0.99; I^2 = 0%;; 3RCTs; 213 participants; Very low certainty of evidence) when directly compared to standard of care **(Figure 3, Figure 4).**Chloroquine also showed no statistically significant effect in decreasing the time of viral negativity at both Day 7 (RR 1.20; 95%CI 0.64, 2.25; P = 0.57) and Day 14 (RR 1.08; 95%CI 0.85, 1.36; P = 0.53).

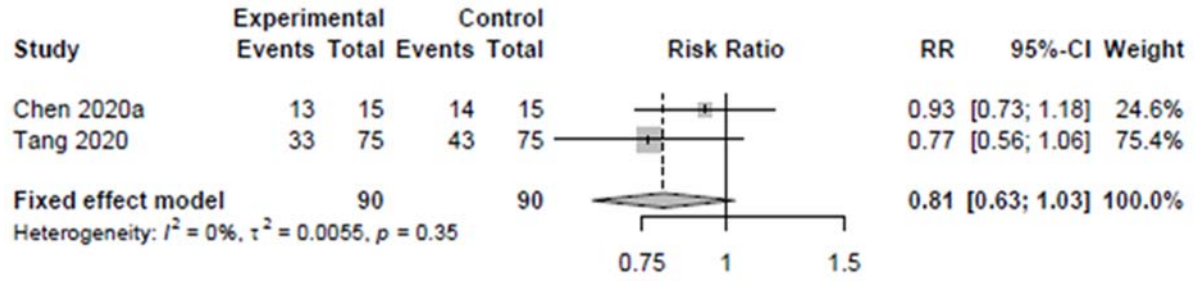

Figure 3: Forest plot of hydroxychloroquine versus standard of care in viral clearance at Day 7.

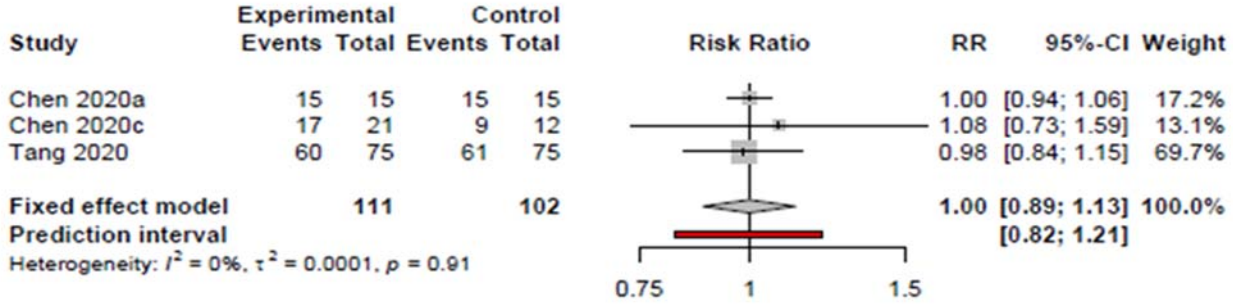

Figure 4: Forest plot of hydroxychloroquine versus standard of care in viral clearance at Day 14.

Disease progression

Two reviews (42, 44) reported on the need of mechanical ventilation for hydroxychloroquine and confirmed that hydroxychloroquine when used alone (RR1.15, 95%CI 0.92–1.38, P > 0.05;5339 participants;3 RCTs and RR 1.11,95%CI 0.91-1.37; 4521participants; 3 RCTs) or in combination with azithromycin (HCQ+AZI) (RR1.61; 95% CI 0.82, 3.15; 444 participants) demonstrated no statistically significant benefits.

Adverse events

A meta-analysis from three reviews indicated increased risk of adverse events of treatment with hydroxychloroquine compared to standard of care (RR2.71; 95%CI 1.66, 4.43; p-value <0.0001; I^2=81.4%;2802, participants; 8RCTs; Very low certainty of evidence).

Similarly, hydroxychloroquine plus azithromycin therapy versus usual care found a statistically significant increase in causing any adverse effects (RR1.74; 95%CI 1.27, 2.38,416 participants; 1RCT; Moderate certainty of evidence) (**Figure 5**). However, one review that included nine hydroxychloroquine trials and one hydroxychloroquine with azithromycin compared to standard care. The findings showed that hydroxychloroquine with or without azithromycin increased the risk of cardiac toxicity, nausea, and/or vomiting. Additionally, hydroxychloroquine alone increased the risk of cognitive dysfunction/delirium (41)

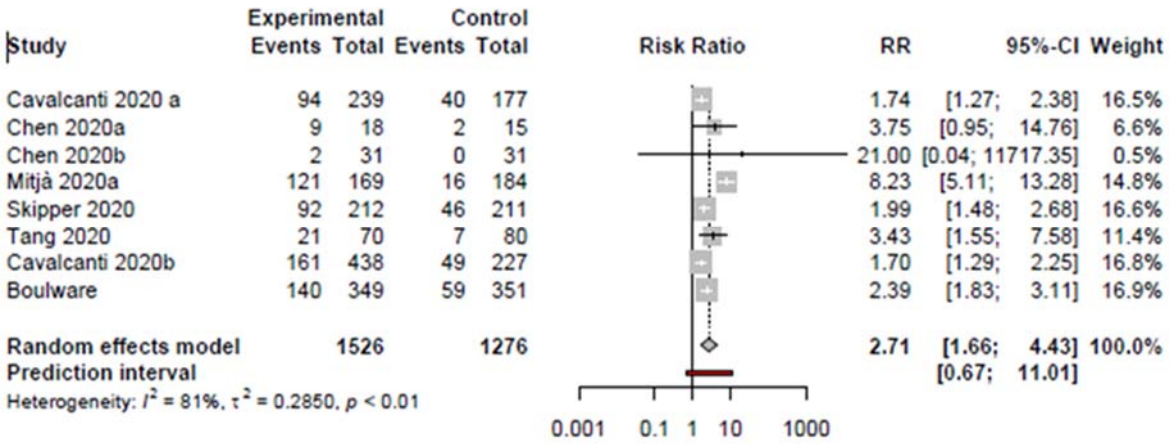

Figure **5: Forest plot of hydroxychloroquine versus standard of care in adverse events**

Discussion

In this umbrella review, we included systematic reviews and meta-analyses of RCTs to evaluate the relative efficacy of chloroquine and hydroxychloroquine, with or without adjunct azithromycin, against the standard of care among COVID-19 patients in terms of viral clearance, need for mechanical ventilation, mortality, and adverse events.

We find that hydroxychloroquine alone or in combination with azithromycin had no positive effect in reducing time to viral clearance compared to standard treatment. This was despite some clinical trials that indicating faster viral clearance(47)(48), and a meta-analysis reporting that treatment with hydroxychloroquine was associated with faster clinical and radiological improvement (49) and favorable safety profile (50).

The need for mechanical ventilation for hydroxychloroquine plus azithromycin was not better than standard care, which is in line with previous study that reported hydroxychloroquine alone was not better than standard care (51). In our review, hydroxychloroquine with or without azithromycin had no significantly difference in mortality reduction compared to standard care, , which is similar to findings reported to previous reports (52-61)..Further exploration of the effect of age (56)and other demographics and clinical characteristics that tend to be associated with increased risk of mortality (62) should be explored further. The umbrella review also showed hydroxychloroquine alone or in combination with azithromycin increases the risk of adverse effects compared to the standard of care. Although a review of 14 articles, including 5,048 patients treated with aminoquinolines alone or in combination with azithromycin, found no statistical difference in drug-related adverse critical cardiac events when compared to control groups, the result and interpretation are limited by the small sample size and study design (63).

Concerns about the efficacy and safety of hydroxychloroquine by many national health organizations(64),the European medicines(65) and the WHO were warranted. Many of these agencies, including the US' Food and Drug Administration (FDA) have removed the emergency use authorization of hydroxychloroquine for COVID-19 (66)**.**

This umbrella review has several limitations. First, methodological limitations in the included reviews, such as small number of randomized controlled trials, and small sample size affect the results of the umbrella review. Second, almost all reviews were of low quality, such as prespecified protocols, and risk bias assessments, which affect seriously the conclusions to be drawn from the main outcomes of efficacy and safety. Third, we only included systematic reviews and meta-analyses of RCTs. So, reviews of studies other than RCTs were excluded . However, the umbrella review method provides a useful route to achieving our aim of summarizing evidence from reviews relevant to the current and future implementation of the intervention.

Conclusion

The findings showed that chloroquine and hydroxychloroquine with or without azithromycin conferred no benefit in decreasing the risk of mortality and time to viral clearance at days 7&14. Similarly, hydroxychloroquine with or without azithromycine increased adverse events among COVID-19 patients. Though access to antivirals is an important challenge in developing countries, the decision to suspend hydroxychloroquine and chloroquine in treating COVID -19 appears right.

The review was conducted after the initial recommendation to not use hydroxychloroquine and chloroquine in the treatment of COVID-19.

Nevertheless, given the potential accessibility of these drugs, we believe it was important to confirm that these drugs have no potential utility through umbrella review.

Abbrvations

Azithromycin(AZI), A Measurement Tool to Assess Systematic Reviews (AMSTAR 2), Confidence Interval (CI), Corona Virus Disease 2019 (COVID-19), Chloroquine (CQ), Grading of Recommendations, Assessment, Development, and Evaluation (GRADE), Hydroxychloroquine (HCQ), Middle East Respiratory Syndrome-Corona Virus (MERS-COV), Medical Subject Heading (MeSH), Mechanical ventilation (MV), Polymerase Chain Reaction (PCR), Preferred Reporting Items for Overviews of Reviews (PRIOR), Randomized Clinical Trial (RCT), Sever Acute Respiratory Syndrome–Corona Virus (SARS-COV), Sever Acute Respiratory Syndrome-Corona Virus-2 (SARS-COV 2), Standard of care (SC), Systemic Lupus Erythematosus (SLE), World Health Organization (WHO).

Declarations

Ethics approval and consent to participate:
Not applicable

Consent for publication:
Not applicable

Availability of data and material:
The data supporting the conclusions of this review are included within the article and its additional files. Any additional materials are also attached in a separate file.

Competing interests:
The authors declare that they have no competing inter-

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Authors' contributions
AF, MD and KD conceived and designed the study. KD and MD did the database searching. KD and DT did the screening, data extraction and quality assessment. KD, MD, and AF did the analysis. KD and MD drafted the manuscript. AF critically revised and substantially contributed throughout the writing of the manuscript. All authors approved the final manuscript to be submitted for publication.

Supplementary files:

Supplementary file 1: https://bit.ly/3Wik2Hn
Supplementary file 2: https://bit.ly/3sOr35i
Supplementary file 3: https://bit.ly/3ztABX9
Supplementary file 4: https://bit.ly/3DV38HA

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