Review Article

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Is Hydroxychloroquine with Azithromycin a Good Combination in COVID-19 Compared to Hydroxychloroquine Alone from Cardiac Perspective? A Systematic Review and Meta-Analysis

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ABSTRACT

Background: The global spread of COVID-19 and the lack of definite treatment have caused an alarming crisis in the world. We aimed to evaluate the outcome and potential harmful cardiac effects of hydroxychloroquine and azithromycin compared to hydroxychloroquine alone for COVID-19 treatment.

Methods: PubMed, Medline, Google Scholar, Cochrane Library, clinicaltrials.gov, and World Health Organization clinical trial registry were searched using appropriate keywords and identified six studies using PRISMA guidelines. The quantitative synthesis was performed using fixed or random effects for the pooling of studies based on heterogeneities.

Results: The risk of mortality (RR=1.16; CI: 0.92-1.46) and adverse cardiac events (OR=1.06; CI: 0.82-1.37) demonstrated a small increment though of no significance. There were no increased odds of mechanical ventilation (OR=0.84; CI: 0.33-2.15) and significant QTc prolongation (OR=0.84, CI: 0.59-1.21). Neither the critical QTc threshold (OR=1.92, CI: 0.81-4.56) nor absolute ΔQTc ≥60ms (OR=1.95, CI:0.55-6.96) increased to the level of statistical significance among hydroxychloroquine and azithromycin arm compared to hydroxychloroquine alone, but the slightly increased odds need to be considered in clinical practice.

Conclusions: The combination of hydroxychloroquine and azithromycin leads to small increased odds of mortality and cardiac events compared to hydroxychloroquine alone. The use of hydroxychloroquine and azithromycin led to increased odds of QT prolongation, although not statistically significant.

Keywords: COVID-19; COVID-19 drug treatment; hydroxychloroquine; macrolides; severe acute respiratory syndrome coronavirus 2

INTRODUCTION

There have been more than 80 million cases of COVID-19, with 1.7 million mortalities worldwide.[1] Despite the escalating burden, there has been no substantial progress in finding the proper treatment.

Hydroxychloroquine (HCQ) and azithromycin (AZT) are two repurposed drugs for COVID-19. HCQ has been shown to inhibit in-vitro severe acute respiratory syndrome coronavirus-2 (SARS-COV-2).[2,3] Cardiac adverse effects are reported as QT prolongation, AV block, and conduction abnormalities along with abnormal liver function and retinopathy with its use.[4,5] AZT, a macrolide antibacterial, has also been associated with QT prolongation.[6,7]

Presently, there have been conflicting findings on the rationale of using HCQ+AZT in the treatment of COVID-19 with some studies supporting the use of combination of HCQ+AZT in COVID-19 while some reporting increased adverse events with the combination therapy.[8-11] We conducted our study to answer the following research question: Do HCQ+AZT lead to increased cardiac side effects in COVID-19 cases compared to HCQ alone?

The objective of our study was to assess cardiac effects, differences in mortality rate, and the need for ventilation

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among treatment (HCQ+AZT) and control groups (HCQ alone) in patients treated for COVID-19 infection.

METHODS

PRISMA guideline was used for our systematic review (Supplementary file 1).[12]

Criteria for considering studies for this review

Types of studies

Studies focusing on mortality, intubation and mechanical ventilation, and cardiac adverse events among patients taking HCQ+AZT compared to patients taking HCQ alone were included.

Types of participants

We included patients diagnosed with COVID-19 who received either HCQ+AZT or HCQ alone.

Types of interventions

Our treatment arm consists of patients taking HCQ+AZT and HCQ alone as a control arm. Patients in both arms received standard of care.

Types of outcome measures

The mortality, intubation and mechanical ventilation, and cardiac adverse effects among the treatment and control group that occurred during treatment were outcomes of interest.

Outcomes

We compared deaths between treatment and control arms, cardiac adverse effects like QT prolongation or ventricular arrhythmia, and intubation and mechanical ventilation requirements between treatment and control arms.

Search methods for identification of studies

PubMed, Cochrane Library, Medline, Clinicaltrials.gov, Google Scholar, and the World Health Organization (WHO) clinical trial registry were accessed by our reviewers (PB and DBS), who independently searched and evaluated the quality of the studies from January 1 to June 2, 2020. We filtered the studies using COVIDENCE and extracted data for quantitative and qualitative synthesis. Any potential conflict was solved by taking the final opinion of another reviewer (SK). Another reviewer (ER) assessed the risk of bias and cross-checked all the selected studies.

Electronic searches

We have documented the detailed search strategy in Supplementary file 2.

Data collection and analysis

We extracted the data for quantitative synthesis through COVIDENCE and did the analysis using RevMan 5.3. Assessment of heterogeneity was done using the I-squared (I^2) test. We used random/fixed effect for pooling of selected studies

Selection of studies

We have included randomized controlled trials (RCTs), retrospective observational studies, and case series that have a treatment arm of patients taking HCQ+AZT and a control arm of patients taking HCQ alone in addition to supportive care. We excluded the recently retracted paper by Mehra et al. which had reported increased cardiac adverse effects among patients taking HCQ and macrolide.[13] We excluded studies in which the control arm consisted of the standard of care alone without HCQ. Different articles like reviews, retracted papers, in-vitro studies, editorials, letters to editors, protocols, commentaries, viewpoints, and studies done in the pediatric population were excluded.

Data extraction and management

We evaluated the quality of the studies thoroughly and took into account only the outcomes that were of our interest.

Assessment of risk of bias in included studies

We used the Cochrane ROB tool for analysis of our RCTs shown in supplementary 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, case series, and cohort studies (Supplementary tables 1,2). We used Revman 5.3 for creating a summary of biases for RCTs using the Cochrane tool.

Supplementary figure 1: Risk of bias assessment

Supplementary table 1**:** NHLBI quality assessment tool for observational cohort and cross-sectional studies[14-16]

Supplementary table 2**:** NHLBI quality assessment tool for case series[17-18]

Assessment of heterogeneity

The I^2 test was used for the assessment of heterogeneity. We interpreted the I^2 test done based on the Cochrane Handbook for Systematic Reviews of Interventions as (i) 0% to 40%: might not be important, (ii) 30% to 60%: may represent moderate heterogeneity (iii) 50% to 90%: may represent substantial heterogeneity, and (iv) 75% to 100%: considerable heterogeneity.

"The importance of the observed value of I^2 depends on (i) the magnitude and direction of 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

Reporting bias was checked by prefixed reporting of the outcome.

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

We used the random effect model in cases of significant heterogeneity.

Sensitivity analysis

We used the inverse variance method during analysis to assess the effect on the results and running the analysis again to look for sensitivity of the findings.

RESULTS

Qualitative synthesis

We identified a total of 2069 studies after electronic database searching. We removed 499 duplicates. Screening of the title and abstracts of 1570 studies was done. We excluded 1386 studies and checked 184 articles for full-text eligibility. We excluded 178 studies with definite reasons mentioned in the PRISMA flow diagram in figure 1. At last, six studies were selected for our analysis. A discussion of these studies is done in table 1.

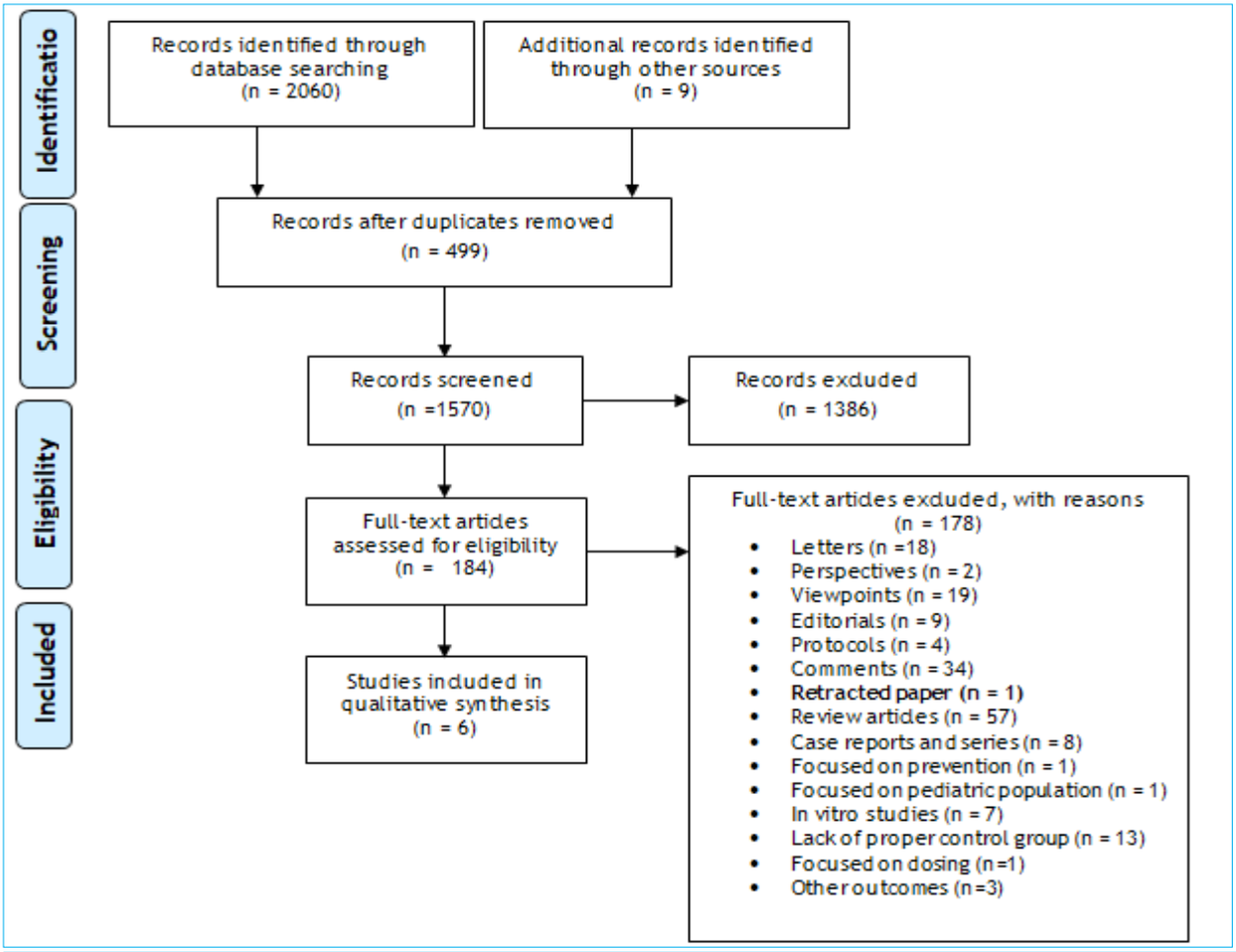

Figure 1. Flow chart for study design (PRISMA 2009 flow diagram).

Table 1. Summary of included studies.

Study	Population	Intervention	Outcome	Limitations
Bessiere[17] 2020, Case series, US	n=40 HCQ : 18 HCQ+AZT : 22 Disease severity: Severe	HCQ 200 mg BD for 10 days AZT 250 mg OD for 5 days	QT prolongation in six patients in HCQ+AZT group versus one patient in HCQ group A total of 30 patients required invasive ventilation and 25 required vasoactive drugs	Lack of generalizability beyond ICU
Gautret[19] 2020, RCT, France	n=36 HCQ : 14 HCQ+AZT : 6 SOC : 16 Disease severity: Mild/ moderate	HCQ 600 mg/day for 10 days	Decreased viral load at day 6 and overall lower decreased in viral load duration	High risk of bias, six patients taking HCQ lost in the follow-up
Magagnoli[15] 2020, Retrospective study, US	n=368 HCQ : 97 HCQ+AZT : 113 SOC: 158 Disease severity: Mild/ moderate	HCQ and AZT given Dose not mentioned	Deaths:- HCQ: 27 HCQ+AZT: 25 Risks of ventilation:- HCQ: 12 HCQ+AZT: 7	Non-randomization of treatment, Selection bias and a large number of confounders
Mercuro[16] 2020, Retrospective observational study, US	n=90 HCQ: 37 HCQ+AZT: 53	400mg of HCQ BD on day 1, then 400 mg OD on days 2 through 5	Prolonged QTc HCQ: 7/37 HCQ+AZT: 11/53	COVID associated cardiomyopathy cannot be excluded, No patients receiving SOC alone without drugs
Ramireddy[18] 2020, Case series, US	n=98 HCQ: 10 AZT: 27 HCQ+AZT: 61 COVID confirmed and suspected cases regardless of disease severity	HCQ, AZT, and HCQ+AZT	QTc prolongation HCQ: 0/27 HCQ+AZT: 7/61	Small sample size, variation in dosing and treatment
Rosenberg[14] 2020, Retrospective cohort, US	n=1438 HCQ+AZT: 735 HCQ: 271 AZT: 211 SOC: 221 All COVID-19 confirmed cases with complete records and not discharged in first 24 hrs	HCQ, HCQ+AZT, AZT, SOC	Mortality:- HCQ+AZT: 189/735, HCQ Alone: 54/271, AZT alone: 21/211, No drug: 28/221 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: 39/271; AZT alone: 15/211 No drug: 13/221	Readmission not considered, mortality limited to in-hospital death and patients discharged assumed to be alive, confounding, the adverse effect might have occurred at any point during hospitalization

AZT: Azithromycin, BD: Twice daily, CQ: Chloroquine, HCQ: Hydroxychloroquine, n = Number of patients, OD: Once daily, RCT: Randomized controlled trial, SOC: Standard of care, US: United States.

Quantitative synthesis of treatment outcome

This meta-analysis compared outcomes of COVID-19 patients like overall death, mechanical ventilation, and cardiac complications (QT-prolongation and de-novo arrhythmias) among randomized and non-randomized studies between treatment and control arms to find if the addition of azithromycin and hydroxychloroquine made any difference. Among the included studies for meta-analysis, we found that there was a mild substantial heterogeneity.

HCQ+AZT versus HCQ: Mortality

The meta-analysis of death as an outcome in comparative studies increased the risk of mortality rate among HCQ+AZT group compared with HCQ alone, even though it was statistically insignificant (RR 1.16, 95% CI - 0.92 to 1.46; participants = 1242; studies = 3; I^2 = 35%; RD 0.03, 95% CI - 0.02 to 0.08; participants = 1242; studies = 3; I^2 = 43%). This indicates that the addition of AZT to HCQ may increase mortality which needs to be assessed based on relevance clinically (Figure 2).

HCQ+AZT versus HCQ: Intubation and mechanical ventilation

The meta-analysis on intubation rate and mechanical ventilation among comparative studies showed no significant differences between HCQ+AZT versus HCQ about the odds of intubation during treatment (OR 0.84, 95% CI 0.33 to 2.15) (Figure 3). Its sensitivity analysis was done using the inverse variance method and showed no significance (Supplementary file 3).

HCQ+AZT versus HCQ: Arrhythmias and significant QT-prolongation

The meta-analysis of non-randomized studies showed that the odds of having de-novo arrhythmias and significant QT-prolongation among those under HCQ+AZT were 1.06 (95% CI 0.82 to 1.37) times higher than HCQ only group. From subgroup analysis, HCQ+AZT group has 0.84 (95% CI 0.59 to 1.21; participants = 2213; I^2 = 20%) odds of developing significant QT-prolongation which shows that combination of these drugs may not increase cardiac events (Figure 4).

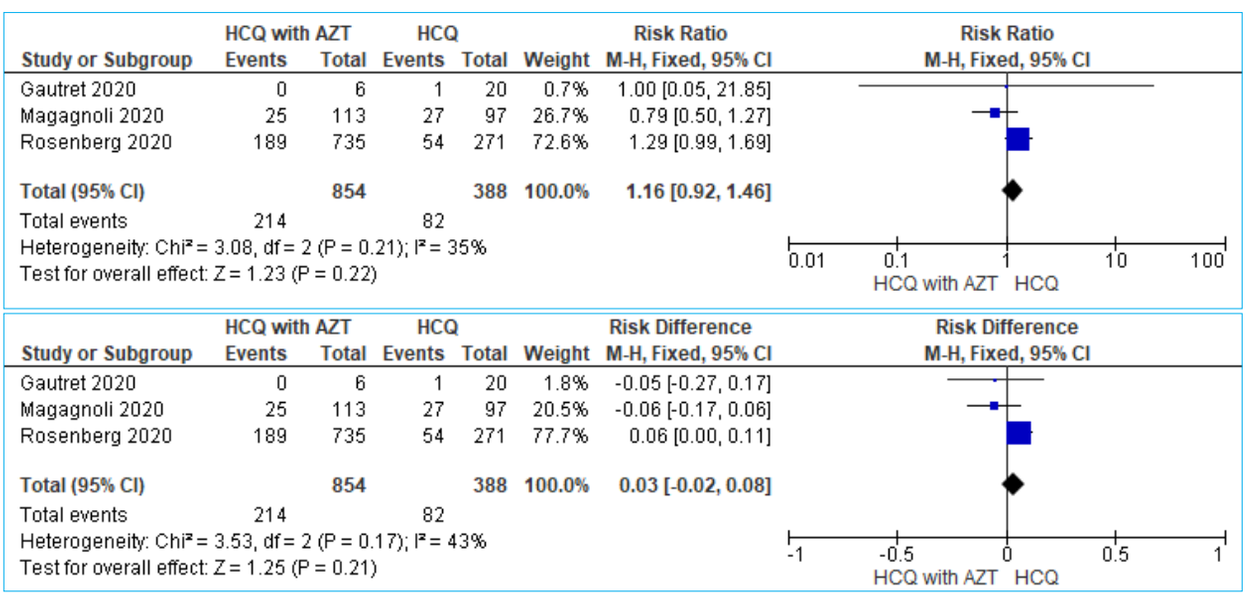

Figure 2. Forest plot for risk ratios and risk differences regarding death HCQ+AZT versus HCQ.

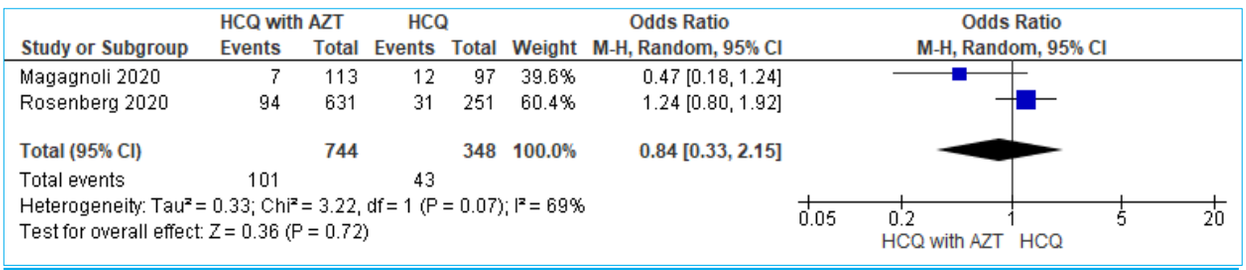

Figure 3. Forest plot for odds ratios among HCQ+AZT versus HCQ: Intubation and Mechanical ventilation.

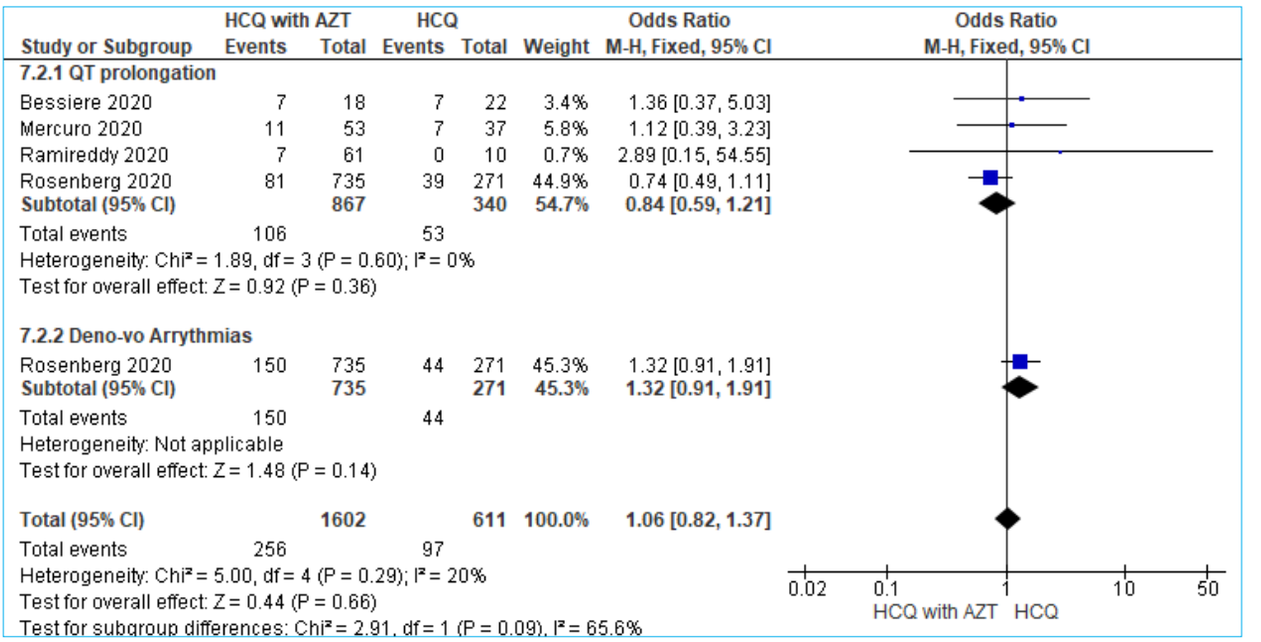

Figure 4. Forest plot for odds ratios among HCQ+AZT versus HCQ: Arrhythmias and significant QT-prolongation.

HCQ+AZT versus HCQ: Critical QTc threshold and absolute ΔQTc ***≥60ms***

Although the above meta-analysis already showed no statistically significant odds of having significant QT prolongation (critical QTc threshold and or absolute ΔQTc ≥60ms) HCQ+AZT versus HCQ, we tried to explore if there are any differences among critical QTc threshold [≥500ms (QRS <120ms) or ≥550ms (QRS ≥120ms)] and absolute ΔQTc ≥60ms between HCQ+AZT versus HCQ. The meta-analysis showed no statistically significant difference among both variables; critical QTc threshold (OR 1.92, 95% CI 0.81 to 4.56; participants = 201; studies = 3; I^2 = 38%) and absolute ΔQTc ≥60ms (OR 1.95, 95% CI 0.55 to 6.96; participants = 161; studies = 2; I^2 = 0%) (Figure 5).

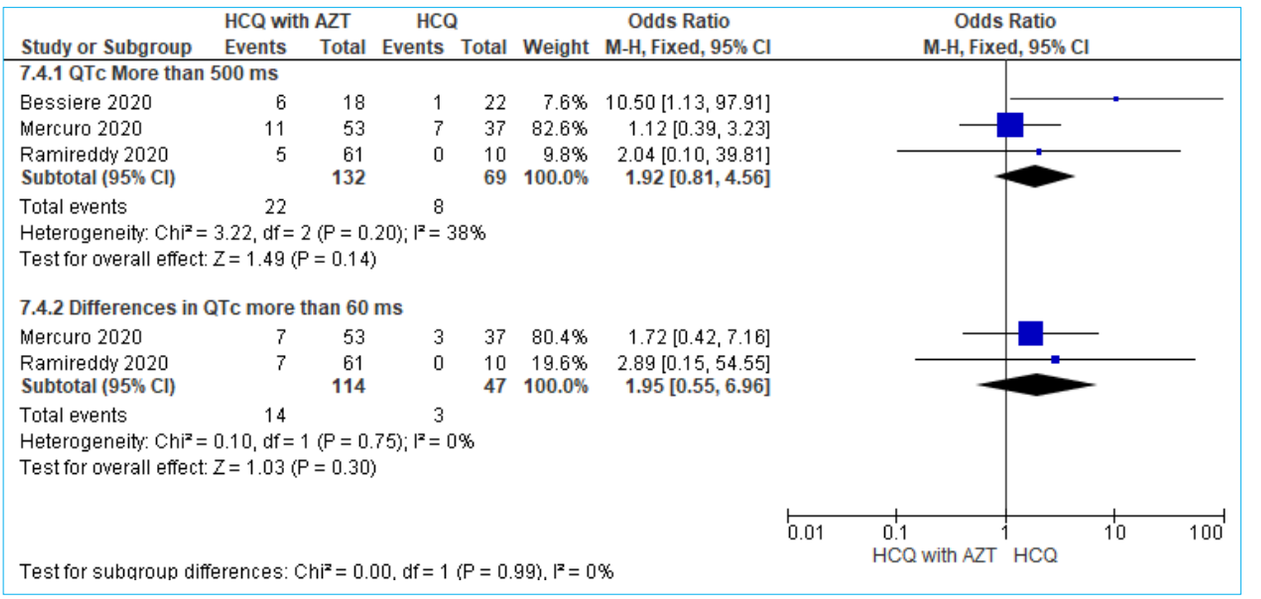

Figure 5. Forest plot for odds ratios among HCQ+AZT versus HCQ: Critical QTc threshold and absolute ΔQTc ≥60ms.

Clinical trials

Among the 210 registered trials dealing with HCQ for COVID-19 treatment till the period of searching databases, 43 trials dealt with HCQ and AZT.[20] The details of these trials are available in Supplementary table 3. These are being conducted to assess the safety and efficacy of HCQ + AZT, or HCQ alone as compared to HCQ+AZT for better therapeutic outcome. Most of these trials are RCTs, with some observational trials with the number of participants ranging from 40 to 12,000. Some of these trials had not started recruiting participants at the time this study was conducted. These trials were being conducted in many parts of the world with majority being carried out in the United States followed by France.

DISCUSSION

Our systematic review and meta-analysis included six studies and focused on assessing the difference between the use of HCQ+AZT compared to HCQ alone. The final analysis of the study showed a small increase in mortality among the treatment arm which used HCQ with a macrolide and the control arm which used HCQ alone, though the increase was statistically insignificant.

The increased risk of death using HCQ+AZT should be kept in mind while using the combination therapy in clinical relevance. This result could be statistically insignificant due to the paucity of data and controlled studies. In contrast, earlier studies have stated that the administration of HCQ+AZT combination before the occurrence of COVID-19 complications is safe and is associated with a very low fatality rate [21] which is in contrast to our meta-analysis. This should draw the attention of clinicians who use the above drugs widely based on the present level of evidence. Another outcome associated with the study was the rate of mechanical ventilation/intubation among the treatment and control arms, which showed no significant difference in patients receiving hydroxychloroquine alone to patients treated with HCQ+AZT.

The QT prolongation seen in our analysis was not statistically significant different from those conducted in the past which showed prolongation of QT interval with use of hydroxychloroquine and azithromycin.[4,5] Although the use of these medications resulted in QT prolongation in other studies, clinicians seldom needed to discontinue therapy.[22] Another study stated that patients who received HCQ for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation. [16] Concurrent treatment with AZT was associated with more significant changes in QTc.[16] We looked into more detail analyzing differences among critical QTc thresholds [≥500ms (QRS ≤120ms) or ≥550ms (QRS ≥120ms)] and absolute ΔQTc ≥60ms between HCQ+AZT versus HCQ, which showed increased odds of the event among HCQ+AZT group but no statistical significance. A proper judgment needs to be made to add both drugs based on the clinical picture.

In our meta-analysis, we found a slight increase in the risk of mortality, critical QTc threshold, and absolute ΔQTc ≥60ms although the findings were not statistically significant. Fiolet et al. and Ghazi et al. found increased mortality with the combination of HCQ+AZT in patients suffering from COVID-19 which was similar to our study.[23,24] The mortality risk appears to be increased with the dual therapy which should be taken with great caution.

We included studies over a range of case series, controlled trials, randomized and non-randomized studies and have tried to look meticulously into the cardiovascular perspective of the treatment along with mortality rates and intubation/mechanical ventilation rates among the treatment and control arms. Sensitivity analysis has added to the detailed analysis, making the results more reliable. Meanwhile, we do need to address the fact that this study has several limitations in the form of mild-substantial heterogeneity due to clinical and methodological diversity. The included studies had their own inherent biases like selection bias and attrition bias which affected the quality of our study. We could not include more RCTs as most trials were ongoing and focused more on a combining these drugs against the standard of care rather than HCQ alone. Regardless of this, significant results will aid in future studies and how the use is controlled and regulated.

CONCLUSIONS

This study found a slightly increased risk of overall de-novo arrhythmias and significant QT-prolongation and mortality with the use of HCQ+AZT compared to HCQ alone, though it was statistically insignificant. For subgroup analysis for critical QTc threshold and absolute ΔQTc ≥60ms, the increased risk is statistically insignificant among HCQ+AZT arm compared to HCQ alone; adding two drugs with the potential to increase QT-interval need to be practiced with great clinical consideration of not harming the patients. There is a slight increase in the risk (no statistical significance) of mortality, critical QTc threshold, and absolute ΔQTc ≥60ms; this result does not guide against the use of a combination of HCQ+AZT or HCQ alone. The study has provided some evidence-based results, but the contrasting results in the past and strikingly few numbers of studies urge to look further into the matter. Many questions remain unanswered

while several studies and trials are being carried out. Until the results of these trials become available, we must use the best available evidence-based treatment for COVID-19.

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