Original Article

The efficacy and safety of hydroxychloroquine for COVID-19 prophylaxis and clinical assessment: an updated meta-analysis of randomized trials

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Background: Coronavirus disease 2019 (COVID-19), a disease that affected tens of millions of people, upended the lives of countless individuals around the globe. The chloroquine (CQ) and its analogue hydroxychloroquine (HCQ) were the most frequently cited as potential treatments and preventatives against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The primary aim of this investigation was to scrutinize the effectiveness and safety of HCQ for COVID-19 prevention and to present powerful evidence and reference for clinical practice.

Methods: PubMed, Ovid and the Cochrane COVID-19 Register of Controlled Trials (CENTRAL) were systematically searched from inception to January 31, 2022. Randomized controlled trials (RCTs) trials that included participants who were SARS-CoV-2 negative at the time of registration were enrolled in this meta-analysis. The intervention group took HCQ or CQ orally. The control group was not blinded by quinine or placebo. Pooled relative risk (RR) of SARS-CoV-2 infection, mortality, hospitalization, adverse events, and compliance were calculated. The software tools utilized for statistical analyses were Stata 14 and Review Manager 5.3.

Results: A total of 9 studies including 7,825 participants were enrolled. Bias of individual studies were assessed as low risk. The pooled RR for SARS-CoV-2 infection was 0.75 [95% confidence interval (CI): 0.68–0.83] (z=–4.01, P<0.0001; I^2=11%). The pooled RR for hospitalization was 0.72 (95% CI: 0.35–1.50) (z=0.87, P=0.39; I^2=0.0%). The pooled RR for mortality and adverse events were 3.26 (95% CI: 0.13–79.74) (z=0.72, P=0.47; I^2=0.0%) and 1.90 (95% CI: 1.20–3.02) (z=2.73, P=0.0063; I^2=94%).

Conclusions: Results of this meta-analysis indicated significant impact of HCQ on SARS-CoV-2 infection with higher risk of adverse events. These findings must be considered with caution, and further research is necessary to delineate the specific circumstances where HCQ may be effective for COVID-19 prevention.

Keywords: Coronavirus disease 2019 (COVID-19); hydroxychloroquine (HCQ); efficacy; adverse events; prophylaxis

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Introduction

COVID-19, also known as coronavirus disease 2019, impacted tens of millions of individuals and overturned the lives of countless people around the world (1,2). The number of COVID-19 patients is still increasing globally (3,4). Limiting the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical to reducing the global burden of this pandemic (5,6). The global landscape of the COVID-19 pandemic has continued to evolve since its onset. With the ongoing challenges posed by SARS-CoV-2, including the emergence of new variants such as EG.5 and XBB (7), an upcoming wave of infections anticipated during the autumn and winter seasons, and the potential waning of protection from previous infection and vaccination, the need for effective prophylactic agents remains urgent. Close contact has been proved to be the most common way transmission route (8,9). Theoretically, physical distancing is one of the effective approaches to decrease the transmission, nevertheless, it is not possible in all circumstances. Pre-symptomatic spread is the critical point in transmission features. An estimated 2.89 days before the onset of symptoms, the viral infection was believed to have been transmitted (10). The effectiveness of inhibiting SARS-CoV-2 replication in cell culture has been evaluated for several antiviral drugs. There are two drugs that showed obvious cytotoxicity and promising inhibitory effects *in vitro*: remdesivir is in the developmental stage as a drug for treating Ebola virus infection, and chloroquine (CQ), a well-known medication for its efficacy in addressing malaria and autoimmune conditions, is also notable (11). The most frequently reported potential treatments and preventive measures against SARS-CoV-2 among the tested drugs were CQ and its analogue hydroxychloroquine (HCQ) (12,13). It possesses the inhibitory potential through cytopathic effect and reduces the replication of virus (14).

Previous meta-analysis (5) was conducted in 2021 to assess the safety and efficacy of HCQ in the context of COVID-19 prevention. The findings indicated that prophylactic HCQ did not provide any clinical advantage and exhibited an increased risk of adverse events when contrasted with a placebo or no prophylaxis. Based on the increased number of clinical trials investigating the safety and efficacy of HCQ for COVID-19 prevention, we endeavored to perform an updated meta-analysis by synthesizing the most recent results to present more powerful evidence and to offer guidance for future clinical trials and clinical practice. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1043/rc) (15).

Highlight box

Key findings

- Hydroxychloroquine (HCQ) reduced the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and increased adverse events, but showed no effect on hospitalization or mortality.

What is known and what is new?

- Chloroquine (CQ) and its analogue HCQ are widely cited as potential treatments and preventatives for SARS-CoV-2.
- This study pooled the available evidence on efficacy and safety and concluded that HCQ reduces the risk of infection, but with more adverse events.

What is the implication, and what should change now?

- HCQ might have a role in coronavirus disease 2019 prophylaxis. However, clinical workers should be aware of the adverse effects of HCQ when using it and adjust the medication choice according to the individual patient's symptoms.

Methods

All the studies incorporated into this meta-analysis were previously published and had obtained ethical approvals. It's worth mentioning that no ethical approval was sought for this particular study. To be eligible for inclusion in this meta-analysis, studies had to meet the following criteria: randomized controlled trials (RCTs) that included participants who were SARS-CoV-2 negative (by laboratory test or asymptomatic) at the time of registration. Individuals in the intervention group took HCQ or CQ orally, either before or after exposure, as a preventive measure, with flexibility in terms of dose, frequency, and duration. The control group took quinine or placebo. If studies enrolled participants during the same time frame or were conducted within the same study institute, we included only the study with the largest sample size or the one that offered the most extensive outcomes to eliminate redundancy. In the exclusion criteria, we considered case reports, review articles, comments, and conference abstracts that lacked extractable outcomes.

Literature search and study selection

We systematically scoured the databases PubMed, Ovid,

and the Cochrane COVID-19 Register of Controlled Trials (CENTRAL), starting from their inception and continuing through January 31, 2022. Only the English language was considered. The electronic database research utilized the following key terms: chloroquine, hydroxychloroquine, coronavirus disease-2019, SARS-CoV-2, and COVID-19. The search strategy of PubMed was ((("coronavirus disease 2019"[Title/Abstract] AND "english"[Language]) OR ("SARS-CoV-2"[Title/Abstract] AND "english"[Language]) OR ("COVID-19"[Title/Abstract] AND "english"[Language])) AND "english"[Language] AND ((("chloroquine"[Title/Abstract] AND "english"[Language]) OR ("hydroxychloroquine"[Title/Abstract] AND "english"[Language])) AND "english"[Language])) AND (english[Filter]). The references cited in the articles were also scrutinized to uncover any further studies that may have been overlooked during the preliminary literature review.

The eligibility of each article was verified by two reviewers (X.H. and Y.Y.), who independently screened the titles and abstracts. Afterwards, full-text reading was performed to determine the final inclusion of studies. Any disagreements between the reviewers were settled through open discussion.

Data extraction and quality assessments

To minimize bias, two researchers (X.H. and Y.Y.) extracted data from the studies while being unaware of each other's findings. The following details were obtained: author name, year published, sample size, mean age of participants, and gender distribution (percentage of women), dose and frequency of HCQ, the use of placebo or usual care, duration of follow-up, SARS CoV-2 infection, hospitalization, mortality at the end of follow-up, admission to hospitalization, medication compliance, and adverse events of any type. In cases where the two authors had differing opinions, they sought the input of a third reviewer to reach a mutual agreement.

Risk of bias in each study included was appraised by the Cochrane Collaboration's tool for assessing risk of bias (16,17).

Statistical analysis

We used the Stata 14.0 software and Review Manager 5.3 Software for statistical analyses. For each analysis of the outcome, the combined relative risks (RRs) and their 95% confidence intervals (CIs) were estimated for COVID-19 infection, hospitalization, mortality, and adverse events. If the heterogeneity index (I^2) exceeded 50%, we employed the DerSimonian and Laird random-effects model to estimate the pooled effects across all analyses of the outcome (18,19). An evaluation of heterogeneity between studies was conducted using a Cochran Q test, with the resulting I^2 statistic providing a measure of the level of heterogeneity (20,21). Subgroup analysis based on was carried out to investigate the potential source of heterogeneity. A P value of <0.05 was used as the threshold for statistical significance. Sensitivity analysis was conducted in order to assess the stability of pooled outcomes. To evaluate potential publication bias, we performed Egger's regression test and created funnel plots if the number of studies included was ≥10 (22,23).

Results

Study selection and characteristics

Our comprehensive literature search led to the identification of 4,754 publications (*Figure 1*), from which we removed 1,085 duplicates and excluded articles as they were animal studies [156], reviews [1,082], or not relevant to our research question [2,338]. After conducting a detailed full-text screening of the 93 articles, we selected and included 9 studies that met our criteria, with a combined total of 7,825 participants in our meta-analysis (24-32). Studies were performed in Canada, the United States, India, Spain, and Singapore. The average age of participants in the included studies varied between 30.6 and 48.6 years old. *Table 1* showed detailed characteristics of clinical trials included. The primary outcome in the investigations conducted by Boulware *et al.* (32) and Rajasingham *et al.* (26) was the composite COVID-19 infection, while Mitjà *et al.*(27) examined it as a secondary outcome. Boulware *et al.* (32) and Barnabas *et al.* (29) considered clinical worsening to be reflected in hospitalization, while Rajasingham *et al.* (26) used ICU admission as their indicator. In the included trials, HCQ was used as a pre-exposure prophylactic medication for COVID-19 in five studies (24-26,28,30) and as a post-exposure prophylactic treatment in four studies (27,29,31,32).

Risk of bias of individual studies

Dhibar *et al.* (31) had high risk for selection and performance biases. Mitjà *et al.* (27) and Seet *et al.* (25) had

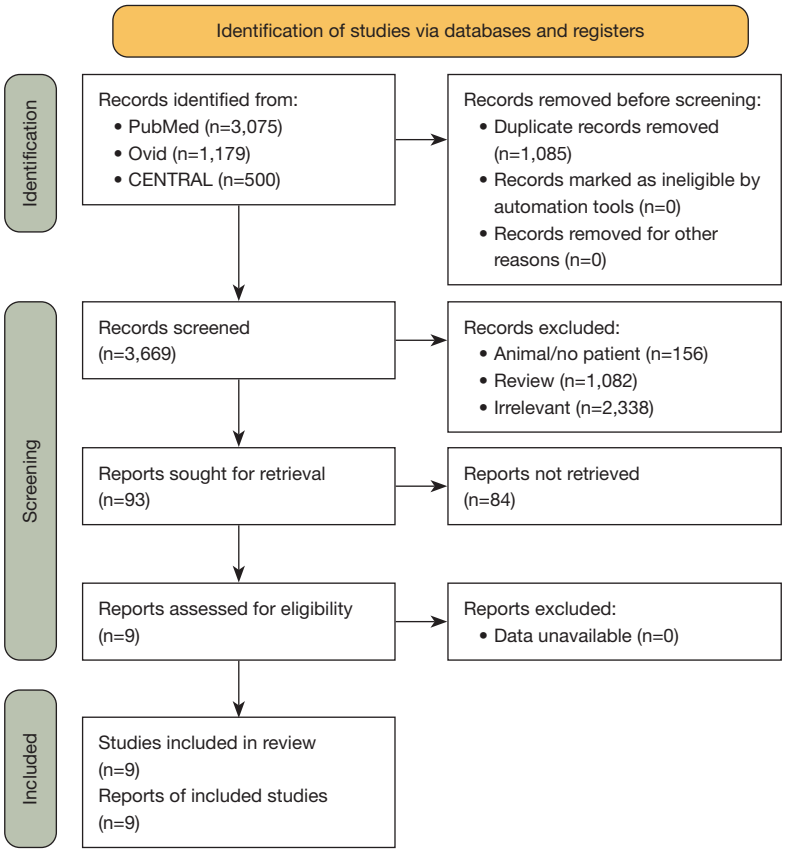

Figure 1 Flowchart of the literature search. CENTRAL, Cochrane COVID-19 Register of Controlled Trials.

unclear risk for performing and detection biases. Other studies included were evaluated as low risk bias. The risk of bias assessments is detailed in *Figure 2*.

SARS-CoV-2 infection

Nine trials reported the results of SARS-CoV-2 infection (24-32). The pooled RR was 0.75 (95% CI: 0.68–0.83) (z=–4.01, P<0.0001; I^2=10.9%) (*Figure 3*), suggesting a promising effect of HCQ in reducing the risk of SARS-CoV-2 infection. Subgroup analysis suggested a significant effect of HCQ in preexposure group (RR =0.71; 95% CI: 0.63–0.79) (Figure S1).

Hospitalization

Four studies reported on hospitalization (26,27,30,32). The pooled RR was 0.72 (95% CI: 0.35–1.50) (z=0.87, P=0.39; I^2=0.0%) (*Figure 4*), suggesting there is not statistical difference for hospitalization between two groups.

Mortality

Five trials reported on mortality of COVID-19 (25-27,30,32). Only 1 case was found in the HCQ arm in the study of Mitjà *et al.* (27). The pooled RR was 3.26 (95% CI: 0.13–79.74) (z=0.72, P=0.47; I^2=0.0%) (*Figure 5*), suggesting there is not statistical difference for mortality between two groups.

Adverse events

Seven studies reported on the occurrence of adverse events (26-30,32,33). The pooled RR was 1.90 (95% CI: 1.20–3.02) (z=2.73, P=0.0063; I^2=93.9%) (*Figure 6*), suggesting a statistically significant increase in the risk of adverse events associated with HCQ. However, there was no increased risk for nausea (RR =1.71; 95% CI: 0.92–3.20) (Figure S2) and

Table 1 Study characteristics

First author's name	Year of publication	Country	No. of participants	Age, years[†]	Female, %	Intervention	Control	Follow-up	Primary outcome
Boulware (32)	2020	Canada and United States	821	40 [33–50]	51.6	Hydroxychloroquine 800 mg PO once, then 600 mg PO 6–8 hours later once, then 600 mg PO daily for 4 days for a total course of 5 days	Placebo	2 weeks	Symptomatic illness of COVID-19 and if possible, laboratory confirmed
Dhibar (31)	2020	India	317	37.2±13.9	45.1	HCQ 400 mg (200 mg × 2 tablets) every 12 h on day 1 followed by 400 mg once weekly for 3 weeks (total cumulative dose, 2,000 mg)	Usual care	4 weeks	Laboratory confirmed COVID-19
Abella (30)	2021	United States	132	33 [20–60]	69.0	Hydroxychloroquine 600 mg PO daily for 2 months	Placebo	8 weeks	Incidence of SARS-CoV-2 infection as determined by a nasopharyngeal swab during 8 weeks of treatment
Barnabas (29)	2021	United States	689	39 [27–51]		Hydroxychloroquine (400 mg/d for 3 days followed by 200 mg/d for 11 days)	Placebo	2 weeks	PCR proven COVID-19
Grau-Pujol (28)	2021	Spain	269	39 [30–50]	73.2	400 mg of hydroxychloroquine daily for the first four consecutive days and subsequently, 400 mg weekly during the study period	Placebo	1 month	Defined by compatible symptoms with COVID-19 with seroconversion or a positive PCR for SARS-CoV-2
Mitjà (27)	2021	Spain	2,485	48.6±19.0	72.9	Hydroxychloroquine 800 mg PO on day 1, then 400 mg PO daily for 6 days	Usual care	4 weeks	Symptomatic and PCR proven COVID-19
Rajasingham (26)	2021	United States and Canada	1,483	41 [34–49]	51.2	2 intervention arms: 1-hydroxychloroquine 400 mg PO once, followed by 400 mg 6 to 8 hours later, then 400 mg PO weekly for 12 weeks; 2-hydroxychloroquine 400 mg PO once, followed by 400 mg 6 to 8 hours later, then 400 mg PO twice weekly for 12 weeks	Placebo	12 weeks	COVID-19 free survival (defined as symptomatic illness or PCR confirmed)
Seet (25)	2021	Singapore	1,051	30.6±6.4	0.0	400 mg (four tablets) once, followed by 200 mg (two tablets) daily for 42 days	Placebo	6 weeks	Laboratory-confirmed SARS-CoV-2 infection
McKinnon (24)	2022	United States	578	44.9±11.9	58.0	400 mg weekly, 200 mg daily	Placebo	8 weeks	Laboratory-confirmed SARS-CoV-2 infection

[†], data are presented as median [interquartile range] or mean ± standard deviation. PO, postexposure; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

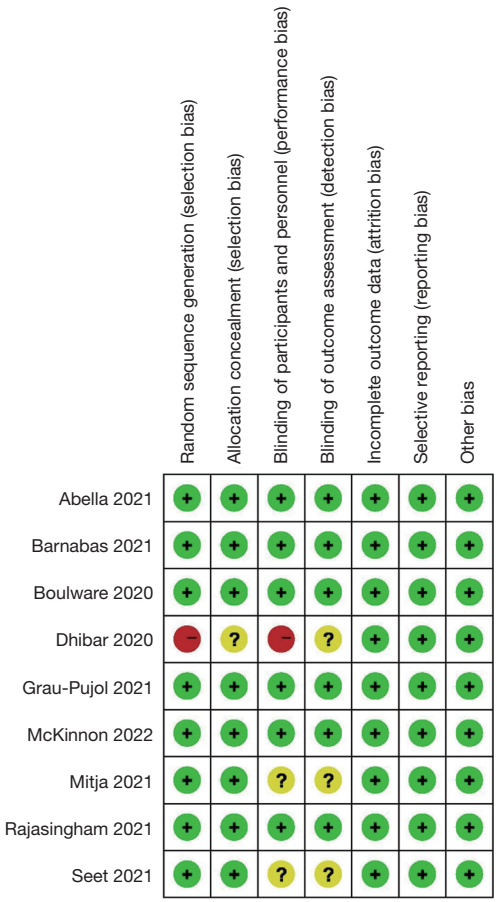

Figure 2 Risk of bias summary.

headache (RR =0.98; 95% CI: 0.74–1.29) (Figure S3).

Compliance

Four trials examined compliance (25,27,30,32). The pooled RR was 0.94 (95% CI: 0.87–1.00) (z=–1.83, P=0.0668; I^2=75.6%) (*Figure* 7), suggesting there is not statistical difference for compliance between two groups.

Sensitivity analysis and publication bias

To evaluate the potential impact of each study on our results, we performed a sensitivity analysis. This analysis confirmed that, upon removing the Seet *et al.* (25) study, the results no longer demonstrated statistical significance (Figure S4). Funnel plots were not structured because the number of studies included was not ≥10.

Discussion

Both CQ and HCQ have shown anti-virus activities *in vitro*, including SARS-CoV-2 and SARS-CoV-1 (11,33-37). Furthermore, HCQ was found to have better efficacy in comparison with CQ *in vitro*, and HCQ is unlikely to accumulate in tissues, serious adverse events such as retinopathy and cardiomyopathy could be avoided (38-41). In this meta-analysis, 9 published RCTs including

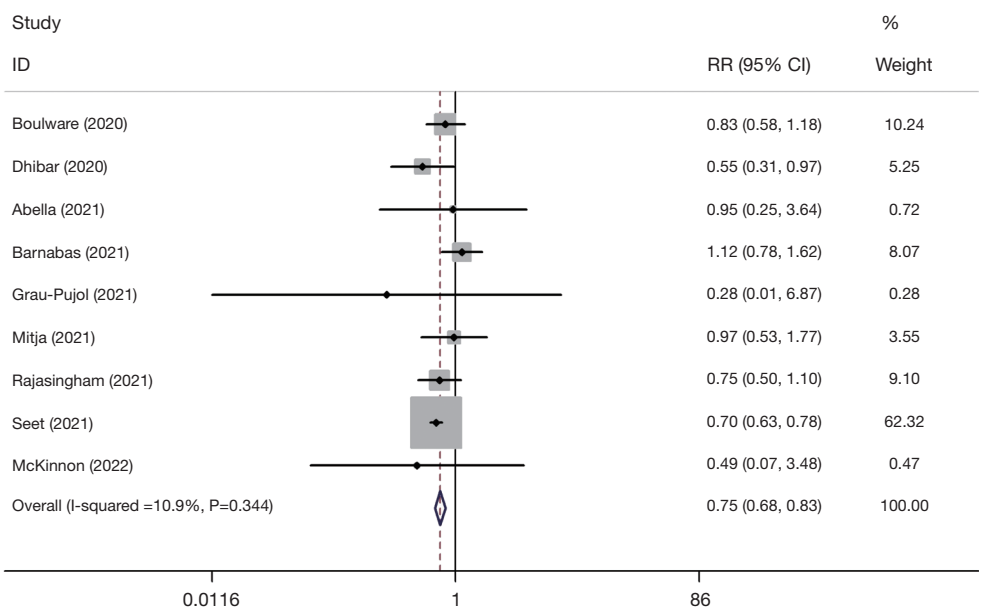

Figure 3 Forest plot of SARS-CoV-2 infection. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RR, relative risk; CI, confidence interval.

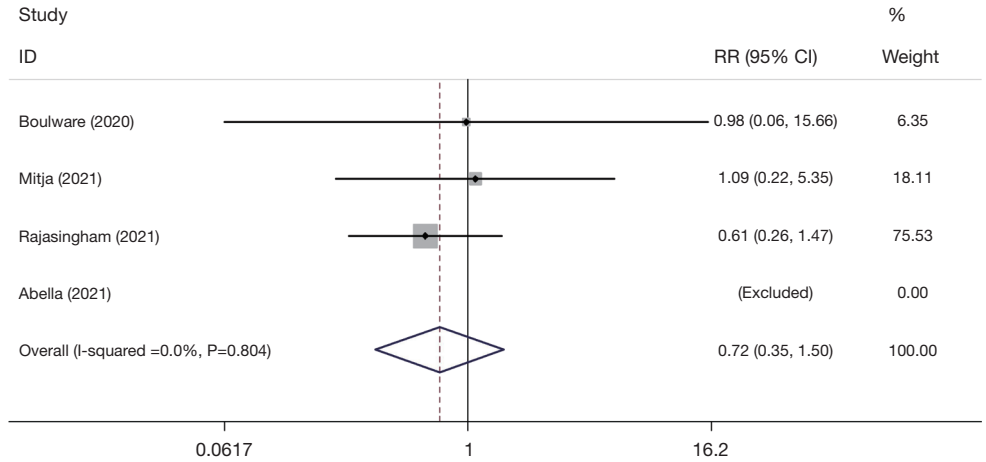

Figure 4 Forest plot of COVID-19 hospitalization. COVID-19, coronavirus disease 2019; RR, relative risk; CI, confidence interval.

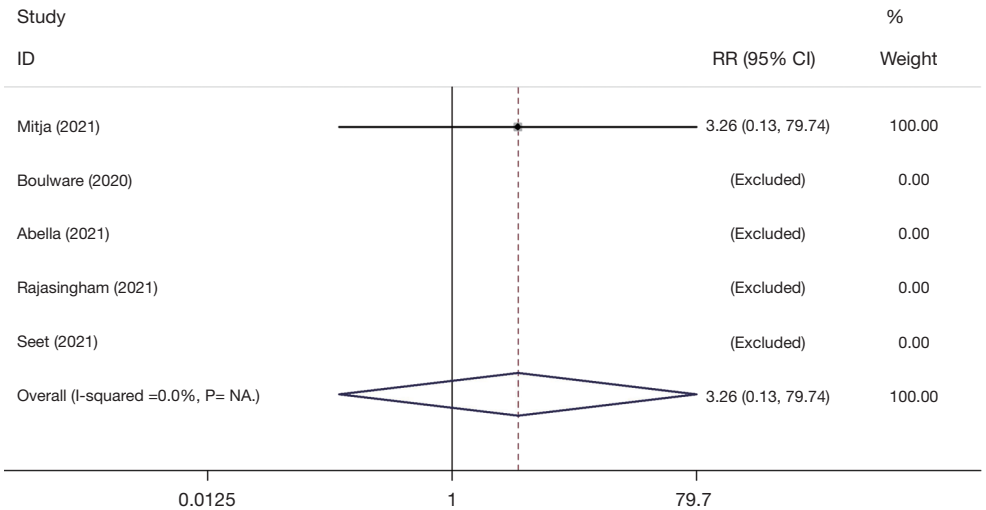

Figure 5 Forest plot of COVID-19 mortality. COVID-19, coronavirus disease 2019; RR, relative risk; CI, confidence interval; NA, not applicable.

7,825 participants who were SARS-CoV-2 negative were enrolled. Combining the data from all studies, we found a statistically significant difference in the reduction of SARS-CoV-2 infections between the HCQ arm and the control arm (RR =0.76, P<0.0001). The results were inconsistent with the result of preceding meta-analysis performed by Lewis *et al.* (5), which indicated that HCQ had no significant effect on the reduction of SARS-CoV-2 infection in SARS-CoV-2 negative population. This meta-analysis included 5 more RCTs which demonstrated a larger overall sample size. Moreover, our analysis found that HCQ use was linked to a higher risk of adverse events, as shown in the pooled results (RR =1.9, P=0.0063), the significant heterogeneity was found between studies analyzed. The heterogeneity may be explained by the difference among the baseline characteristic in participants enrolled and different dosing in each study, we intended to perform subgroup analysis to explore the potential source of heterogeneity, due to limited information on baseline in each study, the subgroup analysis was not conducted. Analysis based on individual data is warranted. The results of this meta-analysis didn't show significant effect of HCQ on hospitalization and compliance. The clinical implications of our research are significant, particularly in the context of the transition of COVID-19 from a pandemic to an endemic state. Our findings offer insights into the potential utility of HCQ

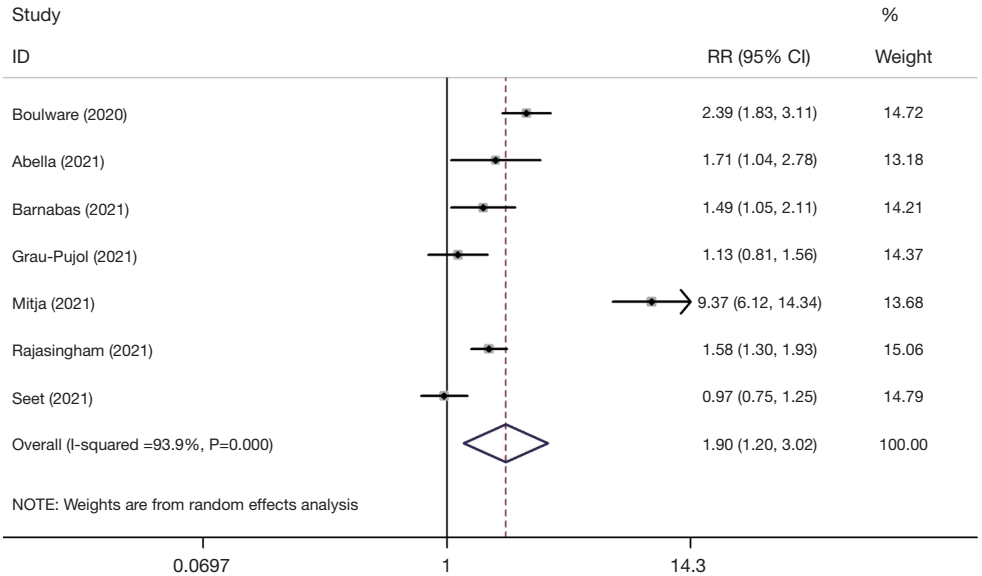

Figure 6 Forest plot of adverse events. RR, relative risk; CI, confidence interval.

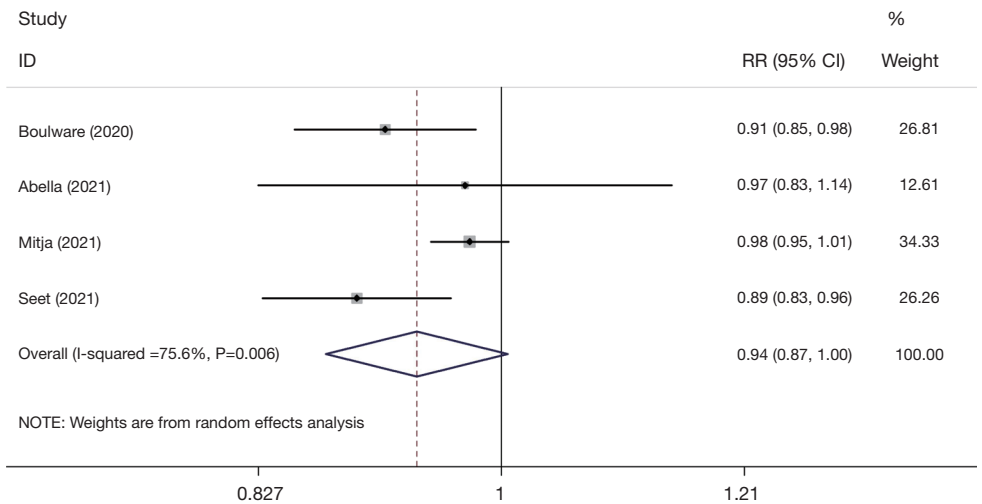

Figure 7 Forest plot of compliance. RR, relative risk; CI, confidence interval.

as a prophylactic agent in various scenarios, considering its efficacy and safety. Furthermore, the consideration of emerging variants underscores the importance of adaptability in prophylactic strategies. As we navigate the challenges posed by SARS-CoV-2 variants, the information presented in this study can inform clinical decision-making and public health strategies. It provides valuable insights for healthcare professionals and policymakers in assessing the role of HCQ in prophylaxis, especially when faced with emerging challenges in the management of COVID-19.

Previous meta-analyses have assessed the effectiveness and safety of HCQ as a prophylactic treatment for COVID-19. Hong and colleagues (42) conducted a meta-analysis focusing on HCQ prophylaxis in healthcare workers, including 10 RCTs. Notably, four of these RCTs overlap with our own study. Their findings differed from our meta-analysis, as they did not observe a significant difference in the prophylactic effect of HCQ. The variations in outcomes may stem from differences in study populations, settings, and methodological approaches.

Hong *et al.*'s focus on healthcare workers highlights the importance of subgroup analyses based on occupation, which can reveal distinct patterns of risk and effectiveness. Garcia-Albeniz and colleagues (43) conducted a meta-analysis in 2022 that included four RCTs also mentioned in our study. Their analysis suggested a possible preventative effect of HCQ against SARs-CoV-2 infection. This result is consistent with our findings. A systematic review by Zhou *et al.* (44) was recently conducted to evaluate the effectiveness of repurposed drugs in preventing laboratory-confirmed SARS-CoV-2 infection and/or COVID-19 among healthy adults. Their extensive review, conducted until September 28, 2022, included a comprehensive assessment of quantitative experimental and observational intervention studies, encompassing 65 studies with 25 trials and 40 observational studies. They found that HCQ prophylaxis was effective in reducing laboratory-confirmed SARS-CoV-2 infection, which is consistent with our findings. A systematic review and network meta-analysis (NMA) conducted by Bartoszko *et al.* (45) evaluated the effects of various prophylactic drugs on COVID-19. Their extensive review, conducted up to March 4, 2022, included 32 randomized trials with a total of 25,147 participants and assessed 21 different prophylactic drugs. They did not find any statistical evidence of a benefit of HCQ prophylaxis for SARS-CoV-2 infection. These discrepancies may be attributed to variations in study design, populations, and the evolving nature of the pandemic. The consideration of emerging variants and changing epidemiological conditions is vital in understanding these differences.

Two investigators independently conducted a systematic database search in English to identify all relevant studies for the meta-analysis. Two independent authors used a predesigned form to extract data from the studies included in the meta-analysis. The qualities of included studies were rated as high according to the Cochrane Collaboration's tool. We used the DerSimonian and Laird random-effects model for our pooled analysis. Differences in sample size, baseline participant characteristics, follow-up duration, and HCQ dosage may contribute to heterogeneity. Nevertheless, subgroup analysis was not performed because the covariates extracted from the included studies were heterogeneous and could be categorized into multiple subgroup, this led to limited numbers of studies in each subgroup. More relevant studies are warranted to be included in further studies in the future. The results of our sensitivity analysis showed that the pooled outcomes were robust. A meta-analysis protocol was not prepared.

In comparison to previous meta-analysis (5) or individual RCTs (32) that investigating the efficacy and safety of HCQ for COVID-19 prevention, results of this meta-analysis suggested significant effect of HCQ on SARS-CoV-2 infection. Higher risk of adverse events was found in the HCQ arm. The conclusion of this study may provide updated evidence on COVID-19 prophylaxis for both researchers and clinical practitioners in their practice. Novel agents for the prophylaxis of COVID-19 with favorable effectiveness and acceptable adverse events are needed to decrease the incidence of COVID-19 and the corresponding disease burden in the context of the COVID-19 pandemic.

Conclusions

Significant effects of HCQ on SARS-CoV-2 infection with higher risk of adverse events were observed in this study. Generalizability must be considered with caution, and further research is necessary to delineate the specific circumstances where HCQ may be effective for COVID-19 prevention.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1043/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1043/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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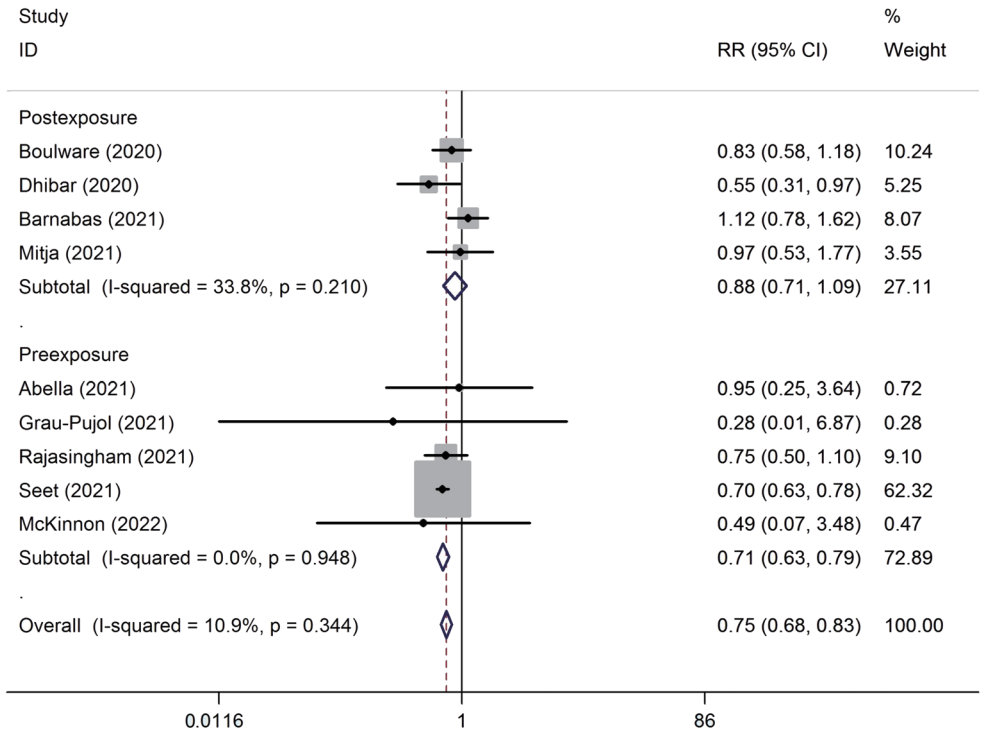

Figure S1 Subgroup analysis of SARS-CoV-2 infection. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

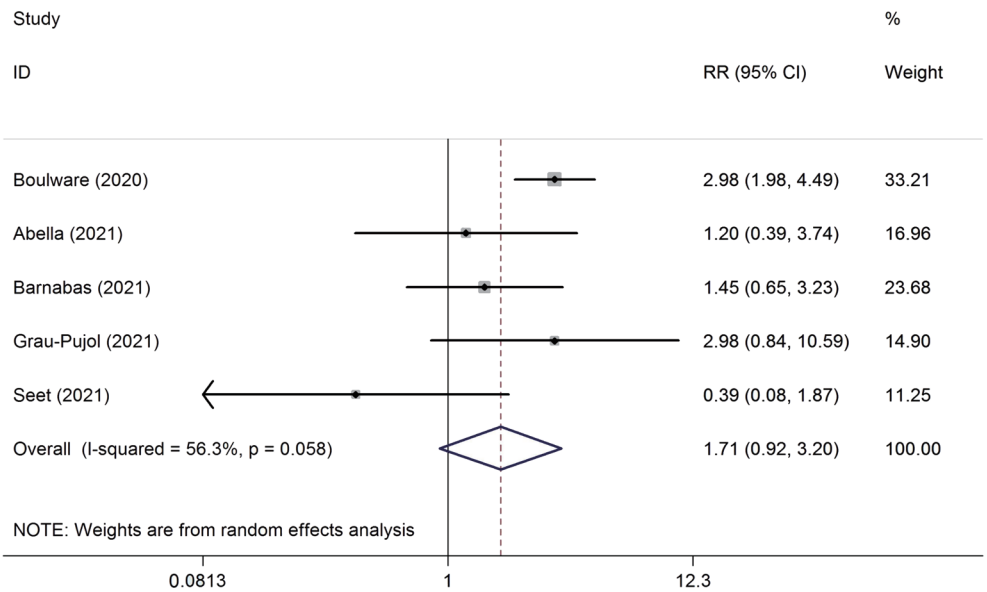

Figure S2 Forest plot of COVID-19 nausea. COVID-19, coronavirus disease 2019.

https://dx.doi.org/10.21037/jtd-23-1043

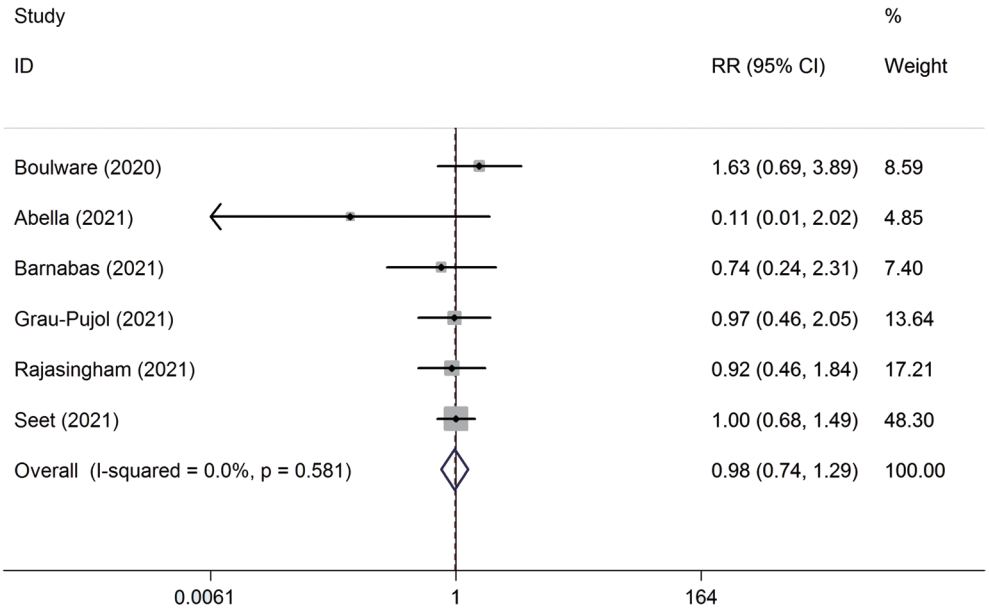

Figure S3 Forest plot of COVID-19 headache. COVID-19, coronavirus disease 2019.

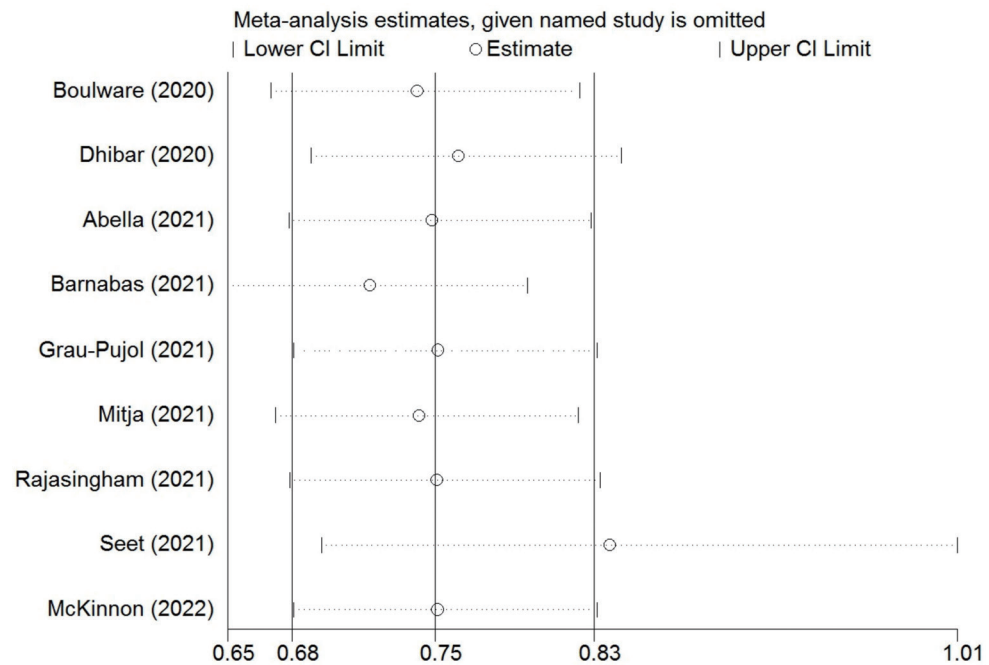

Figure S4 Sensitivity analysis of SARS-CoV-2 infection. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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