

RESEARCH ARTICLE

Effect of azithromycin and hydroxychloroquine in patients hospitalized with COVID-19: Network meta-analysis of randomized controlled trials

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Abstract

Chloroquine or its derivative hydroxychloroquine (HCQ) combined with or without azithromycin (AZ) have been widely investigated in observational studies as a treatment option for coronavirus 2019 (COVID-19) infection. The network meta-analysis aims to summarize evidence from randomized controlled trials (RCTs) to determine if AZ or HCQ is associated with improved clinical outcomes. PubMed and Embase were searched from inception to March 7, 2021. We included published RCTs that investigated the efficacy of AZ, HCQ, or its combination among hospitalized patients with COVID-19 infection. The outcomes of interest were all-cause mortality and the use of mechanical ventilation. The pooled odds ratio was calculated using a random-effect model. A total of 10 RCTs were analyzed. Participant's mean age ranged from 40.4 to 66.5 years. There was no significant effect on mortality associated with AZ plus HCQ (odds ratio [OR] = 0.562 [95% confidence interval {CI}: 0.168–1.887]), AZ alone (OR = 0.965 [95% CI: 0.865–1.077]), or HCQ alone (OR = 1.122 [95% CI: 0.995–1.266]; $p = 0.06$). Similarly, based on pooled effect sizes derived from direct and indirect evidence, none of the treatments had a significant benefit in decreasing the use of mechanical ventilation. No heterogeneity was identified (Cochran's $Q = 1.68$; $p = 0.95$; $\tau^2 = 0$; $I^2 = 0\%$ [95% CI: 0%–0%]). Evidence from RCTs suggests that AZ with or without HCQ was not associated with a significant effect on the mortality or mechanical ventilation rates in hospitalized patients with COVID-19. More research is needed to explore therapeutics agents that can effectively reduce the mortality or severity of COVID-19.

KEYWORDS

azithromycin, chloroquine, coronavirus, coronavirus disease 2019, hydroxychloroquine, mechanical ventilation, mortality, network meta-analysis

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), is an enveloped virus with a positive-sense single-stranded ribonucleic acid (RNA) genome. This virus was identified as the cause of an outbreak of respiratory illness first detected in Wuhan, China. On March 12, 2020 this local epidemic was escalated to a pandemic by the World Health Organization (WHO) due to its rapid rate of global spread. Ever since its emergence, COVID-19 has devastated the healthcare, socioeconomic and educational sectors of society through a ripple effect. Infected patients can have a wide range of presentations ranging from asymptomatic infection to acute respiratory distress syndrome and death.¹ Worldwide case fatality rate ranges between 2% and 3%.^{2,3} In addition to affecting the respiratory tract, SARS-CoV-2 infection has been shown to establish a proinflammatory milieu capable of promoting various complications such as thrombosis, cardiac arrhythmias, exacerbations of heart failure, acute kidney injury, stroke and encephalitis.⁴⁻¹² The medical, economical and psychological impact of social distancing, quarantining and isolation may have lingering effects in the community.¹³⁻¹⁵ These challenges have driven the scientific community to seek therapies aiming at treatment and prevention of COVID-19 in a race against time to curtail the morbidity and mortality associated with this rapidly spreading disease.¹⁶⁻¹⁸ Various pharmacological agents have been studied over the course of the pandemic for their effectiveness on COVID-19. Azithromycin (AZ) and hydroxychloroquine (HCQ) were extensively investigated in a series of observational studies and randomized controlled trials for their real-world efficacy against COVID-19, due to their availability, prior success in the treatment of inflammatory airway disease, in vitro antiviral activity, cost, and publicity. Previous meta-analyses and systematic reviews have analyzed the evidence based on mostly observational studies and noted heterogeneous results. To validate the potential efficacy of AZ and HCQ, a network meta-analysis including only randomized clinical trials was undertaken to estimate the treatment effect of these agents based on higher-quality data.

2 | METHODS

2.1 | Search strategies and selection criteria

Systematic literature searches were performed in PubMed and Embase from inception to March 7, 2021. The selection criteria included (1) randomized clinical trials that investigated the efficacy of AZ, HCQ, or its combination; (2) studies that were published as original research articles; and (3) studies that reported the clinical outcomes at the end of follow-up. All searches were limited to the English language. Duplicates were removed before screening references. Detailed queries are provided in Table S1.

2.2 | Study outcomes and treatment comparison

In this analysis, the outcomes of interest are (1) all-cause mortality and (2) the use of mechanical ventilation. Randomized trials that involve any of the following treatment comparisons were analyzed: (1) AZ plus HCQ (AZ + HCQ); (2) AZ; (3) HCQ; and (4) usual standard of care or placebo (control group).

2.3 | Data extraction and quality assessment

Data extracted from each study included study design, patient characteristics, and the number of events (all-cause mortality and use of mechanical ventilation). Database search, article screening, and study selection were performed independently by two investigators using a standardized approach. Disagreement in extracted data was adjudicated by a third investigator. A flow diagram depicting the process of literature search and screening is provided in Figure 1.

Two independent investigators assessed the quality of included studies with the revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Disagreement in the quality assessment was resolved by discussion and consensus.

2.4 | Statistical analysis

A network meta-analysis using the *netmeta* package was performed to compare the treatment effect. The measure of treatment effect was expressed as odds ratio (OR) with 95% confidence interval (CI). A fixed-effect or random-effect model was fitted to estimate the treatment effect based on the presence of heterogeneity. Heterogeneity across the studies was evaluated using Cochran's Q test (with the threshold of $p > 0.10$) and Higgins's I^2 statistic (with the values of 0.25, 0.50, and 0.75 indicating a low, moderate, and a high degree of heterogeneity, respectively). Analysis was performed using R software (Version 3.5.2; The R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Summary of included studies

A total of 10 randomized controlled trials were included in the final analysis (Figure 1).¹⁹⁻²⁸ The study design and patient characteristics of included studies were summarized in Table 1. Results of risk of bias assessment were presented in Figure S1. Three studies were considered to be at a high risk of bias.

Eight of the studies were open-label. The majority of the studies had two treatment arms and a follow-up duration of 1 month, except for COALITION-I that had a three-arm design and 15 days of follow-up. The mean age of enrolled patients ranges from 40.4 to 66.5 years. Men are slightly more predominant than women in all of the included

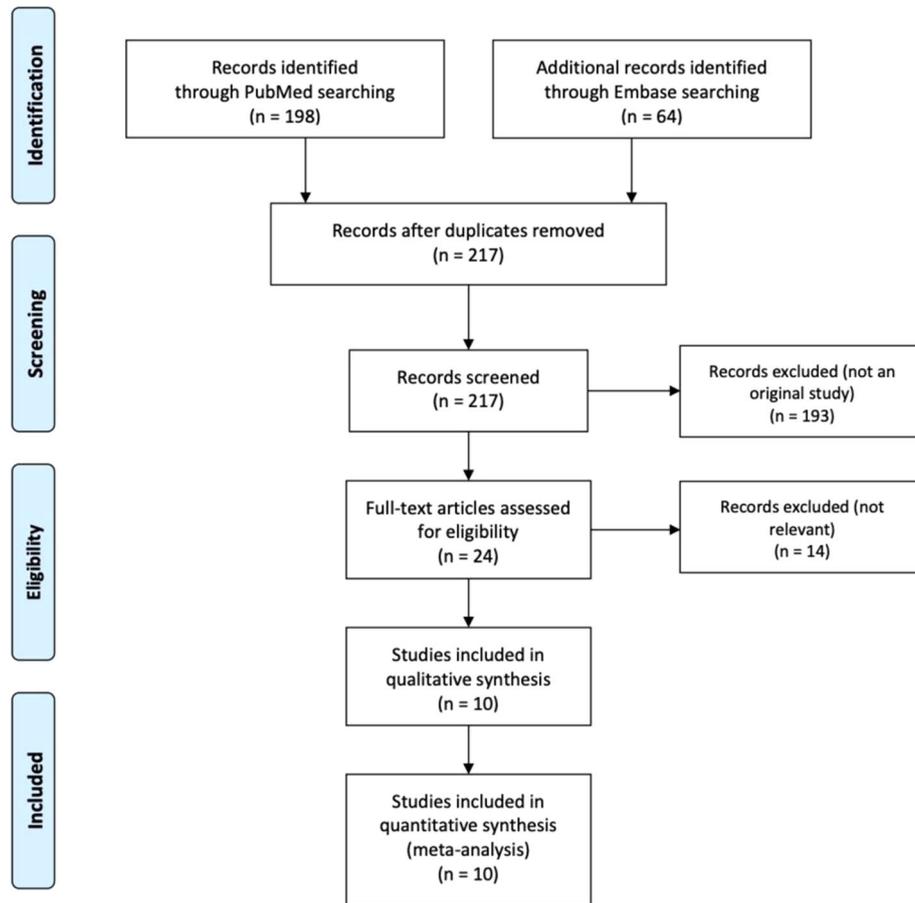


FIGURE 1 Study flow diagram

studies. The prevalence of comorbidities and the proportions of corticosteroid usage vary widely across the studies.

3.2 | Mortality

The network graph was provided in Figure S2. Compared to the control group (i.e., patients who received usual care or placebo), there was no significant effect on mortality associated with AZ+HCQ (OR = 0.562 [95% CI: 0.168–1.887]; $p = 0.35$), AZ alone (OR = 0.965 [95% CI: 0.865–1.077]; $p = 0.52$), or HCQ alone (OR = 1.122 [95% CI: 0.995–1.266]; $p = 0.06$) (Figure 2).

The effect on mortality of all treatment comparisons was summarized in Table 2. Based on pooled effect sizes derived from direct evidence (dark shaded area), none of the pairwise comparisons demonstrated a significant difference in mortality. Similarly, based on pooled effect sizes derived from direct and indirect evidence (light shaded area), none of the treatments had a significant benefit in reducing mortality.

No significant heterogeneity was identified (Cochran's $Q = 3.62$; $p = 0.89$; $t^2 = 0$; $I^2 = 0\%$ [95% CI: 0%–22.2%]). In the design-by-treatment interaction model, no significant inconsistency was detected between designs ($Q = 3.62$; $p = 0.43$). Additionally, there was

no significant inconsistency between direct and indirect evidence (Figure 3).

3.3 | Use of mechanical ventilation

The network graph was provided in Figure S3. Compared to the control group (i.e., patients who received usual care or placebo), there was no significant effect on the use of mechanical ventilation associated with AZ+HCQ (OR = 1.689 [95% CI: 0.892–3.198]; $p = 0.11$), AZ alone (OR = 0.930 [95% CI: 0.788–1.097]; $p = 0.39$), or HCQ alone (OR = 1.125 [95% CI: 0.942–1.345]; $p = 0.19$) (Figure 4).

The effect on the use of mechanical ventilation of all treatment comparisons was summarized in Table 3. Based on pooled effect sizes derived from direct evidence (dark shaded area), none of the pairwise comparisons demonstrated a significant difference. Similarly, based on pooled effect sizes derived from direct and indirect evidence (light shaded area), none of the treatments had a significant benefit in decreasing the use of mechanical ventilation.

No significant heterogeneity was identified (Cochran's $Q = 1.68$; $p = 0.95$; $t^2 = 0$; $I^2 = 0\%$ [95% CI: 0%–0%]). In the design-by-treatment interaction model, no significant inconsistency was detected between

TABLE 1 Summary of included studies

Study name	Design	Intervention	Dose	Follow-up	Age, year	Male, %	White, %	BMI	Diabetes, %	Heart disease, %	Chronic lung disease, %	Severe liver disease, %	Severe kidney impairment, %	ICU admission, %	Use of corticosteroids, %	SARS-CoV-2 test positive, %
RECOVERY ²³	Randomized, controlled, open-label, platform trial	AZ vs. control	AZ 500 mg once per day by mouth or intravenously for 10 days or until discharge	28 days	65.4 (15.6) vs. 65.2 (15.7)	62 vs. 62	76 vs. 77	NR	27 vs. 28	27 vs. 26	24 vs. 25	2 vs. 1	6 vs. 6	NR	61 vs. 61	91 vs. 92
DISCOVERY ²⁴	Randomized, controlled, open-label trial	HCQ vs. control	HCQ: four tablets (200 mg) at hour 0, and at hour 6, and, starting at hour 12, two tablets twice daily for 10 days.	28 days	<50 years: 335 vs. 317; 50–69 years: 410 vs. 396; ≥70 years: 202 vs. 193	50.6 vs. 59.1	199 vs. 205	NR	199 vs. 205	193 vs. 194	62 vs. 66	15 vs. 14	NR	NR	NR	NR
HAHPS ⁵⁰	Randomized Open-Label, Active Comparator Trial	HCQ vs. AZ	AZ loading dose of 500 mg on the first day, followed by 250 mg daily for the next 4 days. HCQ orally as a loading dose of 400 mg	28 days	51 (42–60) vs. 58 (43–68)	67 vs. 54	60 vs. 67	NR	35 vs. 33	9 vs. 7	NR	0 vs. 2	7 vs. 12	NR	2 vs. 5 (before enrollment)	100

TABLE 1 (Continued)

Study name	Design	Intervention	Dose	Follow-up	Age, year	Male, %	White, %	BMI	Diabetes, %	Heart disease, %	Chronic lung disease, %	Severe liver disease, %	Severe kidney impairment, %	ICU admission, %	Use of corticosteroids, %	SARS-CoV-2 test positive, %
			twice on the first day followed by 200 mg twice daily for the following 4 days													
TEACH ²⁷	Double-blind, placebo-controlled, randomized clinical trial	HCQ vs. control	Dosing of both HCQ and calcium citrate was 400 mg (2 tablets) by mouth 2 times per day (day 1) and 200 mg (1 tablet) by mouth 2 times per day (days 2–5);	30 days	66.5 (16.4) vs. 65.8 (16.0)	67.2 vs. 50.8	34.3 vs. 29.5	BMI < 30: 74.7 vs. 52.4; BMI ≥ 30: 36.0 vs. 47.7	28.4 vs. 36.1	31.3 vs. 21.3	7.5 vs. 6.6	NR	10.4 vs. 4.9	13.4 vs. 8.2	10.4 vs. 9.8	100
ORCHID ²⁶	Randomized, blinded, placebo-controlled	HCQ vs. control	HC 400 mg twice daily for 2 doses, then 200 mg	28 days	58 (45–69) vs. 57 (43–68)	55.8 vs. 55.7	31.0 vs. 28.6	31.3 (26–43) vs. 31.1 (26–43)	36.4 vs. 32.9	7.9 vs. 9.7	7.4 vs. 8.9	NR	11.6 vs. 5.9	NR	18.4 of the participants	100

(Continues)

TABLE 1 (Continued)

Study name	Design	Intervention	Dose	Follow-up	Age, year	Male, %	White, %	BMI	Diabetes, %	Heart disease, %	Chronic lung disease, %	Severe liver disease, %	Severe kidney impairment, %	ICU admission, %	Use of corticosteroids, %	SARS-CoV-2 test positive, %
	control-led trial		twice daily for 8 doses					(27.2-36.5)								
RECOVERY ²⁸	Randomized, controlled, open-label, parallel-form trial	HCQ vs. control	hydroxychloroquine sulfate (in the form of a 200-mg tablet) in a loading dose of four tablets (total dose, 800 mg) at baseline and at 6 h, which was followed by two tablets (total dose, 400 mg) starting at 12 h after the initial dose and then every 12 h for the next 9 days or until	28 days	65.2 ± 15.2 vs. 65.4 ± 15.4	61.5 vs. 62.6	75.7 vs. 72.8	NR	27.4 vs. 27.1	27 vs. 25	21.4 vs. 22.6	1.2 vs. 1.5	7.1 vs. 8.3	16.7 vs. 16.9	NR	89.6 vs. 90.9

TABLE 1 (Continued)

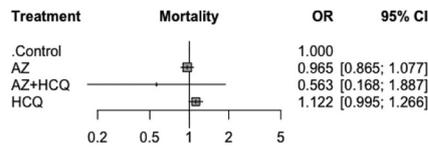
Study name	Design	Intervention	Dose	Follow-up	Age, year	Male, %	White, %	BMI	Diabetes, %	Heart disease, %	Chronic lung disease, %	Severe liver disease, %	Severe kidney impairment, %	ICU admission, %	Use of corticosteroids, %	SARS-CoV-2 test positive, %	
COALITION-11 ²²	Open-label, randomized clinical trial	AZ vs. control	500 mg via oral, nasogastric, or intravenous administration once daily for 10 days	30 days	59.4 (49.3–70.0) vs. 60.2 (52.0–70.1)	65 vs. 67	NR	26.4 (23.5–31.8) vs. 27.2 (23.7–31.7)	38 vs. 39	7 vs. 5	6 vs. 7	NR	12 vs. 10	NR	21 vs. 15	100	
Sekhavati ²⁵	Open-label, randomized controlled trial	AZ + HCQ vs. HCQ	oral AZ 500 mg daily, oral LPV/r 400/100 mg twice daily and oral HCQ 400 mg daily for 5 days	30 days after discharge	54.38 ± 15.92 vs. 59.89 ± 15.55	50.00 vs. 41.82	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	100

(Continues)

TABLE 1 (Continued)

Study name	Design	Intervention	Dose	Follow-up	Age, year	Male, %	White, %	BMI	Diabetes, %	Heart disease, %	Chronic lung disease, %	Severe liver disease, %	Severe kidney impairment, %	ICU admission, %	Use of corticosteroids, %	SARS-CoV-2 test positive, %
Abd-Elsalam ¹⁹	Open-label, randomized controlled trial	HCC vs. control	HCC 400 mg twice daily (in day 1) followed by 200 mg tablets twice daily	4 weeks	40.35 ± 18.65 vs. 41.09 ± 20.07	57.7 vs. 59.8	NR	BMI < 30: 37.1 vs. 39.2; BMI ≥ 6-2.8 vs. 62.8	NR	NR	NR	0.0 vs. 2.1	2.1 vs. 4.1	11.3 vs. 13.4	NR	100
COALITION-1 ²¹	Randomized, open-label, three-group, controlled trial	AZ + HCC vs. HCC vs. control	HCC 400 mg twice daily vs. HCC 400 mg twice daily plus AZ 500 mg once daily for 7 days	15 days	49.6 ± 14.2 vs. 51.3 ± 14.5 vs. 49.9 ± 15.1	56.7 vs. 64.3 vs. 54.2	NR	NR	18.4 vs. 21.3 vs. 17.6	1.8 vs. 1.4 vs. 1.3	1.8 vs. 1.8 vs. 1.8	NR	0.9 vs. 0.5 vs. 0.9	13.8 vs. 14.5 vs. 13.2	1.8 vs. 0.5 vs. 1.3	79.3 vs. 71.9 vs. 76.2

Abbreviations: AZ, azithromycin; BMI, body mass index; HCC, hydroxychloroquine; ICU, intensive care unit; NR, not reported.



Abbreviations: AZ, azithromycin; HCQ, hydroxychloroquine

FIGURE 2 Pooled treatment effect on mortality. AZ, azithromycin; HCQ, hydroxychloroquine

designs ($Q = 0.00$; $p = 0.95$). Additionally, there was no significant inconsistency between direct and indirect evidence (Figure 5).

4 | DISCUSSION

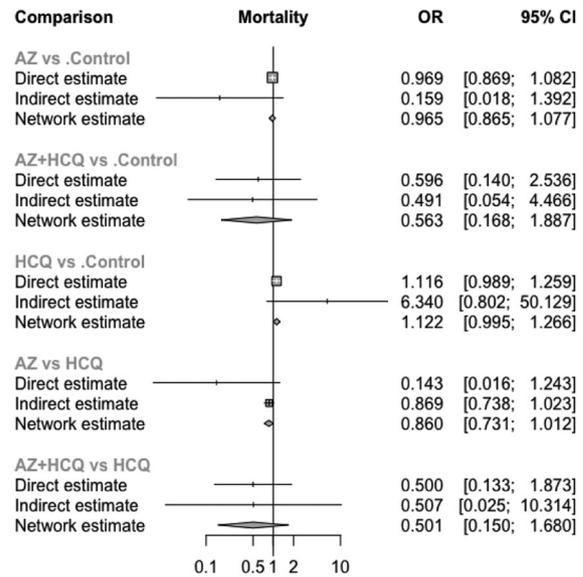
This systematic review and network meta-analysis summarized the current evidence on the efficacy of chloroquine or its derivative HCQ combined with or without AZ on the COVID-19 infection. Based on this data, none of the examined agents either alone or in combination were effective in the reduction of mortality or mechanical ventilation rate.

Following observational studies, several randomized clinical trials were conducted to validate the findings regarding the efficacy of AZ and HCQ. A randomized clinical trial conducted in the early pandemic failed to support the efficacy of HCQ in symptom severity reduction.²⁹ The COALITION I and COALITION II trials showed that for patients hospitalized with mild to moderate COVID-19, management with AZ and HCQ was not associated with any improvement in mortality, duration of hospital stay, or clinical status in terms of invasive and noninvasive ventilation as assessed using an ordinal outcome scale.^{21,22} The RECOVERY trial included 7763 participants to study the benefit of the provision of AZ only to patients hospitalized with COVID-19.²³ Information on laboratory markers of viral load, inflammatory status, immune response, coexistent bacterial infection, or use of nonmacrolide antibiotics was not collected, nor was information on radiological or physiological outcomes. The RECOVERY trial also compared HCQ with control among 4716 patients and showed no difference in mortality between the HCQ group and the usual-care group.²⁸ Of note, patients in the HCQ group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group. With respect to adverse events, there

TABLE 2 Network league table for mortality

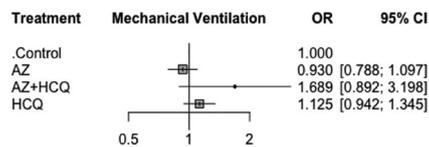
Treatment	Control	AZ	AZ + HCQ	HCQ
Control	-	1.031 (0.924; 1.151)	1.677 (0.394; 7.127)	0.896 (0.794; 1.011)
AZ	1.036 (0.929; 1.156)	-	.	0.143 (0.016; 1.243)
AZ + HCQ	1.778 (0.530; 5.963)	1.715 (0.509; 5.783)	-	0.500 (0.133; 1.873)
HCQ	0.891 (0.790; 1.005)	0.860 (0.731; 1.012)	0.501 (0.150; 1.680)	-

Abbreviations: AZ, azithromycin; HCQ, hydroxychloroquine.



Abbreviations: AZ, azithromycin; HCQ, hydroxychloroquine

FIGURE 3 Comparing direct and indirect evidence on mortality. AZ, azithromycin; HCQ, hydroxychloroquine



Abbreviations: AZ, azithromycin; HCQ, hydroxychloroquine

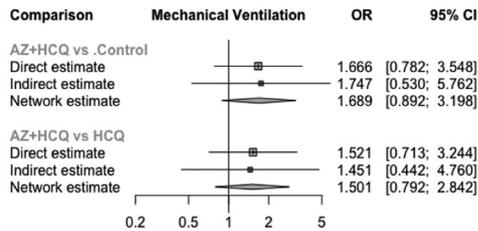
FIGURE 4 Pooled treatment effect on the use of mechanical ventilation. AZ, azithromycin; HCQ, hydroxychloroquine

was no difference in the incidence of new major cardiac arrhythmia among the patients who received HCQ. The TEACH trial was a double-blind randomized controlled trial designed to evaluate the efficacy of a 5-day course of HCQ.²⁷ The results demonstrated that the use of HCQ was not associated with improved mortality or any improvement in markers of clinical severity, such as the use of invasive and noninvasive ventilation. Furthermore, patient enrolled in the HCQ arm had longer hospital stays owing to abnormalities in QT intervals and D-dimer levels which required inpatient management. The ORCHID trial assessed improvement in clinical status in patients

TABLE 3 Network league table for the use of mechanical ventilation

Treatment	Control	AZ	AZ + HCQ	HCQ
Control	-	1.076 (0.912; 1.269)	0.600 (0.282; 1.278)	0.889 (0.744; 1.062)
AZ	1.076 (0.912; 1.269)	-	.	.
AZ + HCQ	0.592 (0.313; 1.121)	0.550 (0.285; 1.065)	-	1.521 (0.713; 3.244)
HCQ	0.889 (0.744; 1.062)	0.826 (0.648; 1.053)	1.501 (0.792; 2.842)	-

Abbreviations: AZ, azithromycin; HCQ, hydroxychloroquine.



Abbreviations: AZ, azithromycin; HCQ, hydroxychloroquine

FIGURE 5 Comparing direct and indirect evidence on the use of mechanical ventilation. AZ, azithromycin; HCQ, hydroxychloroquine

hospitalized with COVID-19 treated with HCQ using a WHO-approved 7-category respiratory status ordinal scale (COVID Outcomes Score).²⁶ The ORCHID study found no benefit of HCQ use. The HAHPs trial compared HCQ with AZ in 85 patients, and showed no benefit of HCQ over AZT; moreover, patients treated with HCQ had a higher rate of acute kidney injury.²⁰ In the open-label DISCOVERY trial, 11 330 patients were randomly assigned to HCQ, remdesivir, lopinavir, interferon, or control.²⁴ In this trial conducted across 30 countries, none of the treatments were successful in reducing in-hospital mortality, initiation of ventilation, and hospitalization duration. Of these, 947 were randomized to receive HCQ and 906 patients were included in the control group. HCQ was not associated with a significant difference in mortality compared to the control group.

Previously reported data indicating the efficacy of chloroquine or HCQ against coronavirus infection were mostly observational or from in vitro experiments.^{30,31} This led to its testing in randomized clinical trials. HCQ is an aminoquinoline derivative primarily used as an antimalarial and immunomodulatory agent.³² The compound also has antiautophagic activity, which has driven widespread testing of its antiviral activity. As a lysosomotropic agent, HCQ alkalizes intralysosomal pH, leading to an impairment of autophagic protein degradation, a step required for successful viral uncoating. It has also been shown that HCQ-induced accumulation of inefficient autophagosomes may result in cell death in tumor cells dependent on autophagy for survival.³³ Macrolides are commonly used to treat bacterial infections of the lower respiratory tract because of their activity against Gram-positive bacteria and atypical pathogens such

as *Mycoplasma pneumoniae* and *Legionella* spp, as well as their excellent tissue penetration.^{34,35} More than 75% of patients with COVID-19 who were admitted to hospital in the UK during 2020 were prescribed antibiotics and the widespread clinical use of macrolides in COVID-19 is likely to stem from concerns of bacterial superinfection rather than previously proposed immunomodulatory action. Prior studies suggesting the efficacy of these agents against Middle East respiratory syndrome and severe acute respiratory syndrome in vitro, were the first pieces of evidence. Later, studies also reported the in vitro efficacy of these agents against SARS-CoV-2.³⁶ Another report also demonstrated that a combination of HCQ and AZ were able to inhibit the replication of SARS-CoV-1 and 2 viruses.³⁷ Interestingly, a study showed that the combination of these two antimicrobial agents possesses synergistic interactions that not only neutralize the viral shedding but also inhibit host lysosomal enzyme activity and cease viral entry to other cells.^{38,39} This study explained that both AZ and HCQ are weak bases and are more prone to accumulate in the endosomal vesicles and lysosomes, increasing their pH and making them dysfunctional. This property was believed to block viral shedding from lysosomes and uncoating of enveloped viruses.⁴⁰ However, in vitro activity does not necessarily confer clinical efficacy. Another important point to consider is the avoidance of adding harm to the patients while using unnecessary treatments based on low-quality evidence. A recent meta-analysis with 11 932 participants showed that the combination of AZ and HCQ can increase mortality among patients with COVID-19 infection.³⁶ One possible mechanism for this observation is that this combination was associated with an increase in life-threatening cardiovascular events. Both HCQ and AZ are associated with prolongation of QT interval and provide a substrate for abnormal arrhythmogenic activity.^{41,42} Furthermore, the combination of these two agents has been observed to prolong the QT interval to a greater extent than each agent alone.^{43,44} In line with this finding, another systematic review of 14 studies reported a higher rate of mortality in patients receiving both HCQ and AZ. This study also reported an increase in the duration of hospital stay among patients receiving these two agents.⁴⁵ Of note, both of these studies included mostly observational studies and the heterogeneity was high among the included studies. Based on a large-sized network meta-analysis with more than 49 000 participants, HCQ reduced neither mortality rate nor disease progression. In addition, a high dose of HCQ (>600 mg/day) was associated with a slight increase in noncardiac side effects. This study shared concerns regarding the cardiac safety of the combination of HCQ and AZ

especially among patients with preexisting cardiovascular disease. Based on the data from this meta-analysis, in the context of using HCQ combined with AZ, the pooled incidence of malignant cardiac arrhythmias, such as torsade de points and severe ventricular arrhythmia, was 12.27% in patients with the cardiac disease while in a healthy population with the normal cardiac function it was 0.01%.⁴⁶ In an attempt to explain the inefficacy of HCQ, one in vitro study revealed that chloroquine was incapable of preventing viral shedding and it does not prevent the virus from entry to the lung cell.⁴⁷ Contrary to our data, one systematic review of 43 reports claimed that HCQ use was consistently associated with better outcomes among patients with Coronavirus 2019, especially when used early in the course of the disease.⁴⁸

Given that the COVID-19 infection-associated acute respiratory distress syndrome is the important constituent of its case fatality in the ICU setting, we also investigated whether the use of HCQ with or without AZ can reduce the need for mechanical ventilation. Our finding showed that HCQ combined with or without AZ was unable to reduce this risk. This finding was in agreement with previous reports.^{49,50} Contrary to our results, there is some evidence suggesting the efficacy of HCQ in preventing the disease progression and namely the need for invasive ventilation. However, the studies either had a small sample size or an observational design and therefore must be interpreted cautiously.^{51,52}

5 | LIMITATIONS

As with any other study, this meta-analysis has some limitations that need to be discussed. First, 8 out of 10 studies were open-labeled, which may have introduced selection bias. Second, the included studies were different in terms of patients' characteristics, comorbidities, and corticosteroid usage. Third, in one of the included trials, the patients were followed for 15 days rather than a month, which may cause an underestimation of the mortality rate. Fourth, individual patient-level data were not available for this analysis. Fifth, due to exclusion of patients at risk of prolonged QT syndrome in some of the included trials, the safety of off-label use of HCQ and AZ may be overestimated across these trials. Sixth, due to large heterogeneity among the trials in terms of studied endpoints, we only used two important outcomes and did not investigate the efficacy of the applied treatment strategies on other endpoints such as hospital stay or symptom severity. Seventh, there was some inconsistency among the studies in terms of the duration and dosage of studied medications. Finally, the results of this study cannot be generalized to patients with mild COVID-19 infection or prolonged QT interval.

6 | CONCLUSION

Evidence from this systematic review and network meta-analysis suggests that chloroquine or its derivative, HCQ, combined with or without AZ did not change the mortality or mechanical ventilation

rates in hospitalized patients with COVID-19. Current evidence does not support using either of these agents alone or in combination in the management of hospitalized patients with COVID-19 infection. Pharmacological agents used as therapeutics and postexposure prophylaxis of hospitalized patients with COVID-19 demand further exploration and research. Despite the successful development of various vaccinations for primary prophylaxis of COVID-19 such as BNT162b2, messenger RNA-1273, Ad26.COV2.S, ChAdOx1 nCoV-19, widespread global availability of such vaccines is limited due to numerous economical and logistical factors.⁵³⁻⁵⁶ Modulation of viral glycoprotein components, receptors, suppression of cytokine storm using interleukin (IL)-1, IL-6, and JAK/STAT signaling pathways, RNA-dependent RNA polymerase inhibition are being studied to reduce disease load.⁵⁷⁻⁶² The success of dexamethasone in reducing in-hospital COVID-19 associated mortality suggests immunomodulation may be an attractive therapeutic target in this patient population.⁶³⁻⁶⁹

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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Supporting information.

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