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Systematic Review & Meta Analysis

Hydroxychloroquine with or without Macrolide and Standard of Care versus Standard of Care Alone for COVID-19 Cases: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: The specific treatment has not yet been approved for the therapy of COVID-19 pandemic. In this review, we aimed at assessing the role of hydroxychloroquine with/without macrolide in terms of efficacy and adverse effects against the standard of care (SOC).

Methods: PubMed, Medline, Google Scholar, Cochrane Library, and Clinicaltrials.gov were searched for the quantitative and qualitative synthesis of 13 studies using PRISMA guidelines. Assessment of heterogeneity was done using I-squared (I^2) test and fixed/random effect analysis was done to determine the odds/risk ratio among selected studies.

Results: Our study demonstrated no significant differences in improvement for virological cure (RR 0.95, 0.67-1.34), whereas a significant relationship was there in radiological progression (RR 1.40, 1.03-1.91) between the two arms. There are 1.52 times the odds of intubation during treatment (CI 0.61-3.77), 1.08 times the risk of mortality (CI 0.65-1.79), and about 2.21 times increased risk of development of adverse effect (OR 2.21, 0.95-5.17). Among randomized controlled trials, the treatment group has 3.5 times (OR 3.48, 1.64-7.42) higher risk of developing adverse effects. There is 2.5 times the likelihood of severe arrhythmias and QT prolongation (OR 2.49, 1.67-3.70) on the treatment arm compared to control.

Conclusions: Hydroxychloroquine with/without macrolide demonstrated no beneficial effect in viral clearance and survival rates while showed significant relation in radiological improvement compared to SOC. The increased risk of intubation, overall side effects, and cardiac complications like arrhythmias and QT prolongation suggests utilizing such treatment to be judged with clinical relevance and proper monitoring.

Keywords: Adverse effects, COVID-19, Hydroxychloroquine, SARS-CoV-2

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INTRODUCTION

COVID-19 pandemic has spread to the whole world and has affected millions of people. During COVID-19 cases surging up, definitive treatment for cure is not yet confirmed with a handful of evidence.[1] Due to the uncertainty of the available therapeutic option for the cure of COVID-19, the focus is also targeted towards preventive measures for breaking the chain of transmission. For quick drug development and treatment modalities; repurposing of many prior available medications is under trial.[2,3] In this regard, an anti-malarial agent like hydroxychloroquine (HCQ) is one of the proposed and most interesting treatment options for COVID-19.[4-6] HCQ acts as an anti-inflammatory molecule during cytokine storm in COVID-19.[7]

Meanwhile, concern arises regarding the clinical efficacy and safety of HCQ with or without macrolide as a treatment option for COVID-19. Hydroxychloroquine use can give rise to mild non-specific adverse effects like nausea, vomiting, headache to severe arrhythmias affecting multiple systems.[5,8] QT intervals prolongation is the commonest cardiac consequence of HCQ with drug-like azithromycin (AZT), for which the patient needs to be monitored carefully before other dire consequences like ventricular arrhythmias.[9-11] Metabolic derangements like hypoglycemia may also occur as other adverse consequences.[12] The increment in the dose of HCQ as compared to its regular use, which may be needed to reach SARS-CoV-2 inhibitory concentration, predisposes more to adverse effects.[13,14] Thus, we decided to evaluate the efficacy and safety concerns of HCQ with or without macrolide in COVID-19 cases as a novel work.

The objective was to assess differences in virological clearance, radiological improvement, overall adverse effects, severe arrhythmias, and death rate between the treatment group (HCQ with or without macrolide and standard of care) and control group (standard of care).

DATA AND METHODS

We used PRISMA for the systematic review of the available literature (Supplementary file 1).[15]

Criteria for considering studies

Types of studies

We included studies conducted to determine the safety and efficacy of HCQ with/without macrolide (AZT) in addition to standard of care (SOC) for COVID-19 diagnosed cases based on guidelines with a comparison control arm were included in the present meta-analysis.

Types of participants

COVID-19 diagnosed cases based on guidelines who were enrolled either in HCQ with/without AZT in addition to standard of care or standard of care alone.

Types of interventions

HCQ with/without AZT in addition to standard of care is taken as the treatment arm and standard of care alone as a control arm.

Types of outcome measures

Clinical improvement of HCQ with/without AZT in the treatment of COVID-19; mortality rate between treatment and control group; adverse effects occurred during treatment; intubation and mechanical ventilation requirements were outcomes of interest.

Outcomes

Clinical improvement measured as virological cure and radiological progression (pneumonia resolution), overall death between treatment and control arm, overall adverse effects occurred during treatment, and de-novo severe ECG changes in the form of QT prolongation or ventricular arrhythmias leading to the necessity to stop treatment or requiring management of the adverse cardiac event, intubation and mechanical ventilation requirement between treatment and control arm were compared.

Search methods for identification of studies

Three reviewers (DBS, PB, and ER) have independently searched and evaluated the quality of the studies using

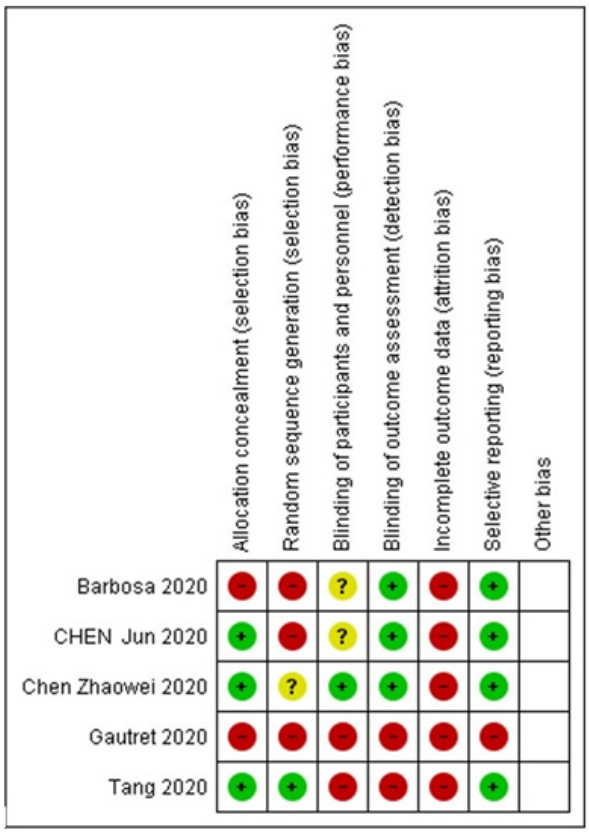
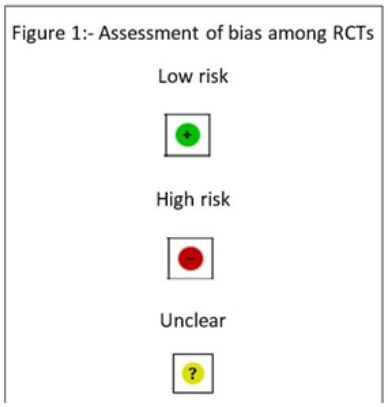


Figure 1: Risk of bias plot



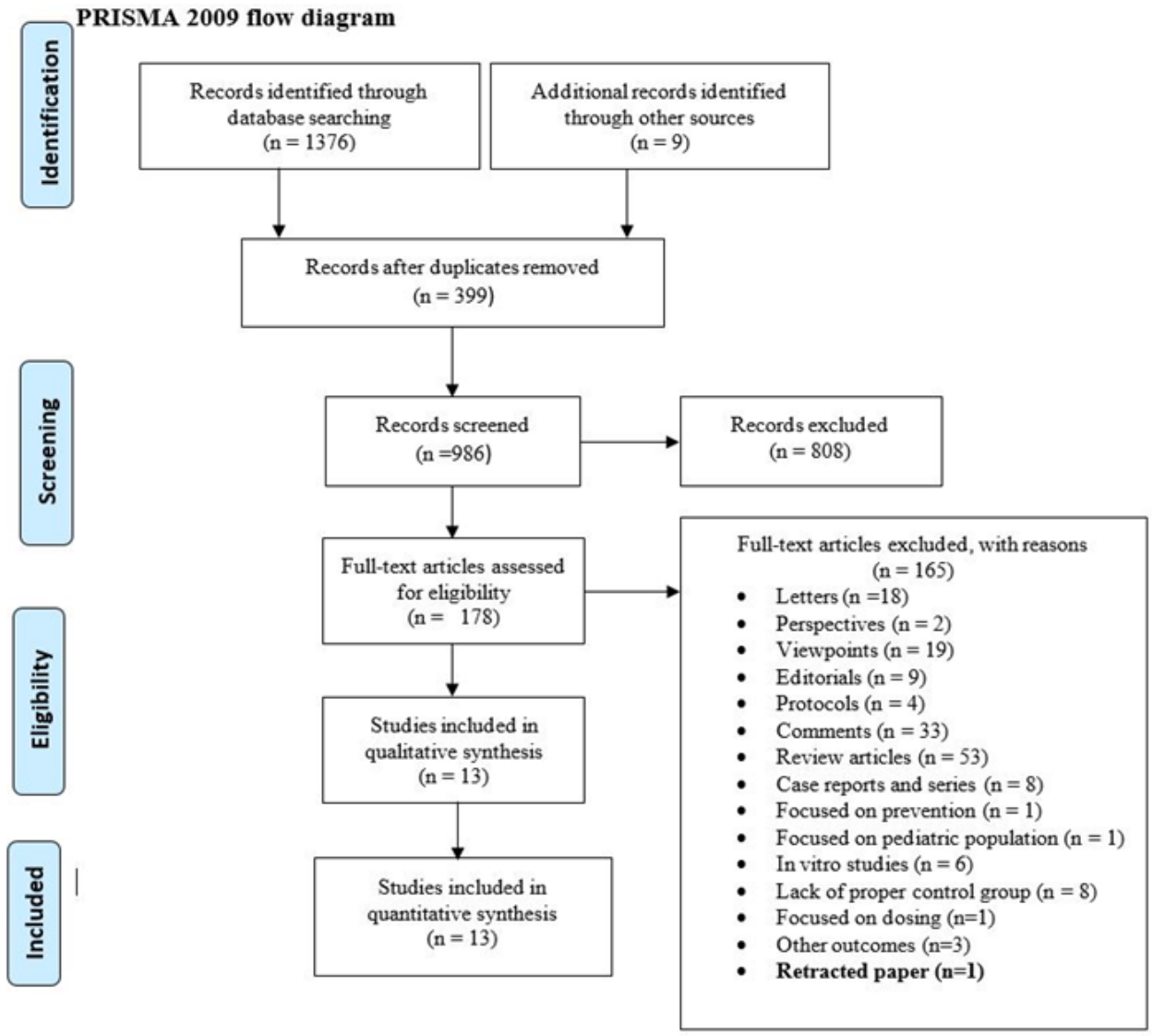


Figure 2: Flow chart for study design

COVIDENCE and extracted data for quantitative and qualitative synthesis, which is reviewed by another reviewer for the resolution of any possible conflict (SK). Assessment of bias and cross-checking of selected studies was done by the reviewers (AS and KA).

Electronic searches

The electronic search strategy is provided in supplementary file 2.

Data collection and analysis

We searched electronic databases like PubMed, Medline, Google Scholar, Cochrane Library, clinicaltirals.gov, and WHO clinical trial registry from 01 April to 01 June 2020. We also checked the references section from published review articles on-screen and identified additional studies for our analysis. Extracted data for quantitative synthesis was analyzed using RevMan 5.3. Heterogeneity was assessed using the I^2 test, and the fixed/random-effects model was used when appropriate for the pooling of studies.

Selection of studies

Due to the inadequate number of published randomized control trials and small-sized published Randomized Clinical Trials (RCTs), we also included prospective/retrospective observational studies with a comparison between HCQ with/without AZT in addition to standard of care and standard of care alone in the present meta-analysis. We excluded 8 studies lacking a control group receiving standard of care in addition to the treatment arm. We excluded 3 studies in which the outcome was compared between HCQ with/without AZT to HCQ alone or AZT alone, as our study is focused on comparing HCQ with/without AZT against the standard of care alone. We excluded the recently retracted paper of Mehra published in Lancet due to data discrepancy.[16] We also excluded commentaries, viewpoints, reviews, in-vitro studies, editorials, letters to editors, protocols, and studies done in the pediatric population.

Data extraction and management

Selected studies were evaluated for the quality of the

studies and among them having the outcome of interest were included for quantitative synthesis.

Assessment of risk of bias in included studies

The Cochrane ROB tool was used to analyze the risk of bias in our included RCTs shown in **figure 1**. We used the NHLBI (National Heart, Lung, and Blood Institute) quality assessment tool to assess the risk of bias in our retrospective studies and cohort studies.[17] Risk-of-bias plots have been created through the RevMan 5.3.

Supplementary table 1: NHLBI quality assessment tool for observational cohort and cross-sectional studies.

Assessment of heterogeneity

Heterogeneity assessment was done using the I^2 test. Interpretation of I^2 test was done based on the Cochrane Handbook for Systematic Reviews of Interventions as follows: "0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity. The importance of the observed value of I^2 depends on (i) the magnitude and direction of the effect and (ii) the strength of evidence for heterogeneity (e.g. P-value from the chi-squared test, or a confidence interval for I^2)."

Assessment of reporting biases

Predetermined outcome reporting documentation assessed to assess reporting bias.

Data synthesis

Statistical analysis was performed using RevMan 5.3 software. Risk Ratio (RR)/ Odds Ratio (OR) was used for outcome estimation whenever appropriate with 95% Confidence Interval (CI). The fixed/random-effects model was used according to heterogeneities.

Subgroup analysis and investigation of heterogeneity

In the case of heterogeneity, the inverse variance, random-effect model, and exclusion of outlier studies based on weight tried. Forest plots were presented to visualize the degree of variation between studies.

Sensitivity analysis

In our study, a sensitivity analysis was performed by examining the effect of studies on the results based on their weight when considered significant, outlier studies were excluded, and the analysis was re-run.

RESULTS

Qualitative synthesis

A total of 1385 studies were identified after electronic database searching. After 399 duplicates were removed, we screened the title and abstracts of 986 studies. 808 studies were excluded and 178 articles were seen for full-text eligibility. A total of 164 studies were excluded with definite reasons mentioned in the PRISMA flow diagram in **figure 2**. We included a total of 13 studies in our study. The summary of the 13 studies is discussed in **table 1.**

Quantitative synthesis of treatment outcome

In the present meta-analysis, we have compared randomized and non-randomized studies to extract outcome on virological clearance, radiological progression, overall death, development of adverse effects (severe, minor), cardiac complications (QT-prolongation, de-novo arrhythmias), the requirement of intubation, and mechanical ventilation. Among the included studies in the meta-analysis, we found there is mild-substantial heterogeneity; which may be due to clinical and variability in study design and the risk of bias among studies which could not be omitted fully may be due to acute surge to COVID-19 cases having diversity in presenting and getting treatment due to pandemic.

HCQ with or without AZT regimen and SOC versus SOC only; effectiveness

Among the treatment group HCQ with or without AZT in addition to SOC versus SOC, we have compared the duration of virological clearance (negative RT-PCR) and radiological progression.

Virological clearance

The meta-analysis of RR for HCQ with or without AZT in addition to SOC effectiveness compared with SOC alone using a random effect model among randomized and non-randomized studies showed that there were no significant differences between the two arms (RR 0.95, 95% CI 0.67 to 1.34; participants = 250; studies = 4; I^2 = 76%). Moreover, there is no significant risk difference (RD) between the two groups for the virological cure of HCQ with or without AZT in COVID-19 patients (RD 0.04, 95% CI -0.27 to 0.34) (**Figure 3a**).

Sensitivity analysis for HCQ with or without AZT in addition to SOC effectiveness compared with SOC alone

To evaluate the impact of inverse RRs as well as studies' weight on the meta-analysis results, we conducted sensitivity analyses as according to the substantial relative weight of Tang et al. on the meta-analysis, by excluding those studies, as follows no significant change, was observed (RR 1.15, 95% CI 0.53 to 2.48) (Supplementary file 3 / **figures 1, 2**).

Radiological progression (Pneumonia resolution)

Among the two studies reported radiological improvement, overall RR for HCQ with or without AZT in addition to SOC compared with SOC alone using a fixed-effect model showed that there were significant improvements among treatment arm (RR 1.40, 95% CI 1.03 to 1.91; participants = 92; studies = 2; I^2 = 0%). Additionally, there is significant RD between the two groups for radiological progression for pneumonia resolution among HCQ with or without AZT in COVID-19 patients (RD 0.22, 95% CI 0.03 to 0.41) (**Figure 3b**).

HCQ with or without AZT regimen and SOC versus SOC only; mortality

The meta-analysis of death outcome in comparative randomized and non-randomized studies showed no significant differences for mortality rate between HCQ with or without AZT regimen and standard treatment group compared with SOC alone (RR 1.08, 95% CI 0.65 to 1.79; participants = 4012; studies = 9; I^2 = 83%; RD -0.01, 95% CI -0.08 to 0.07) (**Figure 3c**).

Figure 3 (3a-3c): Forest plot for risk ratios and risk differences regarding HCQ with or without AZT in addition to SOC (**Figure 3a**: on effectiveness compared with SOC alone, **Figure 3b**: on radiological progression for pneumonia resolution compared with SOC alone, **Figure**

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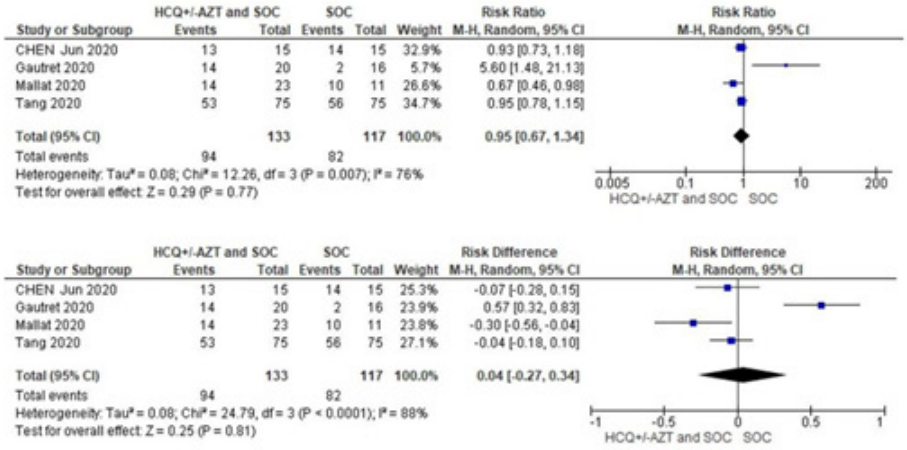

Figure 3a

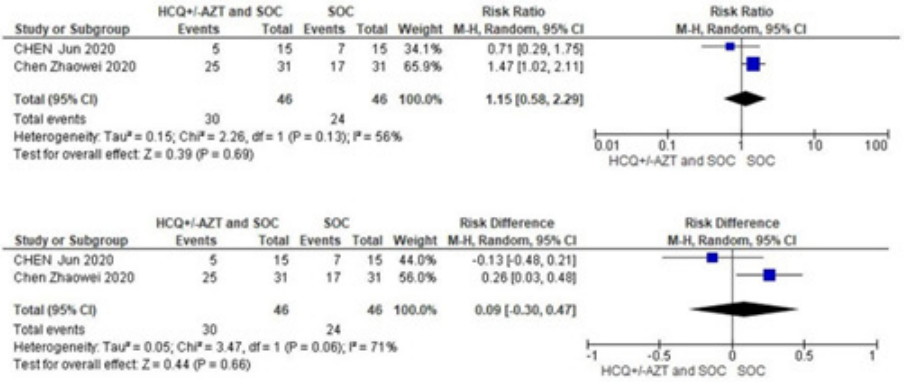

Figure 3b

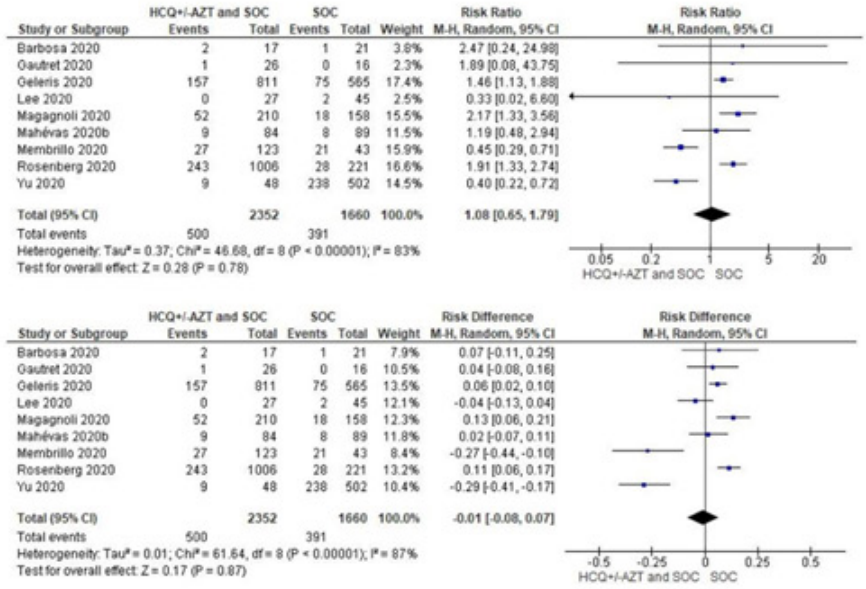

Figure 3c

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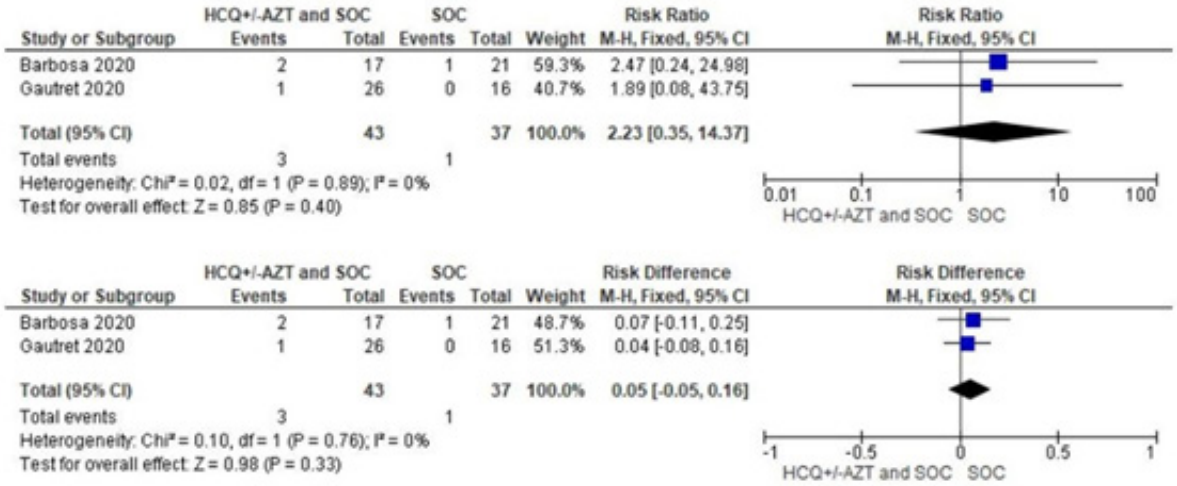


Figure 3d

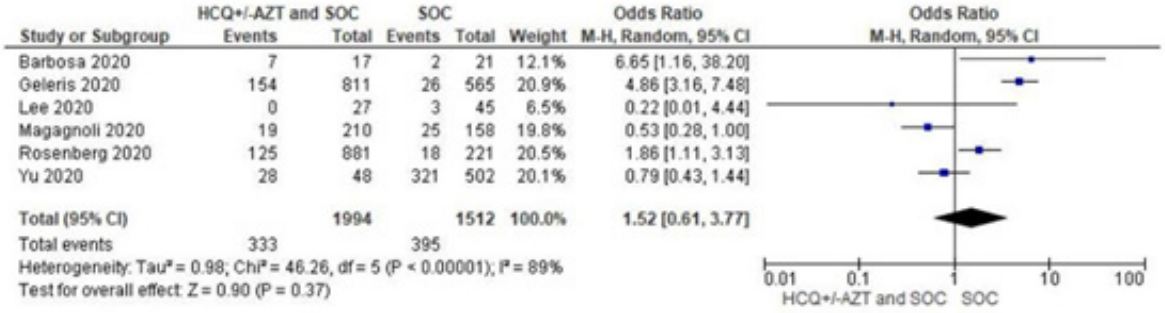
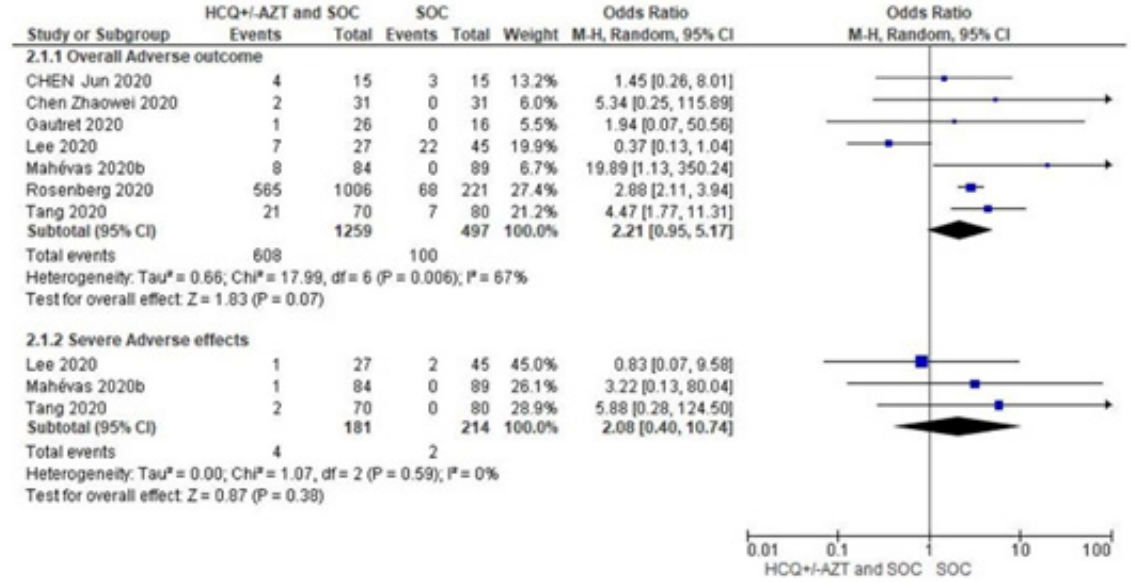


Figure 3e



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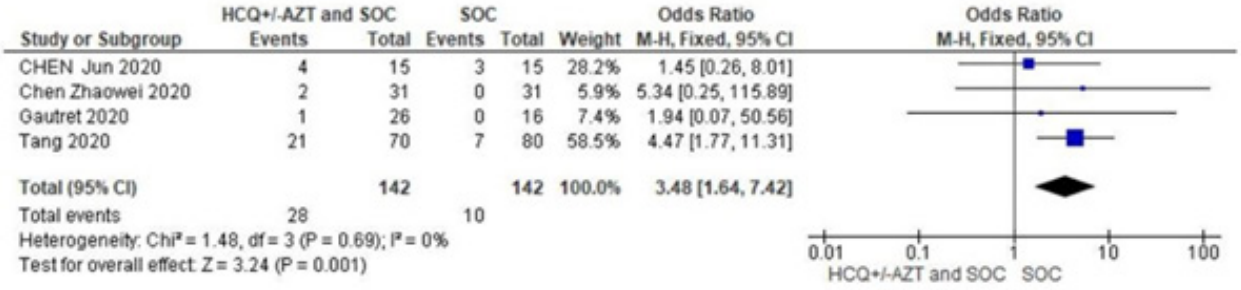

Figure 3g

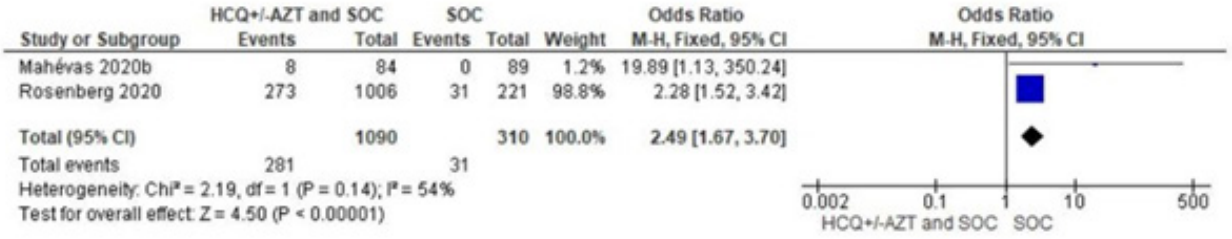

Figure 3h

Table 1: Summary of included studies

Study, Year	Study Type	Study Population	Intervention	Outcome
Barbosa,[26] 2020, USA	Quasi-randomized trial	63 T:- 32 C:-31 Subgroup analysis T:- 17 C:- 21	HCQ 400 mg BD for 1-2 days followed by 200mg OD for 4 days in the treatment group Standard care in control	• Mortality rate 4/32 T and 1/ 31 C • Escalation of respiratory support level compared to 5 days • Among match cases (n=38) • Mortality Rate 2/17 (11.76%) T and 1/21 C • Rate of Intubation (MV) =7/17 (41.18%) T and 2/21 (9.52%) C
Chen Jun,[27] 2020, China	RCT	30 T:- 15 C:- 15	HCQ 400 mg BD for 5 days in the treatment group	• Negative viral load in 13 T and 14 C • Median time for the negative viral load was 4 (1, 9) days T and 2 (1, 4) days in C • Median time for body temperature normalization in HCQ group was 1 (0, 2) T and 1 (0, 3) day] in C • Radiological progression in 5 cases (33.3%) of the HCQ group and 7cases (46.7%) of the control group • All patients showed improvement in follow-up examinations. • 4 cases in T and 3 in C had transient diarrhea and liver abnormalities
Chen,[28] 2020, China	RCT	62 T:- 31 C:- 31	HCQ 400 mg BD for 5 days in treatment group	• Improvement of fever in treatment group [2.2 (0.4) days]. • Improvement of cough in the treatment group. • Rash in one and headache in one patient • Improvement of pneumonia in 67.7% (42/62) of patients with 29.0%(T=6, C=12) ,moderately absorbed and 38.7% (T=19, C=5) significantly improved

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Gautret,[29] 2020, France	RCT	36 (enrolled 42) T:20 C:16 Six HCQ treated patients were lost in follow-up during the survey (1 cured, 1 death, 1 AE)	HCQ 200 mg, TID for 10 days	• Viral clearance at day-6 post-inclusion T :- 70%(14/20) C :-12.5%(2/16) • Number of patients attaining viral clearance HCQ + AZT : 100% (6/6) HCQ: 57.1% (8/14) CG: 12.5% (2/16)
Geleris,[20] 2020, USA	Observational study	1376 T: 811 C: 565	HCQ 600 mg BD on day 1, then 400 mg daily for a median of 5 days And AZT 500 mg on day 1 and then 250 mg daily for 4	• Mortality Rate T 157/811 C 75/565 • Rate of Intubation (MV) T 154/811 C 26/565
Lee,[25] 2020, South Korea	Retrospective sohort Study	72 T: 27 C: 45	C=LPV/r (400/100 mg orally every 6-12 hours) T=HCQ (400 mg orally every 24 hours)	• Progression of clinical disease: (T 12/27; C 8/45) • Adverse effects: (T 7/27; C22/45) Severe Effect: (T 1/27; C 2/45) • Ventilation: (T 0/27: C 3/45) • Death (T 0/27; C 2/45)
Magagnol,[19] 2020, USA	Retrospective analysis	368 HCQ :- 97 HCQ + AZT:- 113 C :- 158	HCQ or HCQ + AZT in combination	• Mortality (C:- 18; HCQ : - 27; HCQ + AZT :- 25) • Risk of ventilation (CG :- 25; HCQ :- 12; HCQ + AZT:- 7)
Mahevas,[21] 2020, France	Comparative observational study	173 T:- 84 C:- 89	HCQ 600 mg within 48 hr of hospital visit	• Survival without transfer to intensive care unit at day 21 (T:- 17; C:- 22) • Survival without ARDS (T:- 25; C:- 23) • Oxygen weaning (T:- 66; C:- 66) • Discharge from hospital to home or rehabilitation (T:- 67; C:- 71) • Death: (T:- 9; C:- 8) • Adverse outcome: 8 patients had abnormal ECG (7 QT prolongation, 1 1st degree AV Block and 1 LBBB)
Mallat[22], 2020, UAE	Retrospective observational study	34 T:- 21 C:- 13	HCQ 400 mg BD for 1 day followed by 400 mg ID for 10 days	• Time for negative viral load (T:- 17 [13-21] days; C:- 10 [4-13] days) • Percentage of patients with negative viral load (T:- 14/23; C:- 10/11)
Membrillo,[23] 2020, Spain	Observational cohort study	166 T:- 123 C:- 43	A loading dose of 1200 mg HCQ followed by a maintenance dose of 400 mg OD	• Mean hospital stay 6 (5) days in T; 5(7) days in the C • Mortality Rate T 27/123; C 21/43
Rosenberg,[18] 2020, USA	Retrospective cohort study	1438 HCQ + AZT :- 735 HCQ:- 271 AZT:- 211 Standard therapy:- 221	HCQ + AZT, HCQ alone, AZT alone	• Death probability HCQ+ AZT 189/735 (25.7%); HCQ Alone 54/271 (19.9%); AZT alone 21/211(10.0%); No drug 28/221(12.7%) • Abnormal ECG: HCQ+ AZT 199/735; HCQ Alone 74/271; AZT alone 34/211; No drug 31/221: Cardiac arrest HCQ+ AZT 114/735; HCQ Alone 37/271; AZT alone 13/211; No drug 15/221 • QT prolongation: HCQ+ AZT 81/735; HCQ Alone 3/271; AZT alone 15/211; No drug 13/221

3c: on mortality compared with SOC alone).

Sensitivity analysis for HCQ with or without AZT in addition to SOC on mortality compared with SOC alone

To evaluate the impact of inverse RRs as well as studies' weight on the meta-analysis results, we conducted sensitivity analyses as according to the substantial low relative weight excluding four studies <50 participants in treatment groups; Barbosa 2020[26], Gautret 2020[29], Lee 2020[25], and Yu 2020[24]; with total 702 participants from all 4 studies on the meta-analysis. By excluding those studies, no significant changes were observed (RR 1.28, 95% CI 0.75 to 2.17) (Supplementary file 3 / **figures 3, 4**). While swapping events between the treatment group with the control group also did not show significance in preventing from dying [(RR (Non-event) 0.93, 95% CI 0.86 to 1.01] (Supplementary file 3 / **figure 5**).

HCQ with or without AZT regimen and SOC versus SOC only; mortality among RCTs

The meta-analysis of death outcome in randomized studies using fixed effect showed no significant differences for mortality rate between HCQ with or without AZT regimen and standard treatment group compared with SOC alone (RR 2.23, 95% CI 0.35 to 14.37; participants = 80; studies = 2; I^2 = 0%; RD 0.05, 95% CI -0.05 to 0.16) (**Figure 3d**).

HCQ with or without AZT regimen and SOC versus SOC only; intubation and mechanical ventilation

The meta-analysis on intubation rate and mechanical ventilation among randomized and non-randomized studies showed no significant differences between HCQ with or without AZT regimen and SOC versus SOC only about the odds of intubation during treatment (OR 1.52, 95% CI 0.61 to 3.77; participants = 3506; studies = 6; I^2 = 89%) (**Figure 3e**).

Excluding the three studies, Barbosa 2020,[26] Lee 2020,[25] and Yu 2020[24] with substantial low relative weight (<50 participants in the treatment group) showed no significant odds of intubation during/after the beginning of treatment among HCQ with or without AZT regimen and SOC on the meta-analysis sensitivity (OR 1.72, 95% CI 0.51 to 5.83) (Supplementary file 3 / **figure 7**).

HCQ with or without AZT regimen and SOC versus SOC only: overall adverse effects

The meta-analysis of among randomized and non-randomized studies showed that the odds of having overall adverse effects among those under HCQ with or without AZT regimen addition to SOC regimen was approximately 2.2 times higher than SOC only taking individuals without HCQ regimen though it was not statistically significant (OR 2.21, 95% CI 0.95 to 5.17) (**Figure 3f**). Patients under HCQ with or without AZT regimen and SOC regimen were having 2 times higher odds of having severe adverse effects, though it is also not statistically significant (OR 2.08, 95% CI 0.40 to 10.74) (**Figure 3f**).

Figure 3 (3d-3h): Forest plot for odds ratios regarding HCQ with or without AZT in addition to SOC (**Figure 3d**: on mortality among RCTs compared with SOC alone, **Figure 3e**: on intubation and mechanical ventilation compared with SOC alone, **Figure 3f**: on overall and severe adverse effects compared with SOC alone).

We conducted sensitivity analyses as according to the substantial relative weight of Rosenberg 2020[18] (>500 participants in events) on the meta-analysis, by excluding that study also no statistically significant findings observed on odds of having Overall adverse effects among HCQ with or without AZT regimen and SOC on the meta-analysis (Overall: OR 2.22, 95% CI 0.61 to 8.04) (Supplementary file 3/ **figure 8**).

HCQ with or without AZT regimen and SOC versus SOC only: overall adverse effects among RCTs

The meta-analysis of among randomized controlled trials showed that the odds of having overall adverse effects among those under HCQ with or without AZT regimen addition to SOC regimen was approximately 3.5 times higher than SOC only taking individuals without HCQ regimen (OR 3.48, 95% CI 1.64 to 7.42; participants = 284; studies = 4; I^2 = 0%; RD 0.14, 95% CI 0.06 to 0.22) (**Figure 3g**).

Arrhythmias and significant QT-prolongation

The meta-analysis of non-randomized studies showed that the odds of having Arrhythmias and significant QT-prolongation among those under HCQ with or without AZT addition to SOC regimen were approximately 2.5 times higher than SOC only taking individuals without HCQ regimen (OR 2.49, 95% CI 1.67 to 3.70; participants = 1400) (**Figure 3h**). While for sensitivity analysis done using random effect and inverse variance, it showed no significant odds of developing arrhythmias and QT prolongation (Supplementary file 3 / **figure 9**).

Figure 3 (3g-3h): Forest plot for odds ratios regarding HCQ with or without AZT in addition to SOC (**Figure 3g**: on overall adverse effects among RCTs compared with SOC alone, **Figure 3h**: on Arrhythmias and significant QT-prolongation compared with SOC alone).

Clinical trials

There are 207 trials registered focusing on the safety and efficacy of hydroxychloroquine for COVID-19 treatment along with different parameters around the globe[31] (Supplementary file 3). Among these, 5 trials have recently been completed. A total of 103 trials are recruiting participants, 74 trials have not yet started recruiting, 9 trials are active but not recruiting participants, and 10 trials are enrolling by invitation. Out of these, 16 trials are observational and the rest are RCTs. Altogether, 6 trials are either suspended or terminated or withdrawn due to different reasons. According to the location provided, around 42 countries are regulating trials on such subjects, where the USA is at the highest position conducting most of the 52 trials followed by France which is managing 24 trials. The largest trial is RCT conducted in Thailand with 40,000 cases, while the smallest trial is an observational type conducted in Belgium with 12 participants.[31]

DISCUSSION

COVID-19 pandemic has become an alarming issue as it continues to spread all over the world and affect people globally. About the impact this has made over global health, studies dedicated to finding out an effective treatment for

this issue remain inadequate. Therefore, to contribute to establishing an evidence-based treatment for such an issue, this meta-analysis was done including 13 studies from all over the globe. The drug hydroxychloroquine (HCQ) has been used as an antimalarial and anti-rheumatic drug for a long time and its side effects have been studied well over time. Although its repurposed use in the treatment of the newly discovered viral pandemic, COVID-19 necessitates us to look further into the clinical efficacy of this drug in curing patients. Although few meta-analyses have been done, we found that they were limited to small sample sizes and had some errors in data entry as well. These factors aided in the rationale for conducting this study.

The primary outcome for the meta-analysis was the mortality rate between the treatment and control group, 9 studies were included which showed no statistically significant difference between the two groups (RR 1.08, 95% CI 0.65 to 1.79). This contrasts with Singh's meta-analysis which showed an increased risk of death (RR, 2.17; 95% 1.32 to 3.57) in patients taking HCQ.[32] Our analysis contained 9 studies compared to Singh's study and a larger sample size may have led to differences in results. Our study, however, was similar to Chacko's meta-analysis where no difference in mortality was seen (OR: 1.41, 95% CI: 0.76–2.62; p = 0.28).[33]

Evidence of adverse effects was seen in the treatment group compared to the control group with 7 studies (1756 cases) included. Overall adverse effects were present 2.2 times more in the treatment group, although statistical significance was not established (OR 2.21, 95% CI 0.95 to 5.17), though clinical relevance needs to be judged while using HCQ with or without AZT in treatment. However, the overall adverse effect among the treatment arm is approximately 3.5 times (OR 3.48, CI 1.64-7.42) higher than the control arm while taking 4 RCTs only, but the power is low because of small-sized studies. The risk of severe side effects was 2.08 times more in the treatment group without statistical significance (OR 2.08, 95% CI 0.4 to 10.74). Chacko and Ren both found a statistically significant increased side effect risk with the use of hydroxychloroquine.[33,34] Even though the results were not proven statistically, the presence of side effects must be kept in mind while the use of HCQ is considered. Cardiac adverse effects have been an important concern with the use of HCQ and a significant result establishes the need for caution while using the drug. The statistically significant result showing 2.49 times higher odds of having arrhythmias and significant QT prolongation in cases treated with HCQ with/without AZT with SOC (OR 2.49, 95% CI 1.67-3.70). It is in concordance with multiple studies that have shown an increased risk of QT among patients taking hydroxychloroquine.[9, 10]

The secondary outcomes for the meta-analysis were clinical improvement where no significant difference (RR or RD) was observed based on the virological cure (negative RT-PCRs), while it showed improvement in radiological progression where 4 studies (250 cases) and 2 studies (92 cases) were included respectively. No improvement in virological clearance was similarly seen in Sarma, Singh, and Chacko's meta-analysis.[32,33,35] Our finding of radiological improvement among patients taking HCQ with/without AZT is similar to Chacko and Sarma's analysis of improvement in CT findings following intake of HCQ.[33,35]

Strengths and limitations

Other meta-analyses have been performed to assess the efficacy of HCQ in COVID-19 patients, however, this meta-analysis included 13 studies that fairly increased the sample size and provides updated studies along with the sensitivity analysis that helped refine the results as most of the outcomes were in a similar direction even when the study with the most weight was excluded. Meanwhile, we do need to acknowledge the fact there have been multiple limitations to the study with mild to substantial heterogeneity, which might be due to the methodological or clinical diversity of studies as some studies had patients with severe disease while other had patients with mild disease. We included both randomized controlled trials and retrospective studies as only small size underpowered RCTs have been completed at the moment. This might have impacted the robustness of the outcome. There are evident biases in the form of selection, performance, attrition, reporting along with multiple studies. Despite the shortcomings, the meta-analysis worked on cumulating data and providing evidence for the effects of treatment modalities being used and points towards why the use of treatment must be kept under check.

CONCLUSION

The final synthesized evidence of the study shows no improvement in survival, need for intubation following treatment, whereas improvement in radiological progression compared to the standard of care is demonstrated. There were increased overall and severe adverse effects among all studies, although not statistically significant. While analyzing taking only RCTs, there is an increased risk of adverse effects on the treatment arm. There was statistical evidence of de- novo ECG changes like arrhythmia and QT prolongation in patients taking hydroxychloroquine with/without macrolide compared to standard of care alone. Only when large ongoing RCTs are completed, we will have less heterogeneity and biases and a further accurate assessment can be made regarding the role of hydroxychloroquine with/without macrolide in terms of efficacy and adverse effects.

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