Is hydroxychloroquine with macrolide a good combination in COVID-19 compared to hydroxychloroquine alone from cardiac perspective? A systematic review and meta-analysis

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Systematic Review

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Abstract

Background: The global spread of COVID-19 and the lack of definite treatment has caused an alarming crisis in the world. Hydroxychloroquine (HCQ) and azithromycin (AZT) are considered a possible treatment option. We aimed to evaluate the outcome and potential harmful cardiac effects of AZT+HCQ compared to HCQ alone for COVID-19 treatment.

Methods: Pubmed, Medline, Google Scholar, Cochrane Library, and clinicaltrials.gov were searched using appropriate keywords and identified six studies using PRISMA guidelines. The quantitative synthesis was performed using fixed and random effects for the pooling of studies.

Result: In this systematic review and meta-analysis, the risk of mortality (RR 1.16; 0.92-1.46) and adverse cardiac events (OR 1.06; 0.82-1.37) demonstrated a small increment though of no significance. There are no increased odds of mechanical ventilation (OR 0.84; 0.33-2.15) and significant QTc prolongation (OR 0.84, 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) is increased to the level of statistical significance among HCQ+AZT arm compared to HCQ alone; but its slightly increased odds need to be considered in clinical practice.

Conclusion: The combination of AZT+HCQ leads to small increased odds of mortality and cardiac events compared to HCQ alone. It is of no statistical significance for the critical QTc threshold and absolute ΔQTc ≥60ms, but increased odds with HCQ+AZT arm need to be considered in clinical relevance. Our result does not guide against the use of combination or HCQ alone based on the present level of evidence.

Introduction

In mid-march of 2019, the World Health Organization (WHO) declared COVID-19 as a global pandemic.[1] At present, there are more than 6 million cases worldwide with 371,166 mortalities.[2] Despite the escalating cases and mortalities, there has been no substantial progress in finding the proper treatment. The development of a vaccine is currently ongoing, but it will likely require more time. COVID-19 is a respiratory illness that is spread by droplets or touching a contaminated surface in which infected people sneeze. Its clinical spectrum ranges from asymptomatic to mild respiratory symptoms like rhinorrhea, coughing, fever but may also manifest as pneumonia and lead to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction.

Hydroxychloroquine (HCQ) is an antimalarial drug that has also been used for autoimmune diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Azithromycin (AZT) is a macrolide group of antibiotics used to treat bacterial infection. HCQ has been shown to inhibit in-vitro severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) by inhibiting terminal glycosylation of the receptor angiotensin-converting enzyme-2 that prevents viral binding and inhibition of infection.[3,4] HCQ has been

attributed to various side effects like hypoglycemia, diarrhea, abnormal liver function, and retinopathy.[5] Cardiac side effects like QT prolongation, AV block, and other conduction abnormalities have been reported across many studies. AZT has also been associated with QT prolongation.[6,7]

Presently, there have been conflicting reports on the rationale of the use of HCQ and AZT in the treatment of COVID-19. Some studies demonstrated decreased mortality, clinical recovery, and resolution of pneumonia among patients taking the drug.[8,9] There have been other studies that did not reported any clinical benefits and instead reported more adverse effects with its use.[10,11] There is a lack of proper studies about how the outcome of patients receiving both HCQ+AZT is different from patients receiving HCQ alone, as most of the studies have focused on comparing the use of both drugs against the standard of care. We conducted our study to answer the following research question: Do HCQ and Macrolide lead to increased cardiac side effects in COVID-19 cases compared to HCQ alone?

The objective of our study is to assess cardiac effects like arrhythmia and QT prolongation, differences in mortality rate, and the need for ventilation among treatment (HCQ+AZT) and control groups (HCQ alone).

Methods

PRISMA guideline was used for our systematic review.[12]

3.1. Criteria for considering studies for this review

3.1.1. Types of studies

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

3.1.2. Types of participants

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

3.1.3. 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.

3.1.4. 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.

3.1.5. Outcomes

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

3.2. Search methods for identification of studies

Pubmed, Cochrane Library, Medline, Clinicaltrials.gov, Google Scholar, and 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 taking the final opinion of another reviewer (SK). Another reviewer (ER) assessed the risk of bias and cross-checked all the selected studies.

3.2.1. Electronic searches

We have documented the detailed search strategy in **supplementary file no. 1**

3.3. 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

3.3.1. 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 with HCQ and macrolide.[13] We excluded studies in which the control arm consisted of the standard of care alone without the use of 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.

3.3.2. Data extraction and management

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

3.3.3. Assessment of risk of bias in included studies

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

Figure 1: Risk of bias assessment

Table 1: NHLBI quality assessment tool for observational cohort and cross-sectional studies

Table 2: NHLBI quality assessment tool for case series

Supplementary table 1 and 2

3.3.4. 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 follows:-

i) 0% to 40%: might not be important

ii) 30% to 60%: may represent moderate heterogeneity

iii) 50% to 90%: may represent substantial heterogeneity

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)."

3.3.5. Assessment of reporting biases

Reporting bias was checked by prefixed reporting of the outcome.

3.3.6. 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% Confident Interval (CI). The fixed/random-effects model was used according to heterogeneities.

3.3.7. Subgroup analysis and investigation of heterogeneity

We used the random effect model in cases of heterogeneity.

3.3.8. Sensitivity analysis

We used the inverse variance method to assess the effect on the results and running the analysis again to see for sensitivity analysis.

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 2. At last, 6 studies were selected for our analysis. A discussion of these studies is done in table 3.

PRISMA 2009 flow diagram

Figure 2: Flow chart for study design (PRISMA 2009 flow diagram)

Summary for included studies

Table 3: 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 6 in HCQ + AZT group versus 1 patient 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 Mild/moderate disease severity	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, 6 patients taking HCQ lost in the follow-up
Magagnoli[15]	n=368 HCQ : 97	HCQ and AZT have	Deaths:- HCQ: 27	Non-randomization of treatment, Selection bias

2020, Retrospective study, US	HCQ + AZT : 113 SOC: 158 Mild/moderate disease severity	given No dose	HCQ + AZT: 25 Risks of ventilation:- HCQ: 12 HCQ + AZT: 7	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	HCQ, HCQ + AZT, AZT, SOC	Mortality:- HCQ + AZT: 189/735, HCQ Alone: 54/271, AZT	Readmission not considered, mortality limited to in-hospital death and patients discharged assumed to be alive,

	SOC: 221 All COVID confirmed cases with complete records and not discharged in first 24 hrs		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	confounding, the adverse effect might have occurred at any point during hospitalization

			alone: 15/211 No drug: 13/221	

Quantitative synthesis of treatment outcome

At the present meta-analysis compared outcomes on overall death, mechanical ventilation, cardiac complications (QT-prolongation, de-novo arrhythmias) among randomized and non-randomized studies between treatment and control arm to find is there any difference in the addition of AZT to HCQ. Among the included studies meta-analysis, we found there is mild-substantial heterogeneity.

4.1. 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, though statistically not significant (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%); indicating addition of AZT on HCQ may increase mortality which need to be assessed based on relevance clinically (Figure 3).

Figure 3: Forest plot for risk ratios and risk differences regarding death HCQ+AZT versus HCQ

4.2. 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 4). Its sensitivity

analysis done using the inverse of variance method and showed no significance (**Supplementary file 2**).

Figure 4: Forest plot for odds ratios among HCQ+AZT versus HCQ: Intubation and Mechanical ventilation

4.3. 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; showing combination may not increase the cardiac event (Figure 5). However, critical clinical scrutiny is advised over patients, being both drugs has already been shown independently to be associated with cardiac adverse events.

Figure 5: Forest plot for odds ratios among HCQ+AZT versus HCQ: Arrhythmias and significant QT-prolongation

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

Though 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 is there 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 6).

Figure 6: 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, 43 trials are dealing with HCQ and AZT.[20] The details of these trials are available in **supplementary table 3**. These are being conducted with the aim of assessing the safety and efficacy of HCQ and AZT, or HCQ alone as compared to HCQ+AZT for the better therapeutic outcome. Most of these trials are RCTs with some observational trials with the number of participants ranging from 40 at minimum to 12000 at maximum. Some of these trials are not yet started recruiting participants. These trials are being counducted in many parts of the world. Among them, most of these trials are carried out in the United States followed by France.

Discussion

COVID-19 pandemic has substantially spread over the world, killing millions of people. Effective therapeutic or prophylactic agents, or treatment modalities are still underway and those being used as standard of care along with various other drugs have not been sufficiently studied. Therefore, different studies currently dedicated to discovering effective therapy and related findings are important. Right away, HCQ alone or in adjunct to macrolide is being used for effective treatment, but the lack of ample studies brings many questions into the picture. Similarly, our study, which included 6 studies, focused on assessing the difference in the outcome of the use of HCQ alone and an adjunct to macrolide.

The final analysis of the study shows a small increase in the mortality rate (RR 1.16, 95% CI 0.92 to 1.46) among the treatment arm which used HCQ with macrolide and the control arm which used HCQ alone, though such increase is statistically not significant. The increased risk of death with the use of HCQ with macrolide should be kept in mind while using the combination in clinical relevance. Though this result is statistically insignificant may be due to the paucity of data and controlled studies. In contrast, earlier studies have stated that the administration of HCQ+AZT combination before COVID-19 complications occur is safe and associated with a very low fatality rate in patients[21] our meta-analysis does not support that. This should draw the attention of the clinicians who are using the drug vicariously 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 arm, which showed no significant difference (OR 0.84, 95% CI 0.33 to 2.15).

Assessing further details do the mortality link with the cardiovascular effects of the drug are a big question to be looked into. The well-known cardiovascular effects of macrolide drugs ranging from arrhythmias to torsade raise concerns. Our meta-analysis has further tried to discover the answer to these questions and surprisingly the results have shown no such significant increase in risk, different from the ones conducted in the past. Although the use of these medications resulted in QT prolongation in other studies, clinicians seldomly needed to discontinue therapy.[22] The results in our review and extensive analysis show no significant difference between the treatment arm and control arm, with only 1.06 times higher odds of having de-novo arrhythmias and QT prolongation in the treatment group. Furthermore, from subgroup analysis, the results HCQ+AZT group has 1.32 times higher odds of developing de-novo arrhythmias (95% CI 0.91 to 1.91) meanwhile that for significant QTc prolongation it was not significantly associated (OR 0.84, 95% CI 0.59 to 1.21). Another study stated that patients who received HCQ for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation, and concurrent treatment with AZT was associated with greater 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 increase odds of the event among HCQ+AZT group but no statistically significant. A proper judgment needs to be made to add both drugs based on the clinical picture.

Recently, a multinational registry-based cohort study result was published showing the result of using HCQ/chloroquine with or without AZT compared with the standard of care alone.[13] When we analyzed our data including that of Mehra et al showed a significantly increased risk of mortality rate among HCQ+AZT group (RR 1.24, 95% CI 1.04-1.47). Additionally, the odds of having overall de-novo arrhythmias and significant QT-prolongation among the treatment group was 1.25 (95% CI 1.09 to 1.45) and the odds of developing only de-novo arrhythmias was 1.35 (95% CI 1.15 to 1.58) (**Supplementary file 3**). This study raised high concern for safety issues leading to premature termination of many trials. Recently, scientists found methodical flaws in the study and retracted. Thus, this study is not included in the present analysis. Though combining drugs having similar side effect profiles may be of concern, but judgment should be based on clinical judgment analyzing risk and benefit. In our meta-analysis, there is a slight increase in the risk (no statistical significance) of mortality, critical QTc threshold, and absolute ΔQTc ≥60ms; the current level of evidence does not guide against the use of combination or HCQ alone.

Limitations

Our systematic review and meta-analysis study has included 6 studies over a range of case series, controlled trials, randomized and non-randomized studies and has 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 according to the fact that the study

has had various limitations in the form of mild-substantial heterogeneity due to clinical and methodological diversity. A different form of bias during selection, reporting, attrition has affected the study. We could not include more RCTs as most trials are ongoing and focused more on a combination of 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.

Conclusion

Significant results regarding the cardiovascular impact with the treatment modality currently used are doubtlessly a milestone. We found a slightly increased risk of overall de-novo arrhythmias and significant QT-prolongation and mortality with the use of HCQ and macrolide compared to HCQ alone, though not statistically significant. For subgroup analysis for critical QTc threshold and absolute ΔQTc ≥60ms, the increased risk is not of statistical significance 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 patient. 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 treatment of COVID-19.

Declarations

Declaration of Competing Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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Tables 1 And 2

Table 1: NHLBI quality assessment tool for observational cohort and cross-sectional studies

Studies	Bias risk (2 points not applicable)	Grading and percentage
Rosenberg 2020[14]	10/12	83.3% (Good)
Magagnoli 2020[15]	9/12	75% (Good)
Mercuro 2020[16]	8/12	66.6% (Good)

Good if they fulfilled 60-100% of the tool items, Fair if 50-59%, or Poor if 0-49%.

Table 2: NHLBI quality assessment tool for case series

Studies	Bias risk	Percentage
Bessiere 2020[17]	8/9	88.8% (Good)
Ramireddy 2020[18]	6/9	66.6%(Good)

Good if they fulfilled 60-100% of the tool items, Fair if 50-59%, or Poor if 0-49%.

Figures

Figure 1: Risk of bias assessment

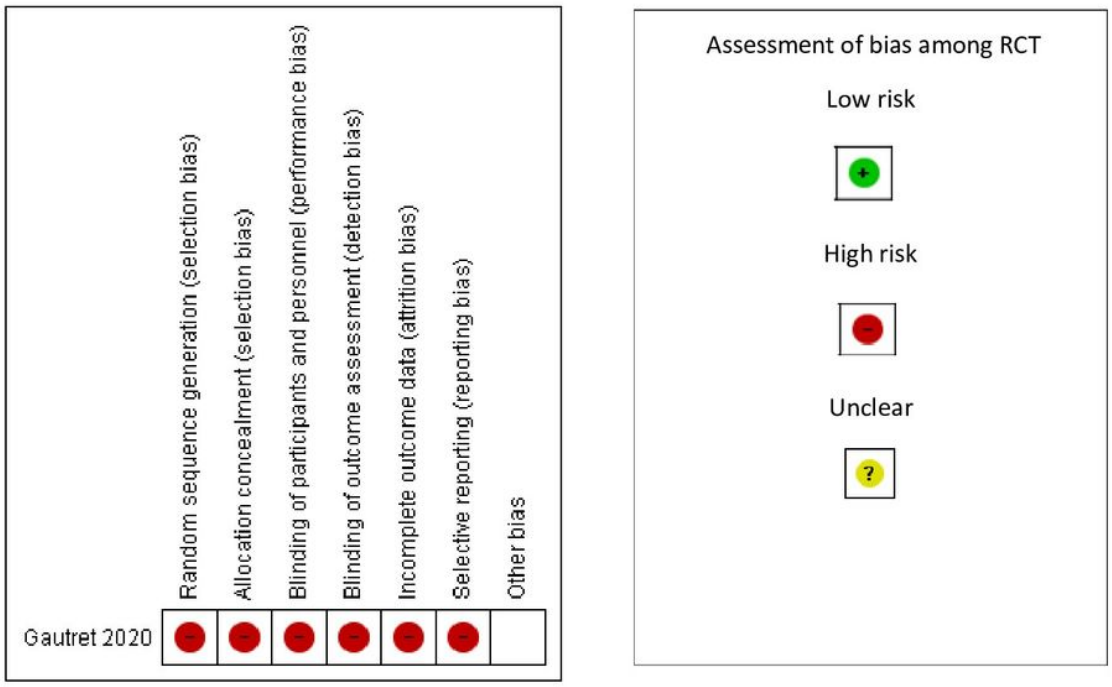

Figure 1

Risk of bias plot

Figure 2: Flow chart for study design (PRISMA 2009 flow diagram)

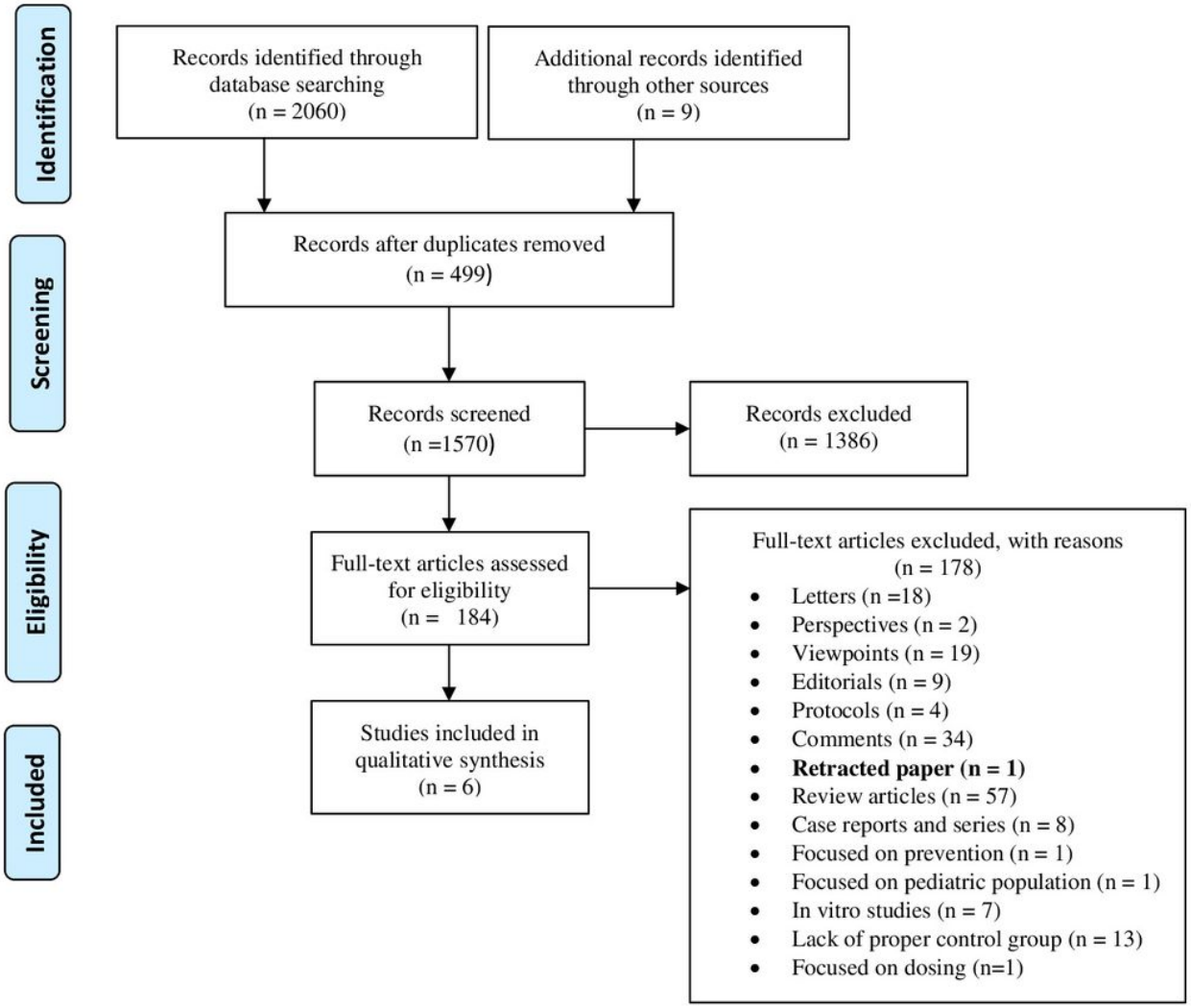

Figure 2

Flow chart for study design

Figure 3: Forest plot for risk ratios and risk differences regarding death HCQ+AZT versus HCQ

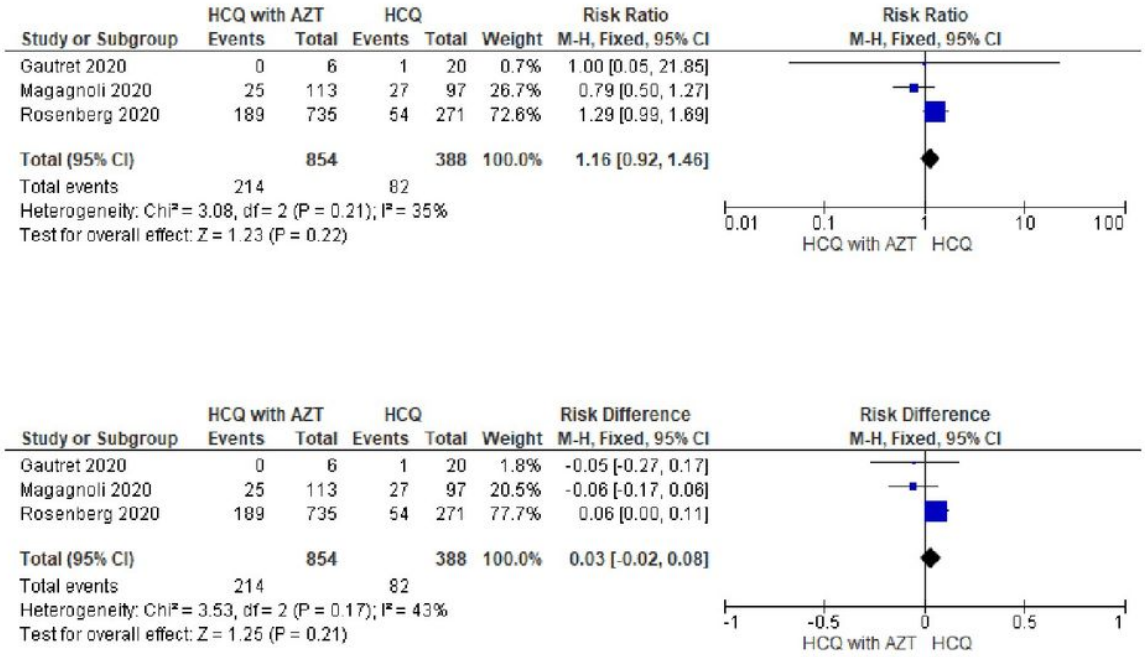

Figure 3

Forest plot a

Figure 4: Forest plot for odds ratios among HCQ+AZT versus HCQ: Intubation and Mechanical ventilation

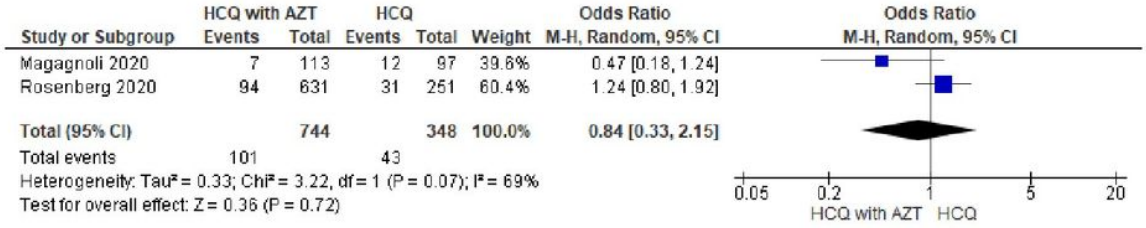

Figure 4

Forest plot b

Figure 5: Forest plot for odds ratios among HCQ+AZT versus HCQ: Arrhythmias and significant QT-prolongation

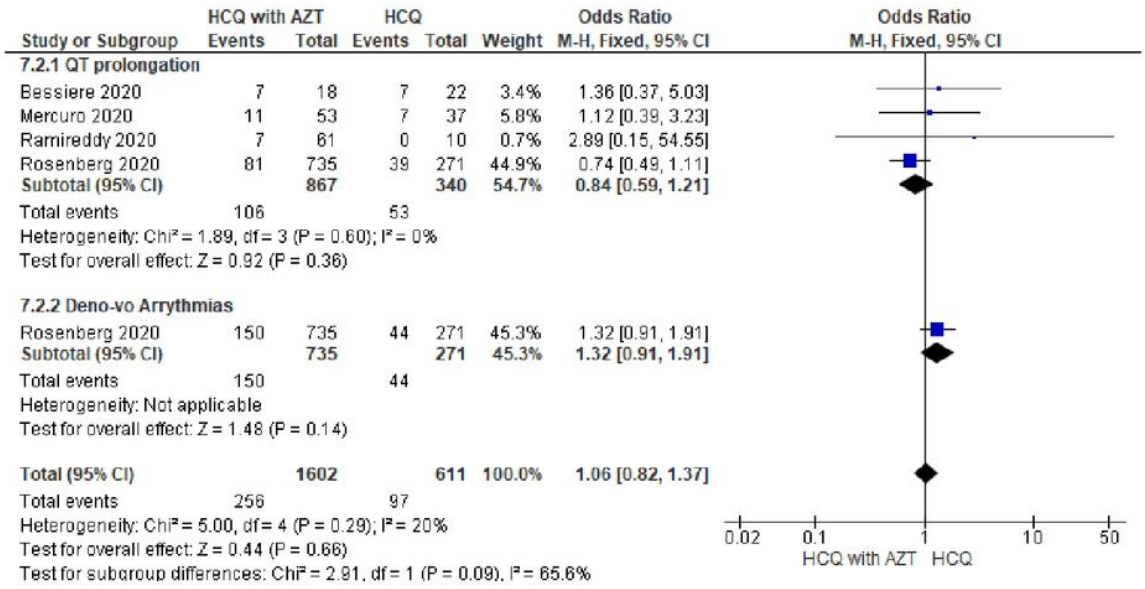

Figure 5

Forest plot c

Figure 6: Forest plot for odds ratios among HCQ+AZT versus HCQ: Critical QTc threshold and absolute ΔQTc ≥60ms

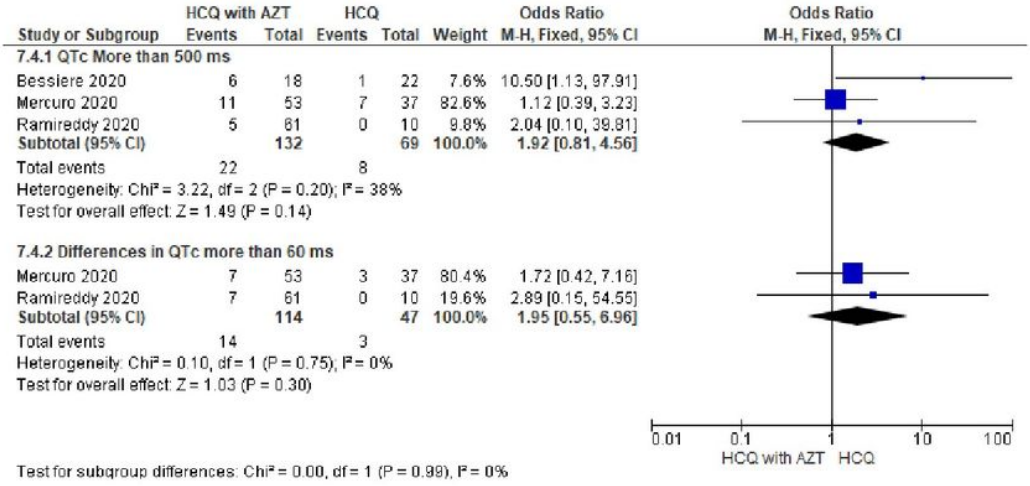

Figure 6

Forest plot d

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfile1Searchdetails.docx
- Supplementaryfile2Sensitivityanalysis.docx
- Supplementaryfile3Synthesiswithretractedstudy.docx
- Supplementaryfile4Prismachecklist.docx
- Supplementarytable1NHLBIqualityassessmenttool.docx
- Supplementarytable2NHLBIqualityassessmenttool.docx
- Supplementarytable3Clinicaltrials.docx