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RESEARCH ARTICLE

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Systematic review and meta-analysis of effectiveness of treatment options against SARS-CoV-2 infection

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Abstract

Treatment options for severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) are limited with no clarity on efficacy and safety profiles. We performed a systematic review and meta-analysis of studies on patients ≥18 years reporting data on therapeutic interventions in SARS-CoV-2. Primary outcome was all-cause mortality and secondary outcomes were rates of mechanical ventilation, viral clearance, adverse events, discharge, and progression to severe disease. Pooled rates and odds ratios (OR) were calculated. Twenty-nine studies with 5207 patients were included. Pooled all-cause mortality in intervention arm was 12.8% (95% confidence interval [CI]: 8.1%-17.4%). Mortality was significantly higher for studies using hydroxychloroquine (HCQ) for intervention (OR: 1.36; 95% CI: 0.97-1.89). Adverse events were also higher in HCQ subgroup (OR: 3.88; 95% CI: 1.60-9.45). There was no difference in other secondary outcomes. There is a need for well-designed randomized clinical trials for further investigation of every therapeutic intervention for further insight into different therapeutic options.

KEYWORDS

COVID-19, HCQ, hydroxychloroquine, meta-analysis, SARS-CoV-2

1 | INTRODUCTION

Severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) is the 7th virus of the coronavirus family known to infect humans.[1] By March, the World Health Organization (WHO) had declared SARS-CoV-2 as a pandemic, the third pandemic in the 21st century after the SARS outbreak in 2003 and H1N1 influenza in 2009. SARS-CoV-2 tends to cause a plethora of symptoms with fever, cough, myalgia, fatigue, loss of taste, appetite, and diarrhea to name a few. It is also known to affect multiple organ systems leading to acute respiratory distress syndrome, encephalitis, myocarditis, hepatitis, acute kidney injury, and hypercoagulable state leading to stroke and pulmonary embolism. The COVID-19 disease caused by SARS-CoV-2 can be classified as mild, moderate, severe, and critical disease based on clinical, imaging and laboratory parameters.[2] The natural history of the disease is such that most patients typically have mild disease with spontaneous resolution of symptoms by 10 to 14 days needing symptomatic management and home self-quarantine. Elderly population, as well as patients with medical comorbidities, are at higher risk of developing moderate to severe disease.[3] As per the Chinese Center for Disease Control and

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; HCQ, hydroxychloroquine; IQR, interquartile range; NIH, National Institute of Health; NNH, number needed to harm; NNT, number needed to treat; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trials; SARS-CoV-2, severe acute respiratory syndrome-related coronavirus-2; WHO, World Health Organization.

Article summary line:
The use of hydroxychloroquine was associated with increased mortality and adverse event rates in Severe acute respiratory syndrome-related coronavirus-2 infection and other therapeutic interventions did not show any difference in outcomes.

Prevention data in a cohort of 72 314 patients, clinical deterioration tends to typically occur in the second week of onset of symptoms with need for hospitalization and close monitoring in 14% of patients and around 5% of patients require invasive ventilation.[4] Several therapeutic interventions like Hydroxychloroquine (HCQ), Chloroquine, Remdesivir, Corticosteroids, Tocilizumab, and convalescent plasma therapy have been attempted, but currently, there is no known intervention that has reduced mortality in COVID-19 patients. These questions bring into focus the need of a comprehensive systematic review of the published literature to collate the available evidence. The aim of this systematic review and meta-analysis is to assess if any intervention provides mortality benefit, other clinically relevant outcomes, and also ascertain the safety profile.

2 | METHODS

This systematic review was performed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[5] The protocol is provided as Appendix 1. Institutional review board approval was not required for this study since no patient identifiers were disclosed.

2.1 | Data sources

A systematic electronic search was performed in PubMed/MEDLINE, Embase, Cochrane Central, Google Scholar, MedRxiv databases to identify published and prepublished studies reporting outcomes related to interventions for SARS-CoV-2 infection, from 1 December 2019 to 11 May 2020. The Medical Subject Heading/Entree terms is provided in Appendix 2. An independent review of the abstracts and full paper articles was done (VT and BV). The duplicates were removed and the titles of articles were evaluated. The full-length papers of the shortlisted articles were assessed for the eligibility criteria. The articles that fulfilled the inclusion criteria were shortlisted for final systematic review. The included study references were cross-searched for additional studies. The articles were reviewed independently by two authors (VT and BV) and any disagreement was resolved by consensus with a third author (MR). Reasons for excluding studies were documented.

2.2 | Eligibility criteria

The inclusion criteria were as follows: (a) studies reporting outcomes for treatment in SARS-CoV-2 infection; (b) all studies including randomized controlled trials (RCTs), prospective, retrospective, and case series; (c) full-length studies; (d) patients more than 18 years of age. Exclusion criteria were: (a) preclinical studies, epidemiological, and descriptive studies without intervention for SARS-CoV-2 patients; (b) abstracts.

2.3 | Data extraction and quality assessment

The data were extracted by two authors independently into predefined forms. The following data were extracted from the studies: first author, mean age, study design, number of patients, gender, rates of: mortality, clinical improvement, mechanical ventilation, progression to severe disease, viral clearance, discharge, and adverse events. Data for both intervention and control arms (for available studies) were extracted separately. Quality assessment was performed only for RCTs as most of the other studies were retrospective in nature with short hospital courses for duration of treatment. Cochrane risk bias tool was used for study quality assessment for RCTs.[6]

2.4 | Definitions and outcomes

The definitions of outcomes that were assessed are provided in Appendix 3. The intervention arm consisted of patients receiving the drug or the therapeutic intervention while the control arm patients received standard of care treatment for SARS-CoV-2 without a specific intervention. The primary outcomes were the all-cause mortality in the intervention arm and in comparison, with control arm. The secondary outcomes were rates of clinical recovery, need for mechanical ventilation, viral clearance, radiological improvement, discharge, and adverse events in intervention arm and comparison with control arm. Median duration for viral clearance and clinical recovery was also calculated from available studies. Number needed to treat (NNT) and number needed to harm (NNH) were defined as the number of patients who needed to be treated to provide benefit or harm in at least one patient, comparing intervention and control arms for respective outcomes.

2.5 | Statistical analysis

Percentages for categorical variables and median with interquartile range (IQR) for continuous variables were presented. Differences in medians were calculated using the Mann-Whitney-Wilcoxon test. Proportions with pooled rates with 95% confidence intervals (CIs) were calculated for individual arms. Odds ratios (OR) comparing with control arm were reported with 95% CI and P value of less than .05 was considered statistically significant. Random effects model described by DerSimonian and Laird was used for analysis. Corresponding forest plots were constructed for both primary and secondary outcomes. NNT and NNH were calculated using the inverse of the differences in benefit or harm between the intervention and control arms for the respective outcomes. Study heterogeneity was assessed using Inconsistency index (I^2 statistic) with low, moderate, substantial, and considerable heterogeneity indicated by I^2 value of 0% to 30%, 31% to 60%, 61% to 75%, and 76% to 100%, respectively. All analyses were performed using statistical softwares Open Meta analyst (CEBM, Brown University, RI) and Review Manager Version 5.3

(The Nordic Cochrane Center, Copenhagen, Denmark). Subgroup analyses were performed for the following, when data were available and also to address heterogeneity in primary outcome if present: (a) intervention specific; (b) disease severity specific; (c) RCTs only.

3 | RESULTS

3.1 | Study search and study characteristics

The literature search resulted in 3664 articles, of which 65 articles underwent full review and 29 were included in the final analysis (Figure 1).[3,7-34] Among included studies, 19 were performed in China, four in France, four in the United States, one in Brazil, and one in South Korea. Eight studies were RCTs, four were prospective studies and the remaining 17 were retrospective studies. Fifteen studies were published and the remaining were prepublished. Seventeen studies had a drug or intervention being tested with a control group for comparison. For intervention, 12 studies used HCQ based treatment (two studies had azithromycin along with HCQ in same arm, three had azithromycin in separate arm, and one study was comparison of HCQ with Lopinavir/Ritonavir), five studies used antiviral agents (two studies with Lopinavir/Ritonavir, one with Baloxavir/Marboxil, and Favipravir and two with Remdesivir), two were Tocilizumab based single-arm studies, five used corticosteroids (three with control arm) and five studies were single-arm plasma therapy based. There were 3624 patients in the intervention arm (mean age: 55.9 ± 8.4 years, 62% males) and 1583 patients (mean age: 52.5 ± 8.5 years, 60.7% males) in the control arm. The median duration of follow-up was 14 days (IQR: 9-24.5) and the range was 6 to 32 days across all studies. The demographics and study characteristics have been provided in Table 1.

3.2 | Risk of bias assessment

Eight RCTs were part of this meta-analysis. Of these three were at low risk of bias and five were at high risk. Risk of bias summary has been provided in Appendix 4.

3.3 | Primary outcome: all-cause mortality

Twenty-four studies provided data on mortality in the intervention arm and the pooled all-cause in-hospital mortality rate was 12.8% (95% CI: 8.1%-17.4%) for a median follow-up duration of 14 (IQR: 10-18.5) days (Table 2). Comparing the mortality between the intervention arm and

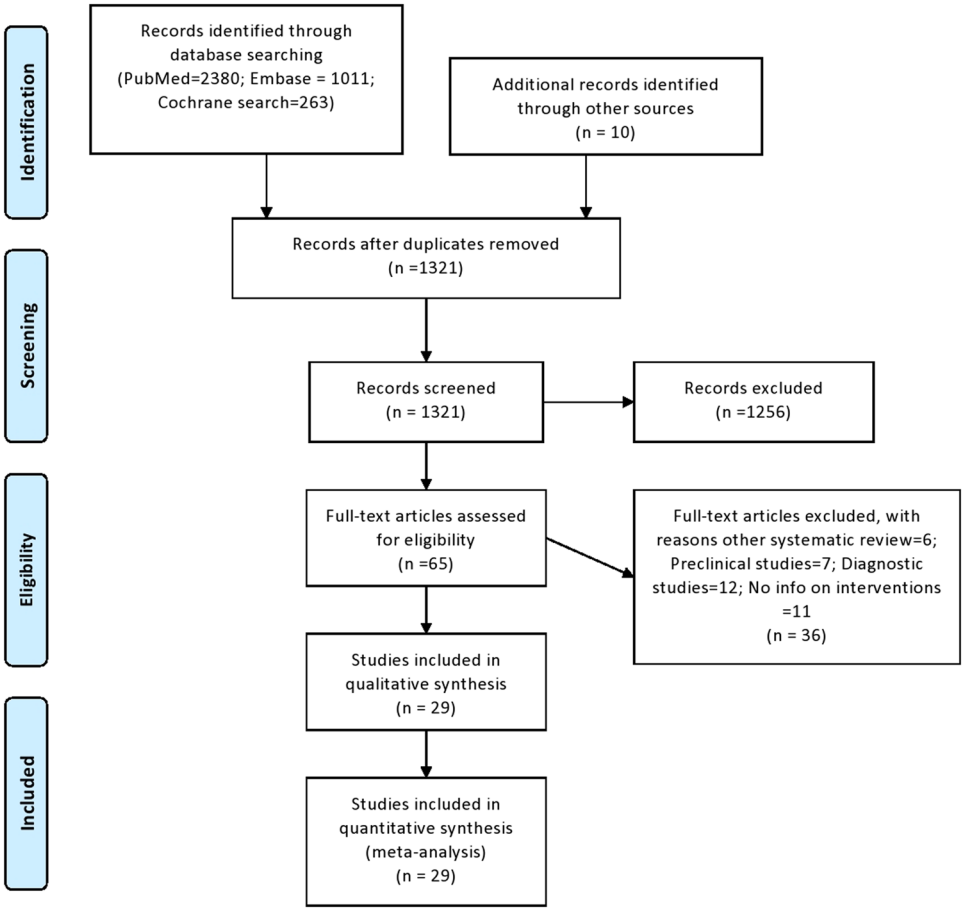

FIGURE 1 PRISMA Flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

TABLE 1 Study design, demographics, intervention arms, and outcomes

					Number of of patients			Mean age			Males			
Study	Country	Design	Arms	Groups	I1	I2	C	I1	I2	C	I1	I2	C	Primary outcome
Chen et al[14]	China	RCT	2	HCQ vs control	31		31	44.1		45.2	14		15	Clinical recovery
Chen et al[15]	China	RCT	2	HCQ vs control	15		15	50.5		46.7	9		12	Viral clearance
Borba et al[16]	Brazil	RCT	2	HCQ low dose vs high dose	41	40		54.7	47.4		10	10		Adverse events
Magagnoli et al[13]	USA	Retrospective	3	HCQ vs HCQ + AZ vs control	97	113	158	70	68	69	97	113	158	Mortality, intubation
Molina et al[12]	France	Case series	1	HCQ high dose + AZ	11						7			Viral clearance
Mahevas et al[11]	France	Retrospective	2	HCQ vs control	84		97	59		62	65		63	ICU, mortality
Gautret et al[8]	France	Prospective	3	HCQ vs HCQ + AZ vs control	14	6	16	51.2		37.3	9		6	Viral clearance
Gautret et al[9]	France	Prospective	1	HCQ + AZ	80			52.5			43			Clinical recovery, viral clearance, length of stay
Tang et al[7]	China	Open label	2	HCQ vs control	75		75	48		46.1	42		40	Viral clearance
Huang et al[32]	China	RCT	2	HCQ vs L/R	10	12		41.5	53		7	6		Viral clearance, imaging recover, LOS
Geleris et al[10]	USA	Retrospective	2	HCQ vs control	811		565				474		307	Intubation, death
Rosenberg et al[34]	USA	Retrospective	4	HCQ + AZ vs HCQ vs AZ vs control	735	271	221	61.4	65.5	64	456	158	110	All-cause mortality, cardiac arrest and ECG abnormalities
Cao et al[26]	China	RCT	2	L/R vs control	99		100	58		58	61		59	Time to clinical recovery
Li Y et al[27]	China	RCT	3	L/R vs arbidol vs control	34	35	17	50.7	50.5	44.3	17	16	7	Viral clearance
Lou et al[28]	China	RCT	3	B/M vs Favipravir vs control	10	9	10	53.5	58	46.6	7	7	7	Viral clearance
Grein et al[23]	USA	Prospective	1	Remdesivir	53			64			40			Clinical course
Wang et al[19]	China	RCT	2	Remdesivir vs Placebo	158		78	66		64	89		51	Time to clinical recovery
Luo et al[21]	China	Retrospective	1	Tocilizumab	15			73			12			Laboratory improvement
Xu X et al[20]	China	Retrospective	1	Tocilizumab	21			56.8			18			Clinical course
Fang et al[29]	China	Retrospective	2	Oral steroids vs control	9		46	40.2		39.9	5		22	Viral clearance
Fang et al[29]	China	Retrospective	2	Intravenous steroids vs control	16		7	60.6		54.3	12		5	Viral clearance
Guan et al[3]	China	Retrospective	1	steroids	204									ICU, intubation, mortality
Lu et al[25]	China	Retrospective	2	Steroids vs control	151		93	64		59	83		45	Mortality
Lu et al[25]	China	Retrospective	2	Steroid vs control	31		31	57		58	16		16	Mortality

TABLE 1 (Continued)

Study	Country	Design	Arms	Groups	Number of patients			Mean age			Males			Primary outcome
					I1	I2	C	I1	I2	C	I1	I2	C	
Wu et al[4,18]	China	Retrospective	2	Steroids vs control	50		34							Mortality
Wang et al[19]	China	Retrospective	2	Intravenous steroids vs control	26		20	54		53	16		10	Clinical course
Zhang et al[17]	China	Case series	1	Plasma	4						2			…
Ahn et al[33]	Korea	Case series	1	Plasma	2			69			1			…
Shen et al[31]	China	Case series	1	Plasma	5						3			Clinical recovery
Duan et al[30]	China	Retrospective	1	Plasma	10			52.5			6			Adverse events
Ye et al[24]	China	case series	1	Plasma	6			64			3			Clinical recovery

Abbreviations: AZ, azithromycin; B/M, baloxavir/marboxil; ECG, electrocardiogram; HCQ, hydroxychloroquine; I1, intervention 1; I2, intervention 2; ICU, intensive care unit; L/R, lopinavir/ritonavir; USA, United States of America.

control arms, 10 studies (n = 3894) provided the data, with a pooled rate of 17.1% (95% CI: 9.1%-27.4%) in the intervention arm and 14.8% (95% CI: 9.4%-20.1%) in the control arm, with no significant difference between the two groups (OR: 1.36; 95% CI: 0.97-1.89; I^2 = 46%; P = .07) (Figure 2A). The NNH was calculated to be 43. When analysis was restricted to only four HCQ based studies (n = 3152), the mortality was significantly higher in the HCQ group (OR: 1.86; 95% CI: 1.38-2.50; I^2 = 29%; P < .001) (NNH—13). (Figure 2B) A further subgroup analysis for only two studies (n = 212) which used only HCQ for treatment without any other confounders like azithromycin and the mortality was still significantly higher in the HCQ group (OR: 2.17; 95% CI: 1.26-3.72; I^2 = 43%) (NNH—9). Comparing intervention and control arms, subgroup analysis performed for antiviral studies only (n = 550) (OR: 0.83; 95% CI: 0.49-1.38), steroid-based studies (n = 192) (OR: 0.96; 95% CI: 0.40-2.31), moderate to severe disease patients (n = 2184) (OR: 1.09; 95% CI: 0.56-1.57), severe disease patients (n = 627) (OR: 0.87; 95% CI: 0.58-1.31) (Appendix Figure 1) and RCTs only (n = 550) (OR: 0.83; 95% CI: 0.49-1.38) (Appendix Figure 2), did not show a statistically significant difference between the two groups (Appendix Table 1).

3.4 | Secondary outcomes

3.4.1 | Rate of mechanical ventilation

Nine studies (n = 1456) reported need for mechanical ventilation in patients in the intervention arm, with a pooled intubation rate of 18.6% (95% CI: 10.9%-26.3%) (Table 2). Comparing the seven studies (n = 2317) which also provided information on control population, the pooled rates in the intervention and control arms were 13.5% vs 9.8%, respectively, with no significant difference between the two groups (OR: 1.58; 95% CI: 0.60-4.15; I^2 = 85%) (NNT—27) (Figure 3A). There was no significant difference in the outcome when analysis was restricted to HCQ and antiviral based studies.

3.4.2 | Viral clearance

Fifteen studies reported data on either the proportion of patients with antiviral clearance at the end of the study or the median duration for antiviral clearance. The pooled proportion of patients with antiviral clearance in the intervention arm (n = 393) was 80% (95% CI: 70.7%-89.4%). Comparing the six studies (n = 461) reporting data on antiviral clearance in intervention and control groups, the pooled rates were 74.9% vs 66.8%, respectively, with no significant difference between the two groups (OR: 1.86; 95% CI: 0.76-4.54; I^2 = 58%) (NNT—10) (Appendix Figure 3). When the analysis was restricted to HCQ based and antiviral based studies, there was still no significant difference between the two groups. The median duration for antiviral clearance in the intervention arm (n = 308) was 6.1 (IQR: 4.3-8.8) days and in the control arm (n = 170) was 9 (IQR: 4.5-14) days, with no significant difference between the two groups (P = .37).

TABLE 2 Study outcomes in the intervention and control groups with odds ratios

Outcome	Intervention group only	Intervention group studies common with control group	Control group only	Odds ratio
All-cause mortality	11.9% (95% CI: 7.7%-16.1%) (n = 2071)	16.2% (95% CI: 8.8%-23.6%) (n = 1557)	15.4% (95% CI: 9.1%-21.6%) (n = 1110)	1.22 (95% CI: 0.85-1.75; I^2 = 39%) (n = 2667)
Mechanical ventilation rate	18.6% (95% CI: 10.9%-26.3%) (n = 1456)	13.5% (95% CI: 7%-19.9%) (n = 1382)	9.8% (95% CI: 4.5%-15.2%) (n = 935)	1.58 (95% CI: 0.60-4.15; I^2 = 85%) (n = 2317)
Antiviral clearance rate	80% (95% CI: 70.7%-89.4%) (n = 393)	74.9% (95% CI: 59.5%-90.3%) (n = 257)	66.8% (95% CI: 42.6%-91.1%) (n = 204)	1.86 (95% CI: 0.76-4.54; I^2 = 58% (n = 461)
Clinical recovery rate	79.7% (95% CI: 78.9%- 88.4%) (n = 558)	64.1% (95% CI: 51.5%-76.8%) (n = 340)	56.9% (95% CI: 43.8%-69.9%) (n = 243)	1.41 (95% CI: 0.99-2.02, I^2 = 0%) (n = 583)
Progression to severe disease	11.6% (95% CI: 5.4%-17.8%) (n = 387)	13.4% (95% CI: 2.2%-24.6%) (n = 218)	12.8 (95% CI: 4.8%-20.8%) (n = 168)	1.19 (95% CI: 0.67-2.13; I^2 = 0%) (n = 386)
Radiological improvement rate	86.3% (95% CI: 77.2%-95.5%) (n = 140)	83.6% (95% CI: 67.6%-99.7%) (n = 107)	82.6% (95% CI: 60.3%-100%) (n = 60)	1.02 (95% CI: 0.13-8.07; I^2 = 63%) (n = 167)
Discharge rate	69.8% (95% CI: 60.3%-79.3%) (n = 1374)	68.6% (95% CI: 62.2%-75%) (n = 1171)	78.6% (95% CI: 67.8%-89.4%) (n = 800)	0.55 (95% CI: 0.29-1.03; I^2 = 81%)
Adverse events rate	23.3% (95% CI: 12.1%-34.5%) (n = 791)	34% (95% CI: 13.9%-54.1%) (n = 436)	29.5% (95% CI: 9.4%-49.6%) (n = 310)	1.44 (95% CI: 0.70-2.94; I^2 = 62%) (n = 754)

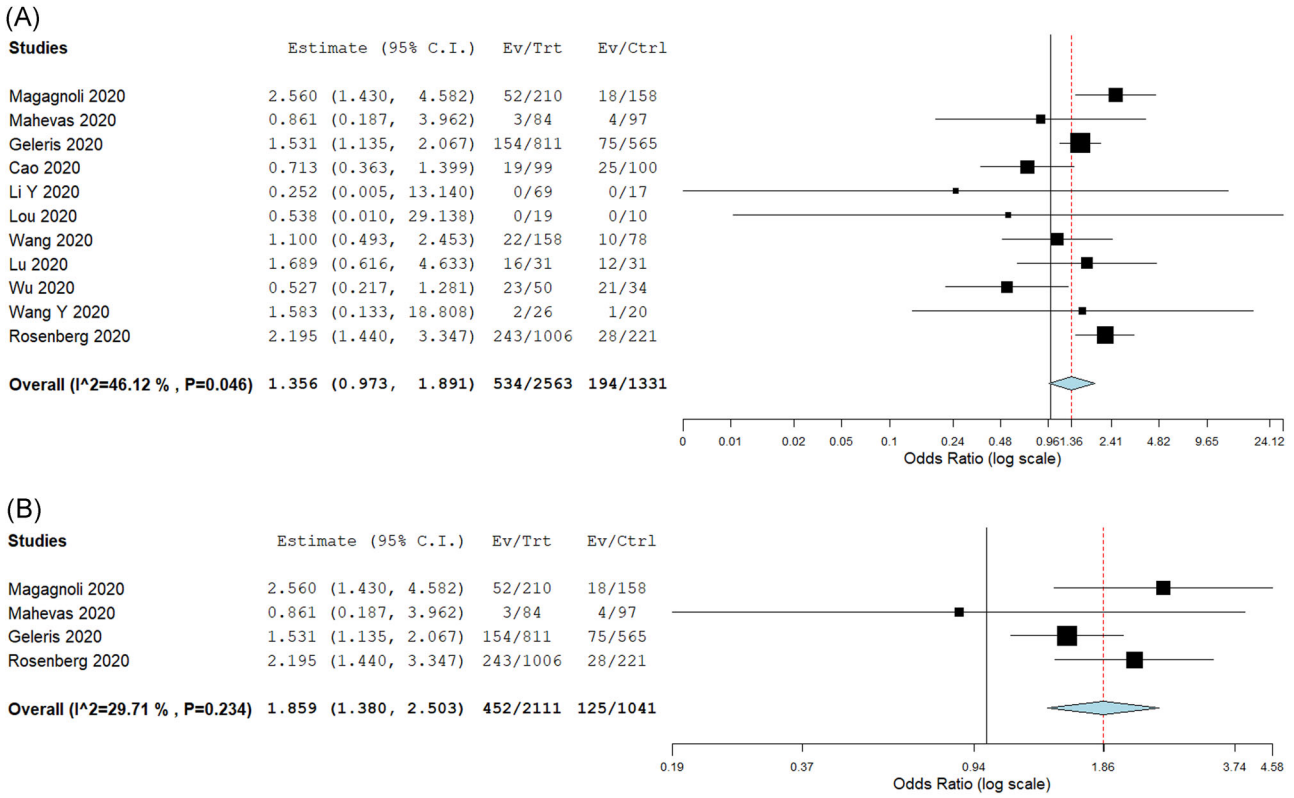

FIGURE 2 A, Odds ratio comparing all-cause in hospital mortality in intervention and control arms. B, Odds ratio comparing all-cause in hospital mortality in intervention and control arms in hydroxychloroquine based studies

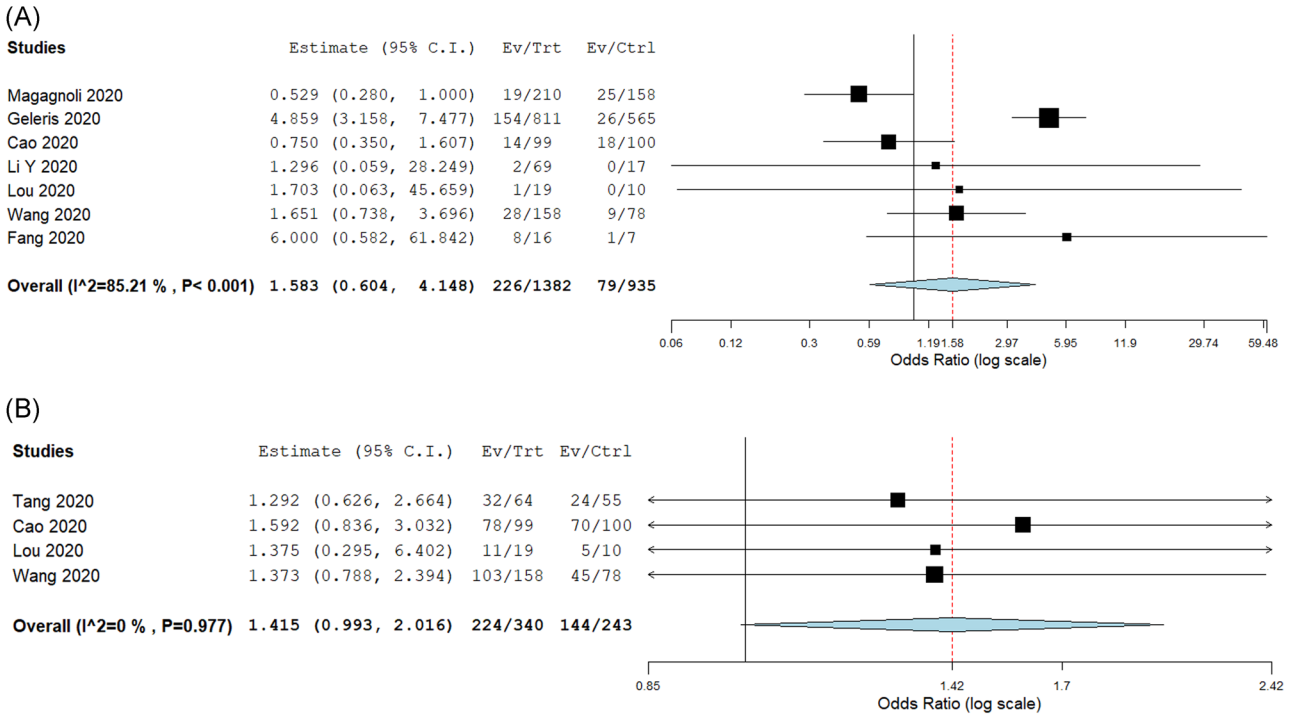

FIGURE 3 A, Odds ratio comparing rates of mechanical ventilation in intervention and control arms. B, Odds ratio comparing clinical recovery rates in intervention and control arms

3.4.3 | Clinical recovery

Fourteen studies reported data on either the proportion of patients who had clinical recovery or median time to clinical recovery. The pooled rate of proportion of patients with clinical recovery in the intervention arm (n = 558) was 79.7% (95% CI: 78.9%-88.4%). Comparing the four studies reporting data in intervention and control arms, the pooled rates were 64.1% and 52.8% (NNT—9), respectively with no significant difference between the two groups (OR: 1.41; 95% CI: 0.99-2.02; I^2 = 0%) (Figure 3B). Decrease in oxygen requirements in both groups was reported in two studies (n = 375), with no significant difference between both the groups (OR: 1.05; 95% CI: 0.65-1.71; I^2 = 3%).

The median time to clinical recovery was 14 (IQR: 8.2-19) days in the intervention group (n = 451) and 16 (IQR: 14.3-22) days in the control group (n = 263), with no significant difference between the two groups (*P* = .25).

3.4.4 | Progression to severe disease

Nine studies reported data on worsening of clinical status in the hospital in mild-moderate severity patients, with a pooled rate of 11.6% (95% CI: 5.4%-17.8%) in the intervention arm (n = 387) over a median duration of 13 (IQR: 9.5-19.5) days. Comparing the pooled rates in five studies reporting the outcome in both groups (n = 386), the pooled rates were 13.4% and 12.8% in the intervention and control groups, respectively, with no significant difference between the two groups (OR: 1.19; 95% CI: 0.67-2.13, I^2 = 0%). Subgroup analysis restricted to HCQ based and antiviral studies also did not reveal any significant difference.

3.4.5 | Adverse events

Sixteen studies (n = 791) reported the rate of adverse events in the intervention group with a pooled adverse event rate of 23.3% (95% CI: 12.1%-34.5%). Six studies (n = 754) compared intervention and control groups with pooled adverse event rates of 34% and 29.5%, respectively, with no significant difference between the two groups (OR: 1.44; 95% CI: 0.70-2.94) (NNT—22) (Figure 4A). On subgroup analysis, the incidence of adverse events was significantly higher in the HCQ group (OR: 3.88; 95% CI: 1.60-9.45; I^2 = 0%) (Figure 4B) with an NNH of 7, but there was no significant difference for studies with antiviral agents.

There was also no significant difference between both the groups in radiological improvement and discharge rates. The individual pooled rates and ORs are provided in Table 2. Subgroup analysis for only RCTs for available outcomes is provided in Appendix Table 2.

4 | DISCUSSION

In this systematic review and meta-analysis of 5207 patients from 29 studies, pooled outcome for any therapeutic intervention including HCQ, Remdesivir, Lopinavir/Ritonavir, Steroids, Tocilizumab, Convalescent plasma therapy did not show a survival benefit compared to control arms. HCQ use was associated with significantly increased all-cause inpatient mortality and adverse event rates. There were no significant benefits with any therapeutic intervention in changing the natural history of SARS-CoV-2 infection assessed in terms of rate of mechanical ventilation, viral clearance, time to discharge, time to clinical recovery, and radiological improvement.

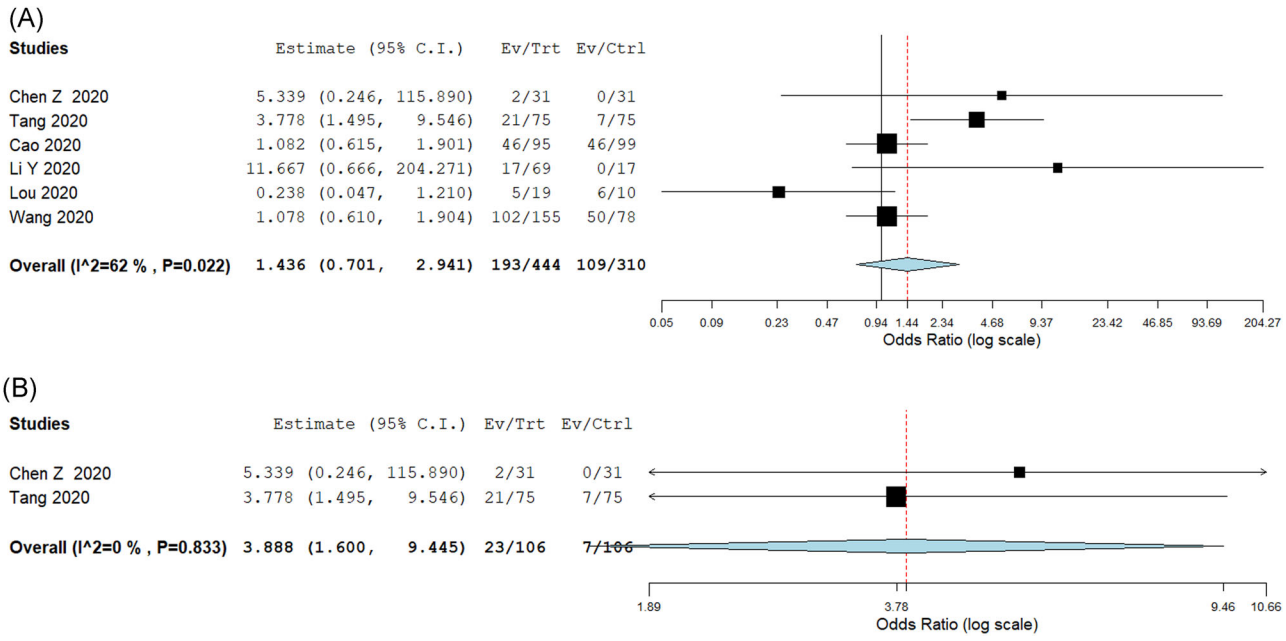

FIGURE 4 A, Odds ratio comparing adverse events rates in intervention and control arms. B, Odds ratio comparing adverse events in intervention and control arms in HCQ based studies. HCQ, hydroxychloroquine

HCQ increases the endosomal pH and prevents fusion of the host membrane with SARS-CoV-2 thereby interfering with the viral replication cycle. Several preclinical studies showed in vitro activity against SARS-CoV-2 leading to clinical use of HCQ in COVID-19 disease.[35,36] An initial case series of 26 patients from France comparing HCQ and control groups suggested that HCQ leads to rapid antiviral clearance in 70% of patients compared to 12.5% in controls. This study was fraught with methodological inconsistencies like enrollment of asymptomatic individuals, omission of six patients from analysis (HCQ patients of whom one died and three were transferred to intensive care unit).[9] In a randomized study of 62 patients from China, patients treated with HCQ showed radiological improvement in resolution of lung lesions as well as reduction in clinical progression of disease. The commonality of the initial studies on HCQ was a relatively small sample size, inappropriate control groups, lack of clarity in defining the study outcomes.[14] Two larger prospective RCTs from France and Brazil show that HCQ/chloroquine use is associated with increased incidence of cardiac events with no survival benefit.[12,16] In view of conflicting data outcomes, the National Institute of Health (NIH), United States recommends that there is insufficient clinical data to recommend either for or against using chloroquine or HCQ for the treatment of COVID-19.[37] There have also been reports of severe drug reaction with generalized exanthematous pustulosis reported with HCQ use.[38] Despite these issues, HCQ is currently one of the most commonly used medications in various parts of the world. Our analysis shows that HCQ based regimens had increased rate of mortality (NNH−13) and adverse events (NNH−7) compared to control patients. We hope our meta-analysis adds more evidence to dampen its use in view of lack of benefit and increased side effects.

Remdesivir was originally designed for use against Ebola. Remdesivir was studied in severe COVID-19 in China showed that the drug did not show any benefit in terms of time to recovery as well as 28-day mortality outcome, though the study was terminated prematurely in view of difficulty in patient accrual.[22] ACTT NIH study showed that Remdesivir accelerated the time to recovery to 11 days compared to 15 days in the placebo arm with no mortality benefit. This prompted an emergency Food and Drug Administration authorization for use in COVID-19 patients. There are calls for Remdesivir to be taken as the standard of care control in future clinical studies. There have been questions raised about the NIH study due to limitations such as change in the primary endpoint of study after initiation of the trial, lack of mortality benefit; study in moderate disease patients who tend to recover spontaneously by the end of second week.[39] There are ethical concerns among the scientific community that drugs without proven mortality benefit or reduction in the need for ventilatory support may be promoted in view of aggressive pharmaceutical lobbying. The current pandemic rings echo bells of the 2009 H1N1 pandemic and the desperate stockpiling of oseltamivir, whose proclaimed efficacy was claimed to be a byproduct of concealed information and aggressive lobbying by pharmaceutical companies.[40] The published or preprint data for other drugs like Favipravir, Baloxavir/Marboxil, corticosteroids, convalescent plasma are currently insufficient to make any specific recommendation and our meta-analysis also suggests the same.

Our meta-analysis shows that none of the so far studied interventions have a tangible benefit to change the course of disease outcomes with the current published evidence. The clinical studies that compare various interventions like the WHO sponsored solidarity trial that compares Remdesivir, chloroquine, or HCQ, lopinavir plus ritonavir, and interferon-beta with control arm and has all-cause mortality as the primary outcome is the need of the hour and the results are eagerly awaited.[41]

The strengths of our study are as follows: we included 29 studies with more than 5200 patients in our analysis with various interventions. Our review is extensive, by including the available interventions and providing clinically relevant outcomes in comparison with controls. Several subgroup analyses were also performed based on study interventions and design. Heterogeneity in most of our outcomes was mild to moderate but we performed subgroup analysis in RCTs to further reduce the heterogeneity.

4.1 | Limitations

Our study has several limitations. The study design, patient population, and the outcomes assessed were variable in different studies. Even though the intervention arms were clearly defined in most studies, some of the patients in those arms also received other medications and outcomes for such patients could not be excluded separately, which could have confounded the results. Different levels of disease severity of patients on study entry could lead to heterogeneity in outcomes but we tried to address it by performing subgroup analyses based on disease severity for outcomes when possible. Duration of follow-up was variable across studies and entire patient data at the end of study may not have been represented which is a limitation of the published literature. Adverse events reported include medication-related adverse events and also symptoms in both groups, which could be related to SARS-CoV-2, but this was unanimously reported across all studies. The dose of medications, especially HCQ, was variable in studies and dose based analysis could not be performed. Data from prepublished studies were also included in our analysis but we had included them to provide a more comprehensive overview to prevent misinterpretation of results to the best of our capabilities. The results of our study should hence be interpreted with caution keeping these limitations in mind.

5 | CONCLUSIONS

In this meta-analysis, there was no overall mortality or clinical benefit for most therapeutic interventions but the use of HCQ was associated with increased mortality rates and increased risk of adverse events in SARS-CoV-2 patients. None of the other therapeutic interventions like Lopinavir/Ritonavir, Remdesivir, Tocilizumab seemed to alter the natural clinical course of the disease based on the available literature. There is a need for well-designed randomized clinical trials to further investigate the efficacy and safety of various therapeutic interventions.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

VTC: conceptualization of the study, data extraction, statistical analysis, drafting of the manuscript, final approval of the manuscript. BV: conceptualization of the study, data extraction, drafting of the manuscript, final approval of the manuscript. HKP: data extraction, critical revision of the manuscript, final approval of the manuscript. MS: Data extraction, critical revision of the manuscript, final approval of the manuscript. JM: critical revision of the manuscript, final approval of the manuscript. MR: conceptualization of the study, critical revision of the manuscript, final approval of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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