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ORIGINAL ARTICLE

Systematic review and meta-analysis of the effectiveness and safety of hydroxychloroquine in treating COVID-19 patients

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Abstract

Background: Since COVID-19 outbreak, hydroxychloroquine (HCQ) has been tested for effective therapies, and the relevant researches have shown controversial results.

Methods: Systematic review and meta-analysis were conducted after a thorough search of relevant studies from databases. Trials that have evaluated HCQ for COVID-19 treatment were recruited for statistical analysis with fixed- and random-effect models.

Results: Nine trials involving 4112 patients were included in present meta-analysis. It was seen that HCQ-azithromycin (HCQ-AZI) combination regimen increased the mortality rate in COVID-19 (odds ratio [OR], 2.34; 95% confidence interval [CI], 1.63–3.36) patients; however, it also showed benefits associated with the viral clearance in patients (OR, 27.18; 95% CI, 1.29–574.32). HCQ-alone when used as a therapy in COVID-19 did not reveal significant changes in mortality rate, clinical progression, viral clearance, and cardiac QT prolongation. Subsequent subgroup analysis showed that HCQ treatment could decrease mortality rate and progression to severe illness in severely infected COVID-19 patients (OR, 0.27; 95% CI, 0.13–0.58). A lower risk of mortality rate was also noted in the stratified group of >14 days follow-up period (OR, 0.27; 95% CI, 0.13–0.58) compared to ≤14 days follow-up period group that conversely showed an increased mortality rate (OR, 2.09; 95% CI, 1.41–3.10).

Conclusion: Our results indicated that HCQ-AZI combination treatment increased mortality rate in patients with COVID-19, but it also showed benefits associated with viral clearance in patients. HCQ-alone used for treatment has revealed benefits in decreasing the mortality rate among severely infected COVID-19 group and showed potential to be used for COVID-19 treatment in long-term follow-up period group. Accordingly, more rigorous, large-scale, and long follow-up period studies in patients with COVID-19 are needed.

Keywords: Azithromycin; COVID-19; Hydroxychloroquine; SARS-CoV-2; Systematic review

1. INTRODUCTION

In December 2019, the sudden outbreak of newly detected coronavirus (SARS-CoV-2) in Wuhan City of China has resulted in a global pandemic.[1] Until May 15, 2020, over 4 million people in more than 200 countries have been infected and over 300 thousand people have died due to this deadly COVID-19.[2] Epidemiologists and researchers are working tirelessly to find effective ways against COVID-19; however, promising pharmacological agents are still not available for COVID-19 treatment, and the preventive strategies such as personal protective measures and social distancing are currently the major means of infection control.

Numerous active clinical trials are underway to validate the effectiveness of agents for COVID-19 treatment, including ribavirin, remdesivir, lopinavir/ritonavir, hydroxychloroquine (HCQ), etc.[3] The pathogenic mechanisms of SARS-CoV-2 have been exemplified by initial viral replication followed by enhanced systemic inflammation[4] and is suggested to correlate with the impact on immune system due to T cell infection.[5] Recently conducted studies have drawn a lot of attention related to the possible benefits of HCQ, an antimalarial agent with immunomodulatory activity, which has been widely used for the treatment of rheumatic disease mainly because of its relatively low price and considerable safety.

The medical application of HCQ or chloroquine (CQ) in combination with a immunomodulatory and anti-inflammatory macrolide, such as azithromycin (AZI) or clarithromycin, is designed to exert the antimicrobial properties in a synergistic manner and has been revealed to be more efficient for virus elimination in a small sample size study. This has rapidly resulted

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in massive adoption by clinicians and is now being used as a regimen of treatment for COVID-19 worldwide.[6,7] However, the US Food and Drug Administration (FDA) has authorized the emergency use of HCQ for hospitalized COVID-19 patients, although evidence from clinical trials are still not available for this indication.[8] Several studies have reported the increased risk of cardiac toxicities when these medications were used alone or in combination and has raised concerns regarding their cardiovascular safety.[9,10] Due to the effect of prolonging QT interval, this medication may put patients at increased risk of Torsades de pointes (TdP) and cause sudden death. Therefore, the US FDA has issued a warning against the use of HCQ and CQ for treating patients with COVID-19.[11] Based on these finding, the World Health Organization has temporarily paused all HCQ-related clinical studies in association with COVID-19 which has led to lot of pending data due to safety concerns.[12]

Several *in vitro* studies have speculated that HCQ has a potent antiviral activity against SARS-CoV-2 and might be the choice in treating COVID-19 patients.[13–15] However, these studies may not complement the clinical situation, and several controversial results have been noticed among researches.[6,16–23] Most of the published clinical studies of HCQ for COVID-19 treatment have small sample size[6,16,17,21] or are nonrandomized clinical trials (non-RCT),[6,18–20,22,23] which are the major limitations in deriving a sound outcome. Currently available review articles that have discussed the use of HCQ in COVID-19 patients also showed several limitations such as few relevant studies were included, significant Chinese studies were omitted, lack of subgroup analysis, and lack of quantified results in presenting treatment effects.[24–27]

Due to the severe outbreak of COVID-19 and the efficacy and safety of HCQ for COVID-19 treatment is still largely uncertain, it is crucial to systematically evaluate the rapid increased relevant studies in a rigorous manner. Hence, we conducted a systematic review and meta-analysis not only to address the benefits and safety issues of HCQ in COVID-19 treatment, but also to evaluate the effects in combination with the use of macrolide, especially AZI in therapy.

2. METHODS

2.1. Data search

We systematically searched the MEDLINE, medRxiv, PubMed, China Academic Journals Full-text Database, Cochrane database and Web of Science database up to May 14, 2020, with no language restriction taken into consideration. In addition, relevant articles were also obtained from the reference list of reports, which were identified using this search strategy. The main keywords included the following terms, "COVID-19," "SARS-CoV-2," and "hydroxychloroquine."

2.2. Study selection

Two reviewers reviewed 295 abstracts and 29 full-text articles independently. Our study included only comparative studies that examined the efficacy or safety of HCQ with or without AZI in comparison with standard treatment (control group) based on factors such as virological cure, degree of progression to severe illness, and all-cause mortality as identified in COVID-19 patients. Among of all the selected search materials, 275 articles were excluded due to their inappropriate study design (Fig. 1).

2.3. Quality assessment

One reviewer extracted study-level data into standardized working tables and the other checked data accuracy. Two independent reviewers critically appraised the eligible articles by using the Modified Downs and Black risk assessment scale.[28] This scale consists of 27 items, which assesses different study characteristics, such as internal validity, statistical power, and external validity. Publication bias was also assessed by using a funnel plot.

2.4. Data synthesis and statistical analysis

In the present study, the efficacy outcomes were evaluated via indexes of viral clearance and progression of disease, while the safety outcomes were investigated through indexes of QT prolongation and mortality rate. The beneficial outcomes were accessed based on the consistency and availability of viral clearance results as reported in the recruited trials, which were defined as a negative result of SARS-COV-2 when detected by real-time RT-PCR method. We performed the meta-analysis by using Mantel–Haenszel method for dichotomous data. Either fixed-effect model or random effect model was applied according to the level of heterogeneity. The odds ratio (OR) was used as the common measure of association across studies. We assessed statistical heterogeneity through the I^2 index. Meta-analysis was undertaken by using Cochrane Collaboration Review Manager (RevMan) software version 5.3.

2.5. Subgroup analysis and sensitivity analysis

Subgroup analysis was carried out by including the disease severity (mild-to-moderate, severe) and follow-up period (≤14 days, >14 days) as well as the dosage of HCQ including low dose (maintenance dose ≤400 mg/day) and high dose (maintenance dose >400 mg/day), so as to assess the impact of these variables on the outcome.

Sensitivity analysis was carried out by including the symptomatic clinical status and age (≥18 years old) so as to assess the impact of these variables on viral clearance results.

3. RESULTS

3.1. Study characteristics

A total of 4112 participants with an average age of 62.76 years were enrolled in present study, and the sample size of included trials ranged from 30 to 1438.[6,16–19,29–32] Table 1 shows the main characteristics of the eligible, studies which were included in the research. Among these nine included trials, five trials have mentioned their exclusion criteria as, the patients who had known allergy to HCQ or any other known contraindication in terms of usage of the study drugs, such as retinopathy or pregnancy.[6,16,17,19,32] However, four trials were conducted without considering any exclusion criteria.[18,29–31]

3.2. Quality of included studies

The risk of bias assessment is reported in Supplementary Fig 1. The average Downs and Black score was 19.9, with a range between 17 and 23 (A higher score indicates less bias). Various studies have shown different degree of bias wherein the open-label, RCT conducted by Tang W et al[32] has displayed the lowest risk of bias and the open-label, non-RCT has shown the highest risk of bias.[6] One Chinese trial was described as randomized although the method of randomization, allocation concealment, and blinding of assessors during outcome evaluation was not mentioned,[16] whereas another RCT properly described the method of randomization and double-blinding[17] and the other RCT was described as open-label.[32] With regard to the study design, one French trial was designed as open-label, non-randomized trial,[6] and five other studies were planned as controlled retrospective studies.[18,19,29–31] A trial reported a loss of follow-up by participants while undergoing treatment; hence, they were excluded during analysis planning due to their withdrawal from the study.[6]

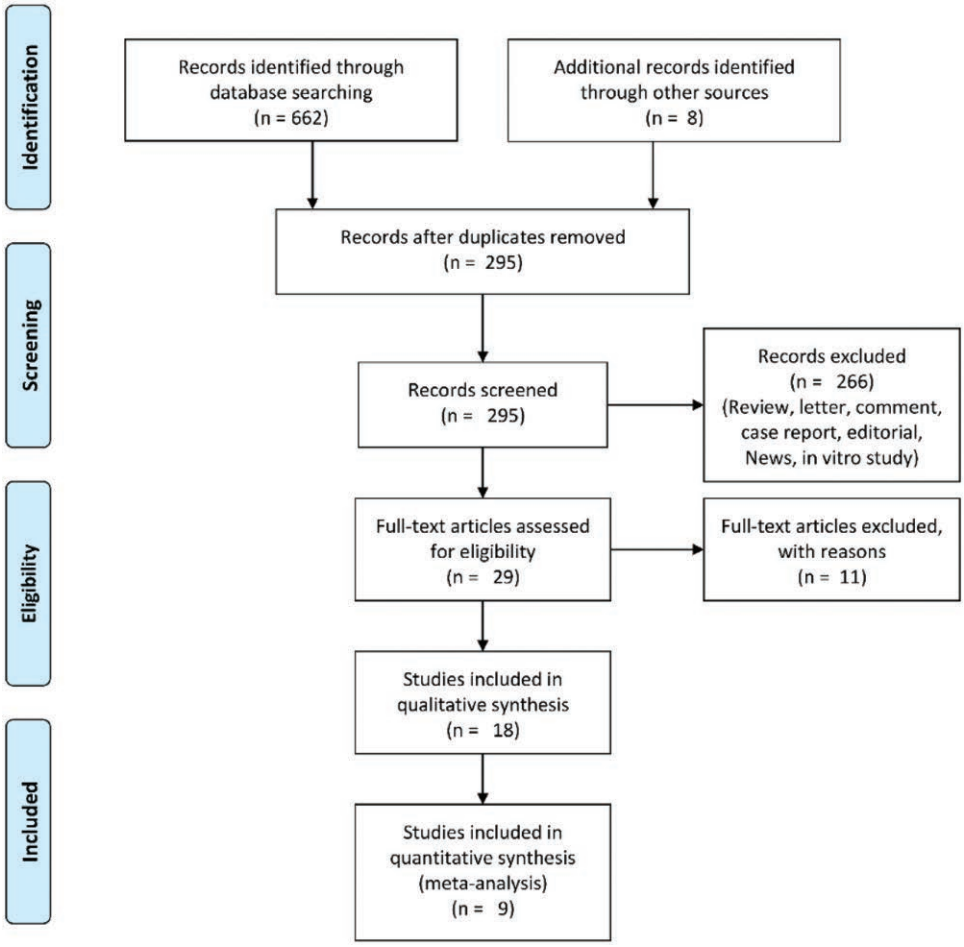

Fig. 1 Prisma flow chart of included studies.

3.3. All-cause mortality

For analyzing all-cause mortality, we included six trials which had relevant results associated with mortality.[6,16,18,19,31,32] The research findings concluded that the combination therapy of HCQ and AZI was associated with increased mortality in COVID-19 patients, but the use of HCQ-alone showed no association with mortality (Fig. 2A).

3.4. Progression to severe illness

During the research period, progression to severe illness as seen in COVID-19 patients in association with the study drug was noticed in the included trials.[6,16–19,32] No benefit of reduction in progression rate was reported in the HCQ usage groups, whether alone or combined with AZI, when compared with standard treatment (Fig. 2B).

3.5. QT prolongation

Two trials were included for meta-analysis to evaluate the safety outcome of QT prolongation.[19,31] Fig. 3 demonstrates that a higher rate of QT prolongation was reported in the HCQ with or without AZI combination group, but there was no significant difference documented when compared with standard treatment (OR 3.51; 95% CI, 0.65–18.90; I^2 = 44%) group.

3.6. Effect on viral clearance

Two trials were included for meta-analysis, assessing a total of 66 participants.[6,16] We found no significant evidence to verify that HCQ when used alone for the treatment was effective in reducing viral carriage (OR, 1.74; 95% CI, 0.51–5.91). Fig. 4 shows the comparative effectiveness of combination therapy of HCQ and AZI with standard treatment, and the results indicated that there was a significant reduction in viral load when combination therapy was used (OR, 27.18; 95% CI, 1.29–574.32). Our data demonstrated that variables of symptomatic clinical status (eg, upper respiratory tract infection or lower respiratory tract infection symptoms) as well as age did not possess significant modulation effect in viral clearance under the use of HCQ-alone or in combination with AZI (Supplementary Fig 2 and Fig 3).

3.7. Subgroups analysis

Based on the outcome of mortality rate and progression to severe illness, subgroup analysis was performed by including severity of COVID-19, HCQ dosage, and duration of follow-up period (Fig. 5). Our results have shown that the mortality rate and progression to severe illness were significantly decreased in groups that were severely infected (OR, 0.27; 95% CI, 0.13–0.58, Fig. 5A) as well as all-cause mortality rate was significantly decreased in groups that had long-term (>14 days) follow-up period (OR, 0.27; 95% CI, 0.13–0.58, Fig. 5C). On the contrary, the mortality rate was exacerbated in the group of short-term (≤14 days) follow-up period (OR, 2.09; 95% CI, 1.41–3.10, Fig. 5C). Our results have also indicated that HCQ dosage did not have significant effects in modulating the outcomes (Fig. 5B).

3.8. Publication bias

In total, nine trials were included in the present study and were appropriately evaluated for publication bias by conducting

Table 1.

Main characteristics of the trials included in the meta-analysis

No.	Author (year, country)	Design	Setting	Age, year (median/ mean)	Male, %	Severity of COVID-19	N	Intervention (no. of subjects)	HCQ regimen	Results, n (%)
1	Chen, et al.[16] (2020, China)	RCT	Single center	48.6	70.0	Mild/moderate	30	(1) Non-HCQ (15); (2) HCQ-alone (15)	400 mg/day × 5 days	HCQ-alone vs. non-HCQ viral clearance on day 7: 13 (86.7%) vs. 14 (93.3%) Radiological improvement on day 3: 5 (33.3%) vs. 7 (46.7%); Adverse drug events: 4 (26.7%) vs. 3 (20.0%); Progression to severe illness: 1 (6.7%) vs. 0; All-cause mortality: 0 vs. 0
2	Gautret, et al.[6] (2020, French)	Open-label, prospective, non-RCT, cohort	Four centers	45.1	41.7	Mild/moderate	36 (36 + 6[a])	(1) Non-HCQ (16); (2) HCQ-alone (14); (3) HCQ + AZI (6) HCQ ± AZI (20 + 6[a])	600 mg/day × 10 days	HCQ-alone vs. HCQ + AZI vs. non-HCQ Viral clearance on day 6: 8 (57.1%) vs. 6 (100%) vs. 5 (12.5%); HCQ ± AZI vs. non-HCQ viral clearance on day 6: 16 (61.5%)[a] vs. 5 (12.5%); Progression to severe illness: 3 (11.5%)[a] vs. 0; All-cause mortality: 1 (3.8%)[a] vs. 0
3	Chen, et al.[17] (2020, China)	RCT	Single center	44.7	46.8	Mild	62	(1) Non-HCQ (31); (2) HCQ-alone (31)	400 mg/day × 5 days	HCQ-alone vs. non-HCQ radiological improvement: 25 (80.6%) vs. 17 (54.8%); Adverse drug events: 2 (6.5%) vs. 0; Progression to severe illness: 0 vs. 4 (12.9%)
4	Magagnoli, et al.[18] (2020, USA)	Retrospective cohort study	Multicenter (VA Medical Centers)	68	100.0	Mild/moderate	368	(1) Non-HCQ (158); (2) HCQ-alone (97); (3) HCQ + AZI (113)	NR	HCQ-alone vs. HCQ + AZI vs. non-HCQ MV: 12 (13.3%) vs. 7 (6.9%) vs. 25 (14.1%); All-cause mortality: 27 (27.8%) vs. 25 (22.1%) vs. 18 (11.4%)
5	Mahévas, et al.[19] (2020, French)	Retrospective cohort study	Four centers	60	72.0	Moderate/ Severe	181	(1) Non-HCQ (89)[b]; (2) HCQ-alone (92)[b]	600 mg/day × 2 days	HCQ-alone vs. non-HCQ All-cause mortality: 9 (9.8%) vs. 8 (9.0%); Transferred to the ICU: 11 (12.0%) vs. 14 (15.7%); Transferred to the ICU or died: 19 (20.7%) vs. 22 (24.7%); Abnormal ECG: 8 (8.7%) vs. 0; QT prolongation: 7 (7.6%) vs. 0
6	Yu, et al.[29] (2020, China)	Retrospective cohort study	Single center	68	63.0	Severe	568	(1) Non-HCQ (520); (2) HCQ-alone (48)	400 mg/day × 7–10 days	HCQ-alone vs. non-HCQ All-cause mortality: 9 (18.8%) vs. 238 (45.8%); Average hospital stay time: 32 (26–41) vs. 30 (18–40)
7	Geleris, et al.[30] (2020, USA)	Retrospective cohort study	Single center	60-79 (38.9-45.3%)	56.8	Moderate/ Severe	1446	(1) Non-HCQ (565)[c]; (2) HCQ-alone (811)[c]	1200 mg/day × 1 days, then 400 mg/day × 4 days	HCQ-alone vs. non-HCQ intubation or death: 262 (32.3%) vs. 84 (14.9%)
8	Rosenberg, et al.[31] (2020, USA)	Retrospective cohort study	Multicenter	63	59.7	NR	1438	(1) Non-HCQ (221); (2) HCQ-alone (271); (3) AZI alone (211); (4) HCQ + AZI (735)	Multiple regimens	HCQ-alone vs. HCQ + AZI vs. AZI alone vs. non-HCQ: All-cause mortality: 54 (19.9%) vs. 189 (25.7%) vs. 21 (10.0%) vs. 28 (12.7%); MV: 51 (18.8%) vs. 199 (27.1%) vs. 13 (6.2%) vs. 18 (8.1%); Cardiac arrest: 37 (13.7%) vs. 114 (15.5%) vs. 13 (6.2%) vs. 15 (6.8%); Abnormal ECG: 74 (27.3%) vs. 199 (27.1%) vs. 34 (16.1%) vs. 31 (14.0%); Arrhythmia: 44 (16.2%) vs. 150 (20.4%) vs. 23 (10.9%) vs. 23 (10.4%); QT prolongation: 39 (14.4%) vs. 81 (11.1%) vs. 15 (7.1%) vs. 13 (5.9%)
9	Tang, et al.[32] (2020, China)	Open-label, randomized controlled trial	Multicenter	46	55.0	Mild/moderate (84%)	150	(1) non-HCQ (75); (2) HCQ-alone (75)	1200 mg/day × 3 days, then 800 mg/day × 2 weeks (mild/ moderate) or 3 weeks (severe)	HCQ-alone vs. non-HCQ Viral clearance on day 28: 64 (85.4%) vs. 61 (81.3%); Adverse events: 21 (30%) vs. 7 (9%); Progression to severe illness: 1 (1%) vs. 0

[a]loss to follow-up.

[b]Azithromycin was administered to 18% of the participants in the treatment group versus 29% in the control group.

[c]Azithromycin was administered to 59.9% of the participants in the treatment group versus 22.5% in the control group.

ARDS = acute respiratory distress syndrome; ICU = intensive care unit; MV = mechanical ventilation; NR = not reported; RCT = randomized controlled trial; VA = veterans affairs; vs. = versus.

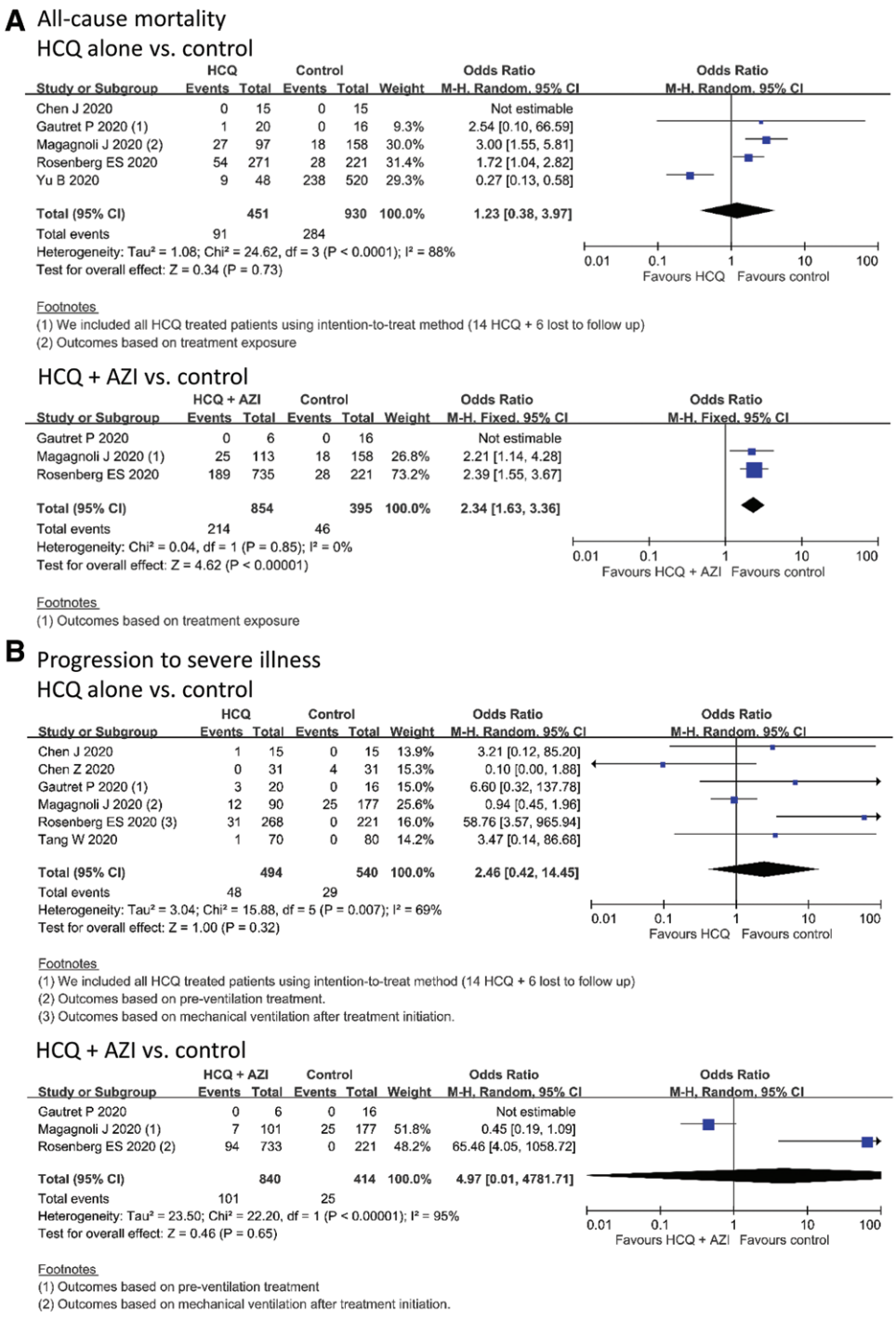

Fig. 2 A, All-cause mortality in COVID-19 patients. B, Progression to severe illness in COVID-19 patients. HCQ-alone=the use of hydroxychloroquine without azithromycin; HCQ + AZI=combination of hydroxychloroquine and azithromycin; Control=the patients with standard care; CI=confidence interval.

funnel plot analysis, and there was no obvious publication bias reported.

4. DISCUSSION

In this 9-trial-included meta-analysis, we demonstrated that COVID-19 patients who received HCQ-AZI combination therapy may improve their viral clearance but also have higher mortality rate when compared with the patients with standard care. Our results have also indicated that COVID-19 patients who received HCQ-alone did not reveal significant changes in mortality rate, clinical progression, viral clearance, and cardiac QT prolongation. In subsequent subgroup analysis stratified by disease severity, follow-up period, and HCQ dosage, our results have shown that HCQ treatment could help severe COVID-19 patients to lower the mortality rate and ameliorate the progression to severe illness. A lower risk of mortality rate was also noted in the stratified group of >14 days follow-up period as compared to ≤14 days follow-up period group that showed an increased mortality rate. To the best of our knowledge, present study is the

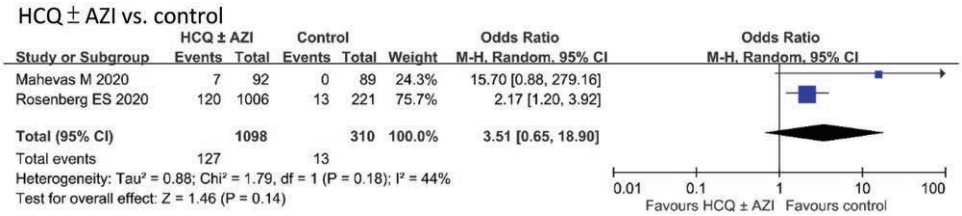

Fig. 3 QT prolongation in COVID-19 patients. HCQ ± AZI=the use of hydroxychloroquine with or without azithromycin; Control=the patients with standard care; CI=confidence interval.

first systematic review and meta-analysis that has addressed the factors (ie, patient disease severity, HCQ dosage and follow-up period), which may modulate the outcome when evaluating the use of HCQ and AZI in COVID-19 treatment by summarizing available results as extracted from the clinical trials.

In terms of safety issues for using HCQ in COVID-19 treatment, several mild adverse effects such as rash and diarrhea have been noted and described.[16,17] The association between HCQ or AZI administration and cardiac QT prolongation has also attracted attention, and hence, it has been warned in some small-scaled retrospective hospital-based cohort studies.[9,10,33] It has been known that extreme cardiac QT prolongation may cause the development of TdP, which would extend the length of hospitalization and exacerbate all-cause mortality rate in patients.[34,35] Therefore, large-scale database study from the US FDA Adverse Event Reporting System (FAERS) concluded an increased risk of TdP/QT prolongation and mortality rate in patients who have received HCQ-AZI combination treatment.[36] In present study, our results are consistent with the previous findings and demonstrated that COVID-19 patients treated with HCQ-AZI combination therapy had a higher mortality rate of 2.34 fold as compared to the control group. Our results have also shown the trend of QT prolongation in COVID-19 patients with HCQ treatment, but did not reach significance in statistics.

Moreover, our results have demonstrated that HCQ treatment was significantly correlated with a 2-fold increased risk of mortality of COVID-19 patients during short-term (≤14 days) follow-up period, while conversely showed reduced risk of mortality of COVID-19 patients to 1/3 of control group in long-term (>14 days) follow-up period. Previous studies have revealed that the duration of follow-up period in studies may play critical roles for analyzing correlations between risk factors and diseases. It has been shown that the incidence of cardiovascular events would be the main cause of mortality for patients with community-acquired pneumonia under short-term follow-up period of study, while infectious disease became the main cause of mortality in long-term follow-up period of study.[37,38] The risk of mortality for treating pneumonia by AZI also showed a time-limited pattern.[39] Therefore, we suggested that HCQ treatment may correlate with the cardiovascular events associated mortality during early stage of COVID-19, but showed benefits in reducing pneumonia associated mortality in COVID-19 patients. Moreover, in the subsequent subgroup analysis, we further found that HCQ use was beneficial to the severe COVID-19 groups for reducing the risk of death and ameliorating the severity of disease progression. However, these phenomena were not seen among mild-to-moderate COVID-19 groups; therefore, we inferred that a "ceiling effect" may be involved.

HCQ has been considered a potential candidate for treating COVID-19; therefore it is necessary to evaluate the dosage that ensures adequate safety and efficacy. However, controversial results have been reported in numerous studies where HCQ was used for COVID-19 treatment under a variety of conditions and dosages.[40–42] Accordingly, we applied subgroup analysis via HCQ dosage in present study, and our results have demonstrated that dosage of HCQ did not significantly modulate the mortality of COVID-19.

In association with the issue of viral clearance of COVID-19, several studies have demonstrated a prompt reduction of viral load and mortality rate after HCQ-AZI combination treatment.[20,23] Conversely, unfavorable outcome of viral elimination under the HCQ-AZI combination use was also reported

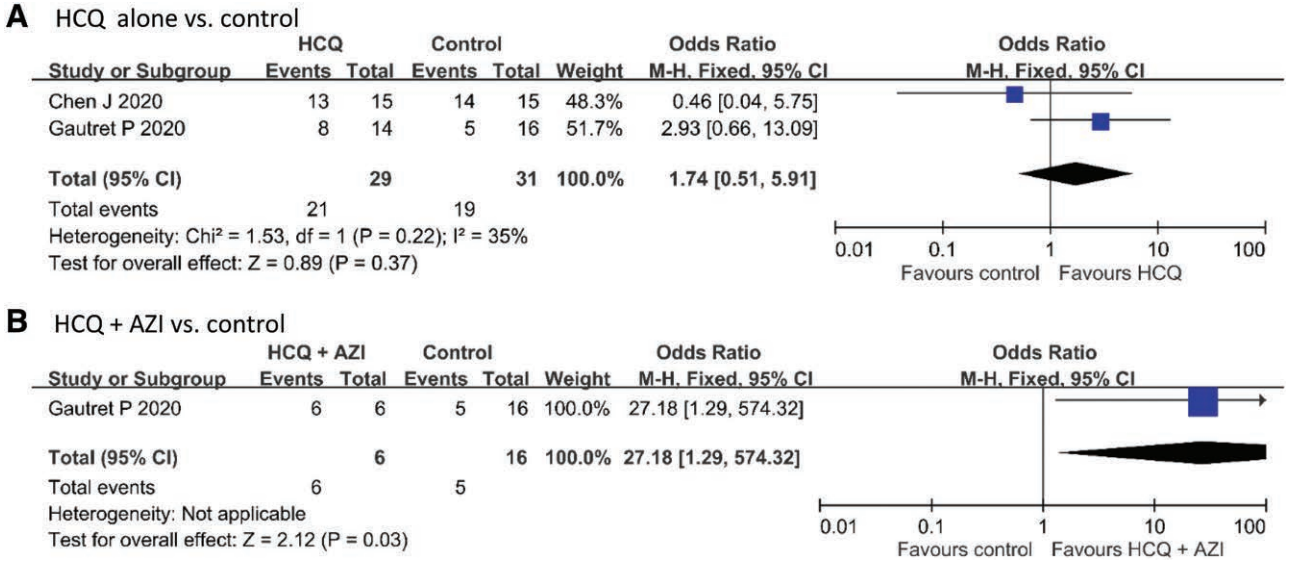

Fig. 4 Viral clearance of SARS-CoV-2 in COVID-19 patients. HCQ-alone=the use of hydroxychloroquine without azithromycin; HCQ + AZI=combination of hydroxychloroquine and azithromycin; Control=the patients with standard care; CI=confidence interval.

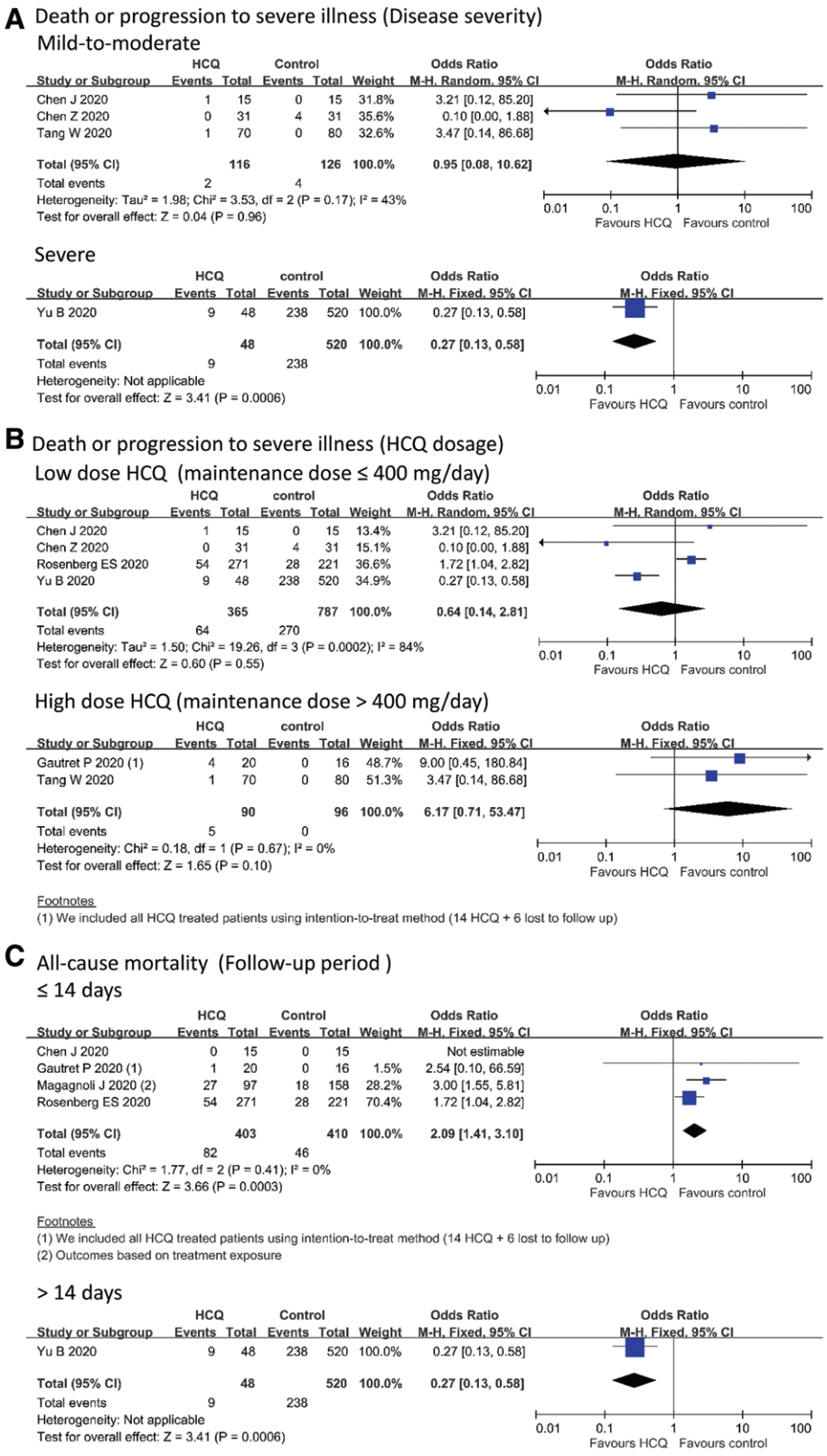

Fig. 5 Subgroup analysis. A, Death or progression to severe illness in COVID-19 patients with different disease severity. B, Death or progression to severe illness in COVID-19 patients taking different HCQ dosage. C, All-cause mortality in COVID-19 patients with different follow-up periods. HCQ = hydroxychloroquine; Control = the patients with standard care; CI = confidence interval.

in a small case series, which has focused on severely infected COVID-19 patients.[21] In present study, our results have revealed that HCQ-AZI combination treatment but not HCQ-alone regiment could provide benefit in reducing the viral clearance in COVID-19 patients. However, our results could not exclude the influence of severity of COVID-19 infection to the outcome of

HCQ-AZI combination use due to various limitations such as the number of studies recruited as well as the small sample size, short observation period, and short duration of drug treatment as seen in the original data source.[6,16] More efforts and further investigations are still needed to clarify these important issues.

Our study has demonstrated some substantial advantages. We performed subgroup analysis stratified by disease severity, HCQ dosage, and follow-up period for evaluating the correlation between HCQ use and the main outcome of interest. We performed a systematic and comprehensive search to locate published and unpublished papers through appropriate database. There were no potentially essential sources excluded with regard to language or methodological features. Consequently, the review process has caused little publication-selection bias. Furthermore, we have used intention-to-treat method and performed subgroup analysis with stable findings.

Despite the pertinent information demonstrated above, our systematic review has its own limitations. As far as the lack of compiling sufficient data with regard to virological cure as efficacy outcome is concerned, we tried to solve this problem by conducting a search for unpublished literature and non-English journals to increase the quantity of relevant integrated literature. Most studies which are published are mainly observational studies and case series with substantial methodology concerns such as no framework of exclusion criteria, and hence, they are susceptible to bias and confounding. Therefore, as there are limited related RCTs in the literature at present, only those were included in our study. Due to the lack of experimental random allocation for the intervention, the effects of the HCQ might be overestimated. Furthermore, the two single-centered RCTs which were conducted in China had some limitations as it included small sample size, did not conduct an international trial, and only limited data was available regarding the viral load. In our present study, bias might be present since little information was provided on demographic data, comorbidity, severity of disease, and the adverse effects of HCQ or AZI such as QT prolongation. Finally, the limited number of available studies which were included made it unworkable to evaluate the true effects of HCQ. Therefore, the present results should be interpreted cautiously, and further large, prospective RCTs needs to be conducted in a methodologically rigorous manner.

In conclusion, our results have suggested that HCQ-AZI combination treatment demonstrated higher mortality rate in COVID-19; however, it has also shown benefit in reducing viral clearance in patients. HCQ-alone treatment has revealed benefits by decreasing mortality rate among severe COVID-19 group and showed potential for COVID-19 treatment during long-term follow-up period of study. Accordingly, more rigorous, large-scale, and studies with long follow-up period are needed for validating aspects of medication interactions, cardiac disease, and electrolyte disorders in COVID-19 patients.

ACKNOWLEDGMENTS

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000264.

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