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# Hydroxychloroquine Causes QT Prolongation but does not Cause Ventricular Arrhythmia in COVID-19 Patients: A Meta-analysis

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## ABSTRACT

### BACKGROUND

Hydroxychloroquine is widely used to treat malaria and autoimmune diseases. Many studies investigating its effectiveness have raised concerns about safety pertaining primarily to cardiac arrhythmias and, specifically, the problem of QT prolongation in patients with COVID-19 infection.

### OBJECTIVE

To examine the rate of QTc interval prolongation and ventricular arrhythmias (VA) in patients with COVID-19 receiving hydroxychloroquine or chloroquine alone or in combination with azithromycin.

### METHOD

Medline and Embase databases were searched for studies of COVID-19 patients treated with hydroxychloroquine or chloroquine with and without azithromycin. Using meta-analytic techniques, the rate of QTc prolongation and VA were calculated using random-effect model and double-arcsine transformation of reported rates.

### RESULT

Twenty-two studies (3,636 patients) met inclusion. Hydroxychloroquine or chloroquine as a single drug or, in addition to azithromycin, resulted in QTc prolongation in 10.9% (6.2% - 16.6%) of patients. QTc increase was more pronounced in studies that included older patients with more severe disease and those with co-morbidities of hypertension, renal failure and diabetes. VA were rare and occurred only in 0.2% of patients and in only 34% of studies.

### CONCLUSION

Although hydroxychloroquine use is associated with a non-negligible risk of QTc prolongation in patients with COVID-19, the rate of VA remains low.

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**KEYWORDS**

COVID-19; Hydroxychloroquine; QT interval; Ventricular arrhythmias; Meta-analysis; Ion channels/membrane transport

## ABBREVIATIONS

HCQ: Hydroxychloroquine; CQ: Chloroquine, AZ: Azithromycin, TdP: Torsades Des Pointes, VA: Ventricular Arrhythmia

## INTRODUCTION

Hydroxychloroquine (HCQ), and its predecessor chloroquine (CQ), are widely used aminoquinolines initially introduced for malaria prophylaxis and with action against autoimmune disorders including rheumatoid arthritis or lupus erythematosus [1]. Their side-effect profile in these circumstances is well-known and verified with over 70-years of use. These drugs are considered safe even during pregnancy and lactation [1]. The most common side effects of HCQ and CQ are gastrointestinal and cutaneous. The side-effects are considered mild and disappear with drug discontinuation. The most serious adverse effect is retinopathy that may develop in up to 1% of patients after 5 years - 7 years of use. Cardiac side effects are rare and include QT interval prolongation due to $IK_r$ blockade and a very rare incidence of Torsades des pointes (TdP) [2]. Other cardiac complications are extremely rare [3].

The incidence of QT prolongation in patient populations with autoimmune disease is low. Hooks et al. retrospectively studied the electrocardiograms of 819 patients treated with HCQ for rheumatologic diseases and found the incidence of QTc prolongation of above 500 msec to be 1.5% over an average of 2.75 years of follow-up. This rate was slightly higher at 3.9% when patients who had either prolongation of QTc >15% or an on-treatment QTc >500 ms were included [4].

The renewed interest towards HCQ and CQ was recently sparked by the COVID-19 pandemic. Despite contradictory results, some of the existing laboratory and early clinical evidence indicated that these drugs may be effective against the novel coronavirus and could be repurposed [5]. However, several subsequent studies have failed to confirm the initial findings on efficacy [6,7]. Conflicting results on the rate of QT prolongation and ventricular arrhythmias (VA) have been reported in studies of HCQ/CQ in patients with COVID-19 [8,9]. HCQ is being widely used for the treatment of infectious and rheumatological conditions including in those infected with COVID-19, underlining the importance of understanding its cardiac side effect profile in this population.

Cardiac complications with severe COVID-19 infections that include myocarditis, heart failure and arrhythmias have been reported in up to 23% of patients [10]. A sicker ICU patient population is more prone to QT prolongation due to higher likelihood of co-morbidities, electrolyte disturbances, and underlying cardiomyopathy even in the absence of HCQ/CQ administration [11,12]. It is unclear whether the knowledge gained with these drugs over the previous 70 years can be applied to COVID-19 patient population at different stages of severity.

Different HCQ/CQ dosing regimens and combinations with other QT prolonging drugs, such as, azithromycin have been used in COVID-19. Their impact, as well as the influence of other factors on QT prolongation and arrhythmias remains unclear. We performed a meta-analysis of the existing data with a particular eye towards the incidence and severity of QT prolongation, development of VA with either HCQ or CQ alone, or combined with other QT prolonging regimens.

## METHODOLOGY

A complete literature search of Medline and Embase was performed using main keywords for CQ and HCQ in conjunction with CDC search guide for COVID-19 (details given in the Supplemental Appendix 1) [13]. All articles from 2019-2020 were included. To find other more recent studies, a search of medRxiv, ClinicalTrials.gov, and the ICTRP (International Clinical Trials Registry Platform) database were performed. Searches were performed on June 27, 2020. After eliminating duplicate papers, a total of 385 papers were reviewed and eligible articles were selected by two independent reviewers (PK, MO). Relevant data was extracted by all authors for analysis. Newcastle-Ottawa quality assessment scale (NOS) was used for assessment and grading of the included studies [14]. The primary end-points of interest included incidence of significant QTc prolongation and VA as defined by each study and summarized in Table 1.

| # | Study | Medication | Location | #Analyzed | Study Population | Drug (Dosage) | Outcomes | Other Information |
|---|---|---|---|---|---|---|---|---|
| 1 | Mahévas et al. [6] | HCQ | France | 84 | Documented severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia that required oxygen but not intensive care. | HCQ (600 mg/day) | QTc prolongation >60 ms or >500 ms.† VA: Not mentioned. Drug discontinuation: 8/80 | - |
| 2 | Tang et al. [7] | HCQ ± Antiviral therapy | China | 70 | Confirmed hospitalized SARS-CoV-2 infected patients (99% mild to moderate severity) | HCQ at a loading dose of 1200 mg/day for 3 days followed by 800 mg/day | No QT prolongation No arrhythmias (no direct mention of VA) | - |
| 3 | Gautret et al. [32] | HCQ + Azithromycin | France | 80 | Patients with PCR-documented SARS-CoV-2 RNA from a nasopharyngeal sample (97.3% mild to moderate severity) | HCQ 600 mg/day + AZ 500 mg on day 1 followed by 250 mg/day for 4 days | QTc and VA not mentioned. Medication discontinued in 1 patient | - |
| 4 | Borba et al. [22] | (High Dose) CQ + Azithromycin + Antiviral therapy (Oseltamivir) | Brazil | 37 | Hospitalized patients with clinical suspicion of COVID-19 and high severity symptoms | CQ 600 mg BID for 10 days | QTcF >500 ms VA (type not mentioned) Discontinuation rate not mentioned. | - |
| 5 | Borba et al. [22] | (Low Dose) CQ + Azithromycin + Antiviral therapy (Oseltamivir) | Brazil | 36 | Hospitalized patients with clinical suspicion of COVID-19 and high severity symptoms | CQ 450 mg BID on day 1 and then daily for 4 days | QTcF >500 ms VA (type not mentioned) Discontinuation rate not mentioned. | - |
| 6 | Mercuro et al. [33] | HCQ | USA | 37 | Hospitalized patients with COVID-19 pneumonia | HCQ 400 mg BID on day 1, then 400 mg/day on days 2-5 | Increased QTc of 60 ms (3%) or prolongation >500 ms (19%)† No VA 11% discontinuation rate due to QTc prolongation or adverse drug reactions. | Risk factor for QT prolongation included use of loop diuretics, baseline QTc≥450 ms, ≥2 SIRS criteria, ICU status, Tisdale score ≥11 |
| 7 | Mercuro et al. [33] | HCQ + Azithromycin | USA | 53 | Hospitalized patients with COVID-19 pneumonia | HCQ 400 mg BID on day 1, then 400 mg/day on days 2 through 5 + AZ | Increased QTc of 60 ms (13%) or prolongation beyond 500 ms (21%)† 1 case of TdP and same patient had other ventricular arrhythmia, 1 patient discontinued therapy due to TdP | Risk factor for QT prolongation included use of loop diuretics, baseline QTc≥450 ms, ≥2 SIRS criteria, ICU status, Tisdale score ≥11 |
| 8 | Boulware et al. [9] | HCQ | Canada | 414 | Post exposure prophylaxis of adults with exposure to someone with confirmed Covid-19 | HCQ 800 mg once, followed by 600 mg in 6-8 hours, then 600 mg/day for 4 additional days | No ECG monitoring. No serious medication-related adverse reactions or cardiac arrhythmias. Medication discontinuation mostly due to adverse drug reaction rate was 24.6%. | |
| 9 | Chorin et al. [9] | HCQ + Azithromycin | USA/Brazil | 251 | Hospitalized Covid-19 patients | HCQ 400 mg BID for 1 day followed by 200 mg BID for 4 days + AZ 500 mg/day for 5 days | QTc prolongation to >500 ms in 13% JTc>410 ms occurred in 14% Change in QTc>60 ms occurred in 20%† 1 case of TdP, 7 patients required discontinuation of therapy | Predictors of QT prolongation included concomitant amiodarone use, prolonged baseline QTc, and renal dysfunction. |
| 10 | Saleh et al. [34] | HCQ | USA | 82 | Hospitalized Covid-19 patients | HCQ 400 mg BID for one day followed by 200 mg BID for 4 days | 7 patients developed QTc>500 ms 2 patients developed monomorphic VT. | 5% of patient received Chloroquine. 40.3% took other QT |

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| | | | | | | | | prolonging medications.<br><br>No Tdp. |
| 11 | Saleh et al. [34] | HCQ + Azithromycin | USA | 119 | Hospitalized Covid-19 patients | 400 BID for one day followed by 200 mg BID for 4 days + AZ 500 mg by mouth or intravenous daily for 5 days | 11 patients developed QTc>500 ms<br>6 patients developed monomorphic VT | No Tdp.<br><br>40.3% took other QT prolonging medications. |
| 12 | Molina et al. [35] | HCQ + Azithromycin | France | 11 | Consecutive hospitalized Covid-19 patients | HCQ 600 mg/day for 10 days + AZ 500 mg day 1 and 250 mg days 2-5) | 1 patient with QTc prolongation >60 ms resulting in therapy discontinuation. †<br>Arrhythmia not reported. | |
| 13 | Million et al. [36] | HCQ + Azithromycin | France | 1061 | Individuals with PCR-documented SARS-CoV-2 RNA from a nasopharyngeal sample | HCQ 200 mg TID for 10 days + AZ 500 mg on day 1 followed by 250 mg/day for 4 days | 9 patients had QTc >60 ms but none >500 ms<br>No arrhythmias<br>3 patients stopped therapy due adverse drug reaction. | |
| 14 | Ramireddy et al. [23] | HCQ + Azithromycin | USA | 61 | Hospital admitted patients with confirmed COVID-19 infection or under investigation who received AZ, HCQ, or both | HCQ 400 mg BID on day 1 then 200 mg BID on days 2 to 5 + AZ 500 mg/day or 500 mg on day 1 followed by 250 mg/day on days 2-5 | QTc ≥500 ms (if QRS <120 ms), QTc ≥550 ms (if QRS ≥120 ms), or change in QTc ≥60 ms occurred in 7 patients. †<br>No TdP | Higher Tisdale scores or Elixhauser comorbidity indexes were not associated with increased risk of QTc prolongation.<br><br>Men had significantly higher mean QTc prolongation than women. |
| 15 | Ramireddy et al. [23] | HCQ | USA | 10 | | | QTc ≥500 ms (if QRS <120 ms), QTc ≥550 ms (if QRS ≥120 ms), or change in QTc ≥60 ms occurred in 0 patients. †<br>No TdP | Higher Tisdale scores or Elixhauser comorbidity indexes were not associated with increased risk of QTc prolongation.<br><br>Men had significantly higher mean QTc prolongation than women. |
| 16 | Bessiere et al. [37] | HCQ | France | 22 | ICU admitted patients with Covid-19 | HCQ 200 mg BID for 10 days | 1 out of 22 patients developed QTc ≥500 ms.<br>5 patients had QTc prolongation >60 ms (abstracted from chart). †<br>No VA, including TdP was recorded. | 50% received other QT prolonging medications.<br><br>Among all patients, the antiviral treatment was discontinued in 7 patients (17.5%) following ECG abnormalities and in 10 (25%) for acute renal failure. |
| 17 | Bessiere et al. [37] | HCQ + Azithromycin | France | 18 | ICU admitted patients with Covid-19 | HCQ 200 mg BID for 10 days + AZ 250 mg/day for 5 days | 6/18 developed QTc ≥500 ms<br>2 had QTc prolongation >60 ms (abstracted from chart)*<br>No VA, including TdP was recorded | 50% received other QT prolonging medications.<br><br>Among all patients, the antiviral treatment was discontinued in 7 patients (17.5%) following ECG abnormalities and in 10 (25%) for acute renal failure. |
| 18 | Rosenberg et al. [24] | HCQ + Azithromycin | USA | 735 | A random sample of Covid-19-confirmed hospitalized patients | Majority of patients received HCQ 400 mg BID on day 1 followed by 200 mg BID thereafter + AZ 500 mg/day | 81 patients (11%) developed QT prolongation*<br>15% cardiac arrest<br>Details of cardiac arrhythmias not provided | |
| 19 | Rosenberg et al. [24] | HCQ | USA | 271 | A random sample of Covid-19-confirmed hospitalized patients | Most patients received HCQ 400 mg BID on day 1 followed by 200 mg BID thereafter | 39 (14.4%) developed QT prolongation<br>13.7% cardiac arrest<br>Details of cardiac arrhythmias not provided | |
| 20 | Maraj et al. [21] | HCQ + Azithromycin | USA | 91 | Consecutive symptomatic patients hospitalized for COVID-19 infection and received hydroxychloroquine/azithromycin | Dosages not mentioned. | 20 patients (23%) developed QT prolongation<br>2 patients developed VA (1 patient with TdP and 1 with polymorphic VT > VF) | Concurrent QT-prolonging medication was administered in 42% of patients.<br><br>Age >75 years, prolonged baseline QTc (> 460 ms), impaired renal function (GFR < 60 ml/min), and concurrent use of a high risk QTc-prolonging drug were each associated with excessive QTc prolongation. |
| 21 | Cipriani et al. [38] | HCQ + Azithromycin | Italy | 22 | All patients aged <80 years admitted for COVID-19 and received hydroxychloroquine and azithromycin for at least 3 days. | HCQ 200 mg BID + AZ 500 mg/day for at least 3 days | 4 patients had QTc ≥480 ms and one >500 ms<br>1 patient had a run of NSVT (5 beats) | Patients with other QT prolonging drugs were excluded. |

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|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Patients with QTc ≥ 480 ms showed higher values of AST and ALT. |
| 22 | Bun et al. [39] | HCQ + Azithromycin | France | 71 | Patients who were hospitalized for COVID-19 infection and received treatment with combination HCQ+AZ | HCQ 200 mg TID for 10 days + AZ 500 mg on day one followed by 250 mg daily for 4 days | 2 patients (2.8%) developed QTc≥500 ms No drug-induced life-threatening VA or death | 2 patient stopped treatment as QTc prolonged >500 ms.<br><br>Patients taking other QT prolonging medications (mostly), channelopathy, severe structural heart disease, and other ECG abnormalities were excluded. |

**Table 1:** Summary and characteristics of included studies.

†Changes in QTc were measured by comparison to the baseline ECG before initiation of therapy. ALT (Alanine Transaminase), AST (Aspartate transaminase), AZ (Azithromycin), CQ (Chloroquine), GFR (Glomerular Filtration Rate), HCQ (hydroxychloroquine), NSVT (Non-Sustained Ventricular Tachycardia), TdP (Torsade de Pointes), VA (Ventricular arrhythmia), VF (ventricular Fibrillation), VT (Ventricular Tachycardia).

The definition of disease severity was based on the seventh version of the Chinese guideline for the management of COVID-19 [15]. Mild disease included patients with mild symptoms but no manifestation of pneumonia on imaging. Moderate disease included patients with fever, cough, sputum production, and other respiratory tract or non-specific symptoms along with manifestation of pneumonia on imaging but no signs of severe pneumonia defined as the presence of $SaO_2/SpO_2$ <94% on room air or a $PaO_2$ to $FiO_2$ ratio of ≤300. Studies which were comprised of >50% of patients with severe disease were categorized as "severe" and the rest as "mild-moderate". For conversion of CQ to HCQ equivalent dose, the following conversion formula was used: Chloroquine phosphate 500 mg is equivalent to 300 mg chloroquine base and hydroxychloroquine sulfate 200 mg is equivalent to 155 mg hydroxychloroquine base [16].

***Statistical Analysis***

Total number of patients in each category of treatment as well as the number of events were collected for calculation of event rates. The Freeman-Tukey double arcsine transformation was performed which computed the weighted pooled estimate. Statistical tests for heterogeneity using Cochrane's Q and I-squared statistics was significant for all the comparisons at a P value of 0.05 level. Given the high degree of heterogeneity, dersimonian and laird method was used for fitting the random effects model for pooled-parameter estimation.

If results were reported by the original studies as median and interquartile ranges, means and standard deviations were derived using the method described by Wan et al. [17].

Meta-regression was performed to investigate sources of heterogeneity within different subgroups based on age, gender, medication combination, medication dosage, frequency of comorbidities, racial composition and disease severity. A generalized linear logistic regression model for the binomial family with a logit link was used to allow for inclusion and meta-regression of relevant independent continuous variables and formal testing of heterogeneity between subgroups of categorical variables. A likelihood test model with and without categorical independent variables defining each subgroup was used to formally test for heterogeneity between subgroups.

Statistical analysis was performed using metaprop and metapreg functions in stata software (stata/IC 15.1 for Mac, Stata Corp LLC), OpenMetaAnalyst, and R Programming Software (Version 1.2.1335) [18]. WebPlotDigitizer software (version 4.3) was used to extract data that was only available in the published graphs [19].

## RESULTS

There were 22 studies (3 randomized trials and 19 observational studies) included in the meta-analysis comprising 3636 patients. Of the 511 papers that met inclusion criteria, studies that did not report any of the primary outcomes, were not peer-reviewed, or were withdrawn after publication, were excluded (Figure 1).

### *HCQ/CQ and the Rate of QTc Prolongation/VA*

HCQ/CQ as a single agent or, in addition to azithromycin (AZ) given for COVID-19 infection, was associated with significant QTc interval prolongation in 10.9% (6.2 - 16.6) of patients (Figure 2). Although, there was a trend towards higher rate of QTc prolongation with drug combinations CQ/AZ, followed by HCQ/AZ and HCQ, but this was not statistically significant (P = 0.84).

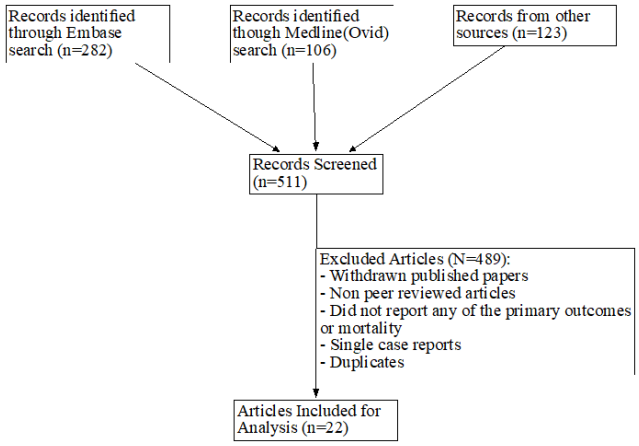



**Figure 1:** PRISMA diagram of included studies.

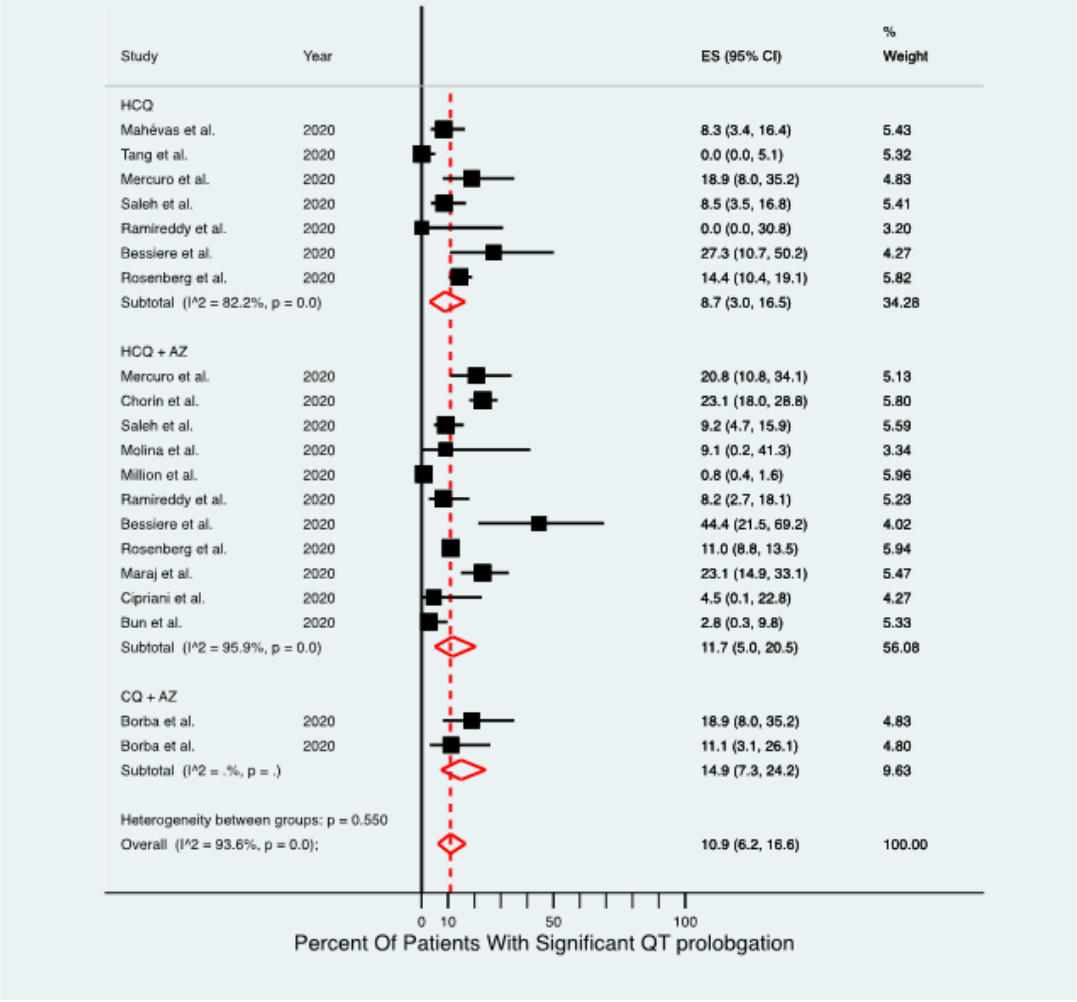



**Figure 2:** Rate of clinically significant QTc prolongation according to medication combination.

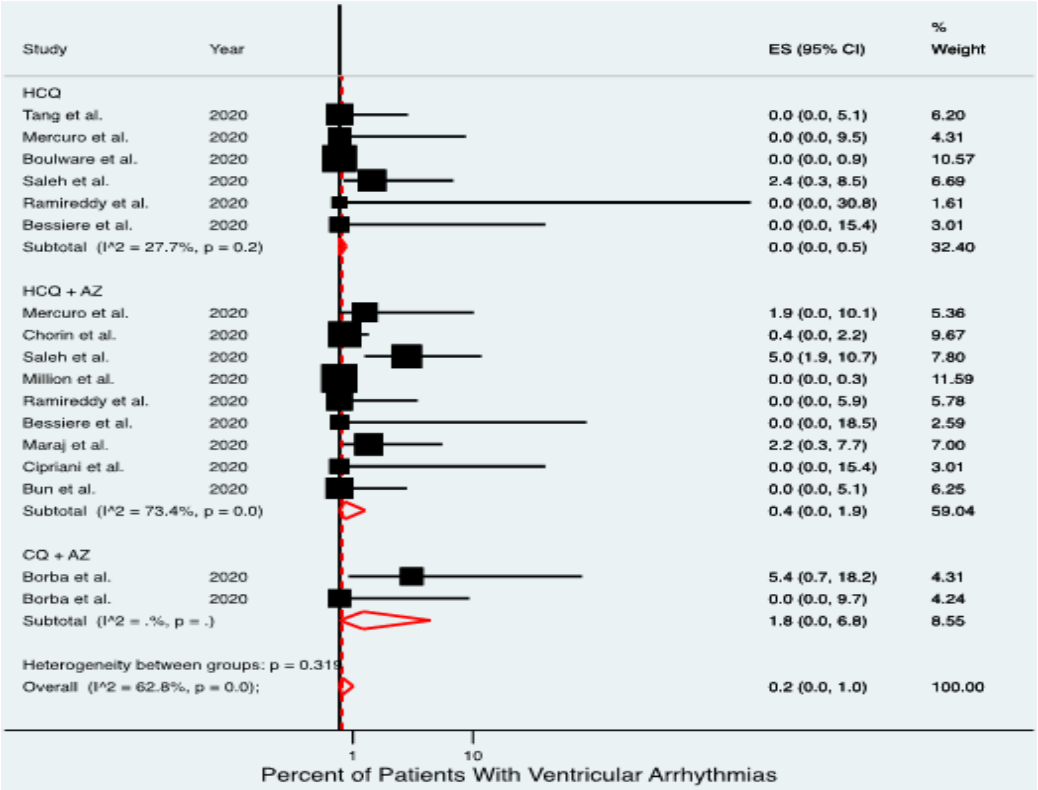
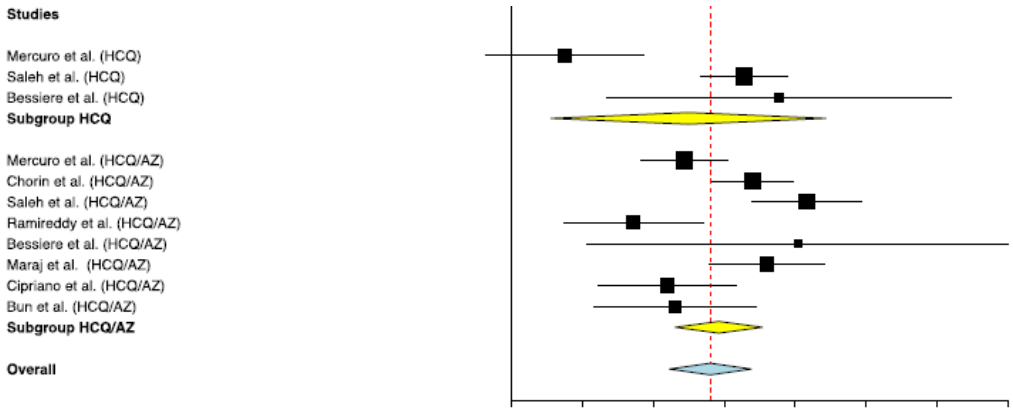


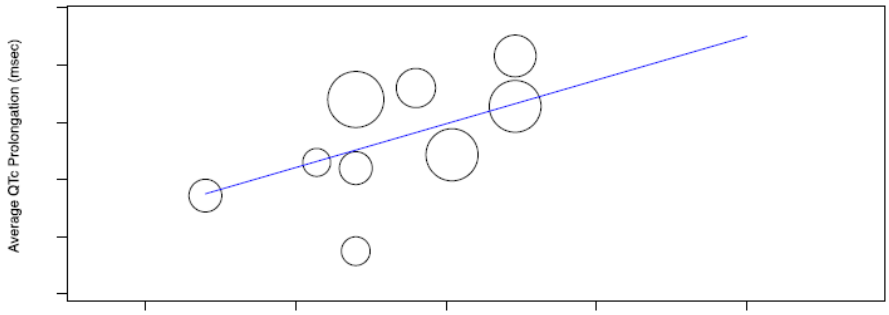

**Figure 3:** Rate of ventricular arrhythmias according to medication combination.

| # | Study | Medication | QTc Change | Fatal Arrhythmia | Other |
|---|---|---|---|---|---|
| 1 | Mahévas [1] | HCQ | - | - | 9/84 deaths. Causes of death not identified. |
| 2 | Tang[2] | HCQ ± Antiviral | - | No fatal arrhythmias. | No death |
| 3 | Gautret[3] | HCQ+Azithromycin | - | - | 1 death but cause of death not identified. |
| 4 | Borba[4] | (High Dose) CQ + Azithromycin + Antiviral (Oseltamivir) | - | 2/37 ventricular arrhythmia before death but not TdP. One died on the same day as VA and one 3 days later. | "No clear association was seen between the first day of prolonged QTc and day of death. |
| 5 | Borba[4] | (Low Dose) CQ + Azithromycin + Antiviral(Oseltamivir) | - | - | No clear association was seen between the first day of prolonged QTc and day of death. |
| 6 | Mercuro[5] | HCQ | Change from median (IQR) of 5.5 (-14-31). N=37 | No TdP during therapy. | 4 patients died. No cases of TdP during therapy. One patient had TdP and other VA 3 days after discontinuation of therapy. |
| 7 | Mercuro[5] | HCQ + Azithromycin | Change from median (IQR) of 23 (10-40). N=53 | No TdP during therapy. | - |
| 8 | Boulware[6] | HCQ | - | No arrhythmia of death reported. | - |
| 9 | Chorin[8] | HCQ + Azithromycin | Change from 439±29 to 473±36 msec. N=251. | 1/251 patient developed TdP requiring DCCV. | 44/251 died from non-arrhythmic causes. 8 patients discontinued therapy because of QT prolongation. |
| 10 | Saleh[7] | HCQ | Change of 32.8±28.6 msec. N=82. | 2/82 patients with monomorphic VT (1 case was non-sustained). Unknown whether QTc was prolonged. No cases of TdP or arrhythmic death. | - |
| 11 | Saleh[7] | HCQ + Azithromycin | Change of 41.6±42.7 msec. N=119. | 6/119 patients had monomorphic VT (all non-sustained). No cases of TdP or arrhythmic death. | - |
| 12 | Molina[9] | HCQ + Azithromycin | - | No VA reported. | 1/11 deaths. 1/11 drug discontinuation due to QTc prolongation. |
| 13 | Million[9] | HCQ + Azithromycin | - | No TdP or arrhythmic deaths. | All deaths due to respiratory failure (8/1061). |
| 14 | Ramireddy[10] | HCQ + Azithromycin | Change of 17.2±39 msec. N=39. | No TdP or lethal arrhythmias. | |
| 15 | Ramireddy[10] | HCQ | Not mentioned | No TdP or lethal arrhythmias. | |
| 16 | Bessiere[11] | HCQ | Change from median (IQR) of 398 (384-416) to 437(404-470) msec. Derived from digitization of graph. N=22 | No ventricular arrhythmias observed. | |
| 17 | Bessiere et al.[11] | HCQ+Azithromycin | Change from median (IQR) of 431 (414-456) to 480 (437-505) msec. Derived from digitization of graph. N=18 | No ventricular arrhythmias observed. | |
| 18 | Rosenberg[12] | HCQ+Azithromycin | - | 189/735 deaths. 35/118 cardiac arrests. 150/735 arrhythmias. | The details of cardiac arrest and arrhythmias not mentioned. |
| 19 | Rosenberg[12] | HCQ | - | 54/271 deaths. 14/38 cardiac arrests. 44/271 cardiac arrhythmias. | The details of cardiac arrest and arrhythmias not mentioned. |
| 20 | Maraj[13] | HCQ+Azithromycin | Change from 437±25 to 473±31 msec. (n=91 patients). | 6/21 death in patients with significant QTc prolongation. 2 cases of TdP and VF. | Outcome of death in patients with TdP and VF not mentioned. |
| 21 | Cipriani [14] | HCQ+Azithromycin | Change from median(IQR) of 426(403-447) to 450 (416-476) msec. (n=126 patients). | No cases of SCD, fatal arrhythmia or syncope. 1 case of NSVT. | - |
| 22 | Bun[15] | HCQ+Azithromycin | Change from 415±29 to 438± 40 msec (n=71 patients) | No drug induced arrhythmia or death | 2/71 patients discontinued therapy because QTc prolongation. |

**Supp Table 1:** Summary of the effects of HCQ on QTc prolongation and fatal arrhythmias.
CQ: Chloroquine; DCCV: Direct Current Cardioversion; HCQ: Hydroxychloroquine; IQR: Interquartile Range; NSVT: Non-Sustained Ventricular Tachycardia; SCD: Sudden Cardiac Death; VA: Ventricular Arrhythmia; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia




**Supp Figure 1:** The effect of HCQ on mean QTc prolongation.




**Supp Figure 2:** The effect of prevalence of diabetes and mean QTc prolongation.

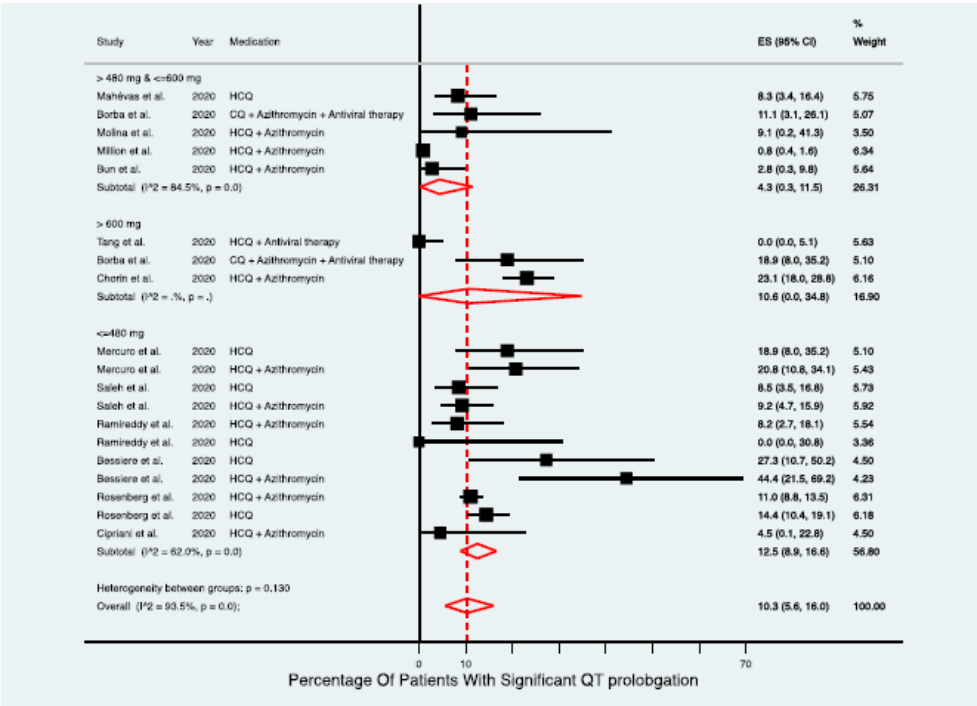
Average rate of VA was 0.2% (0% - 1%) in patients treated with HCQ/CQ as a single agent or in combination with AZ. VA were observed in 0% (0% - 0.5%) of patients treated with HCQ as a single agent and in 0.4% (0% - 1.9%) and 1.8% (0% - 6.8%) of patients treated with combination of HCQ + AZ or CQ + AZ, respectively, with no statistically significant difference between various drug combinations (P = 0.51) (Figure 3). Of note, 64% of studies did not report any VA.

The amount of QTc prolongation after HCQ, with and without AZ, was extracted from 8 studies (Supplemental Appendix 2, Table 1). HCQ use was associated with an average QTc prolongation of 28.0 msec (95% CI of 22.2 to 33.8) (Supplemental Appendix 2, Figure 1). There was no difference in QTc prolongation between studies using HCQ or HCQ/AZ combination (24.9 ± 9.9 and 29.2 ± 3.1, respectively). There was no relationship between QTc prolongation and average daily dose of HCQ, maximum daily dose of HCQ, or patient characteristics including age, gender, hypertension, coronary artery disease, heart failure or renal failure. There was an association of QTc prolongation with diabetes (P = 0.01) (Supplemental Appendix 2, Figure 2).

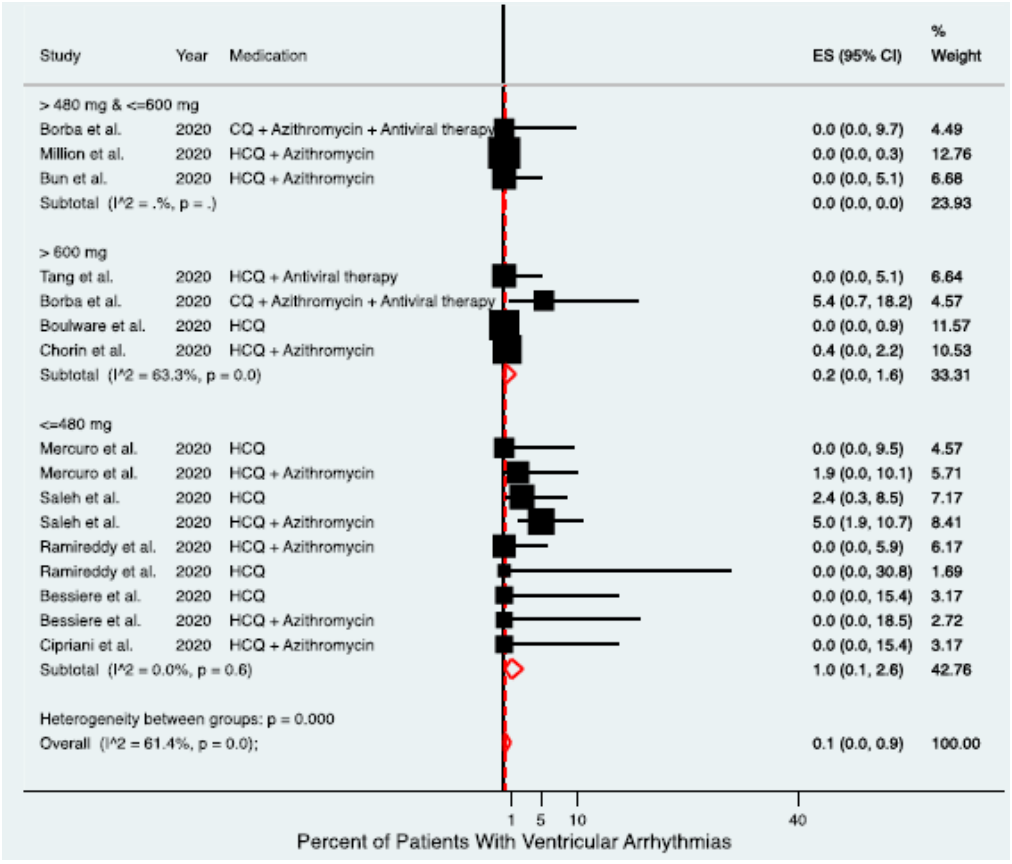
***HCQ Dose and the Rate of QTc Interval Prolongation/VA***

The average daily dose of HCQ in these studies ranged from 480 mg - 1200 mg (median 600 mg). Given the difference in HCQ dosage, the studies were grouped into low-dose (<480 mg/day), medium dose (480 mg/day -600 mg/day) and high-dose (>600 mg/day). When comparing low to medium and high-dose HCQ, no significant difference was found in the rate of QTc prolongation (P = 0.09): 12.5% (8.9% - 16.8%) *vs.* 4.3% (0.3% - 11.5%) *vs.* 10.6% (0% - 34.8%) but slightly higher rates of VA was seen at higher average daily dose of HCQ (1.0% (0.1% - 2.6%) *vs.* 0 % (0% - 0%) *vs.* 0.2 % (0% - 1.6%),

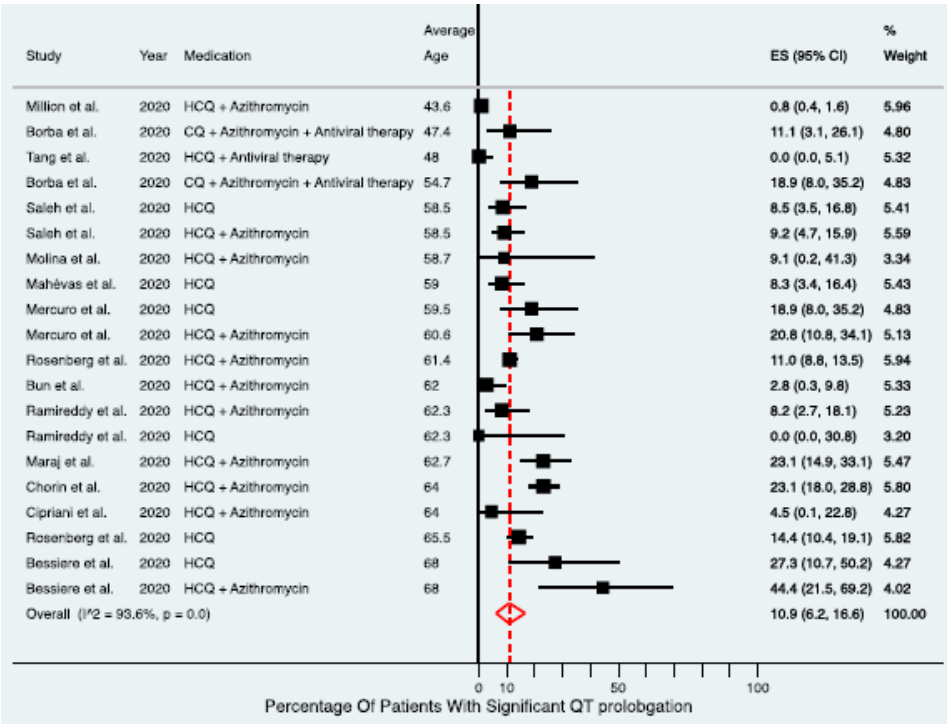
respectively (P = 0.02) (Supplemental Appendix 2, Figure 3 and Figure 4).



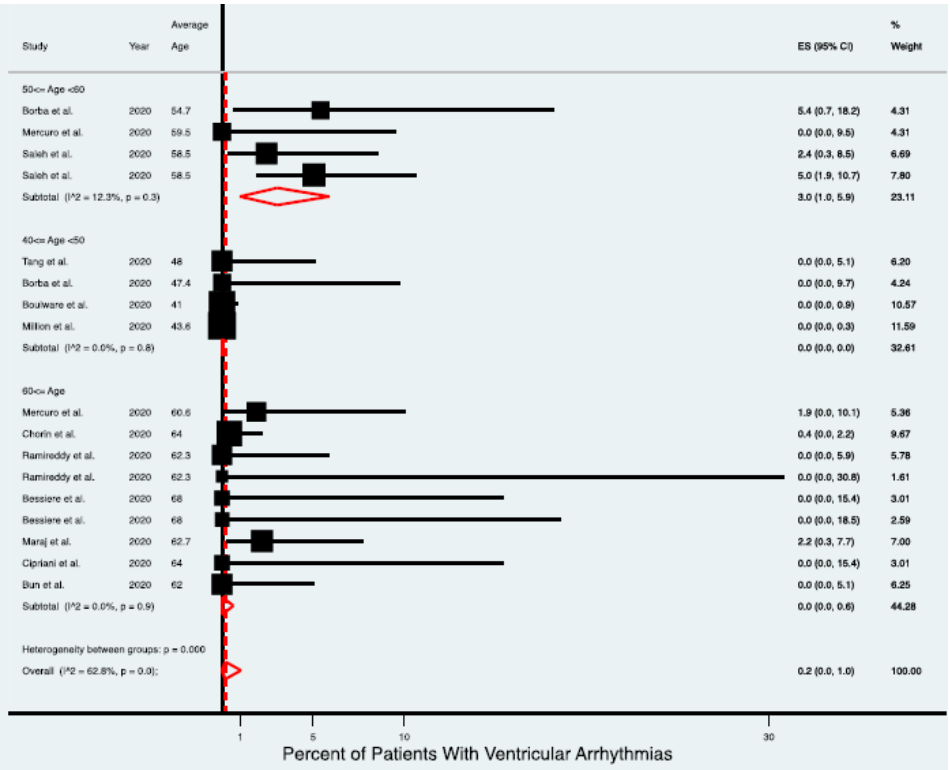

**Supp Figure 3:** HCQ dose and the rate of QTc interval prolongation.




**Supp Figure 4:** HCQ dose and the rate of ventricular arrhythmias.




**Supp Figure 5:** Age and the rate of significant QTc prolongation.




**Supp Figure 6:** Age and the rate of ventricular arrhythmia.

Studies were also categorized according to the loading dose of HCQ into three groups: ≤600 mg, >600 mg to ≤900 mg and ≥900 mg. The loading dose of HCQ did not correlate with the rate of QTc prolongation (P = 0.77). Of

2548 patients included in studies that reported occurrence of fatal or near-fatal arrhythmias, only 5 cases could be attributed to QTc prolongation. Borba et al reported 2 patients who developed a non-TdP ventricular arrhythmia before death and only one expired the same day [8]. Chorin et al. reported 1 case of TdP requiring cardioversion [20]. Maraj et al. reported 2 cases of TdP and VF [21]. Thus, the rate of fatal or near-fatal arrhythmias due to HCQ administration in patients with COVID-19 was 0.20%.

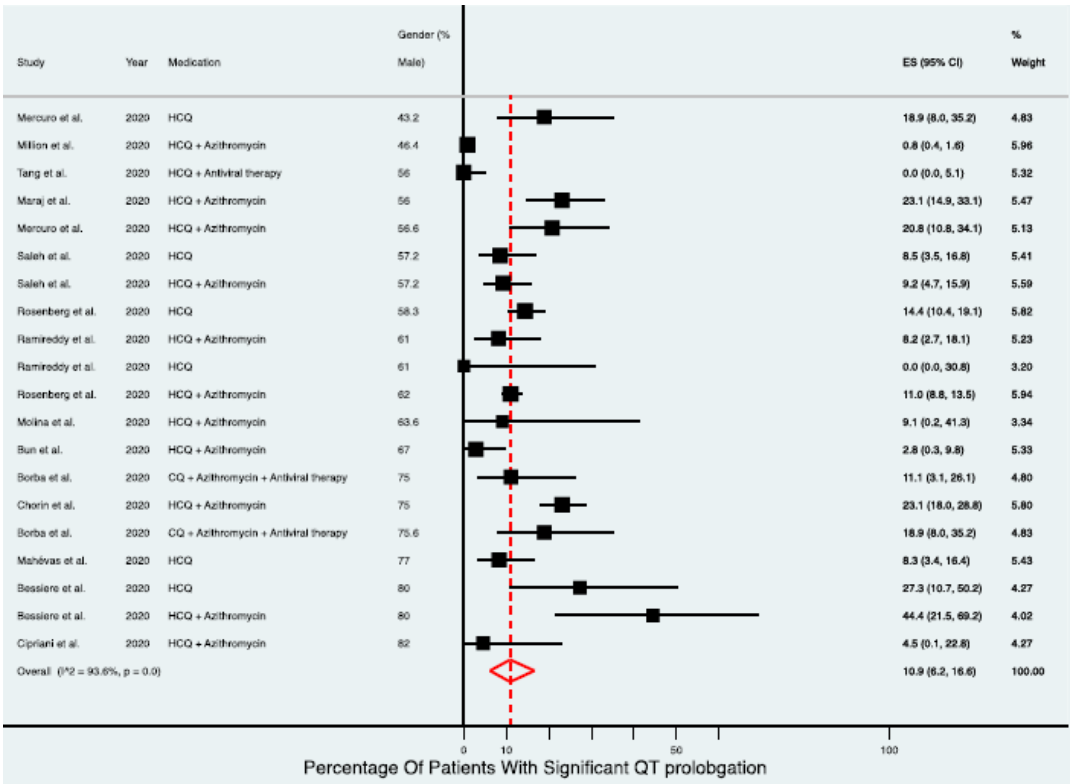
***The Effect of Age and Gender on the Rate of QTc Interval Prolongation/VA***

All studies were performed exclusively in adults (Median age: 60; Range: 41 years - 68 years, 63.3% male). A higher risk of significant (P <0.001) QTc prolongation was identified in older patients (Supplemental Appendix 2, Figure 5 and Figure 6). Patients in the 5th decade of life had higher rate of VA vs. younger and older patients (P <0.0001) (Supplemental Appendix 2, Figure 6) with the overall risk of VA remaining low.

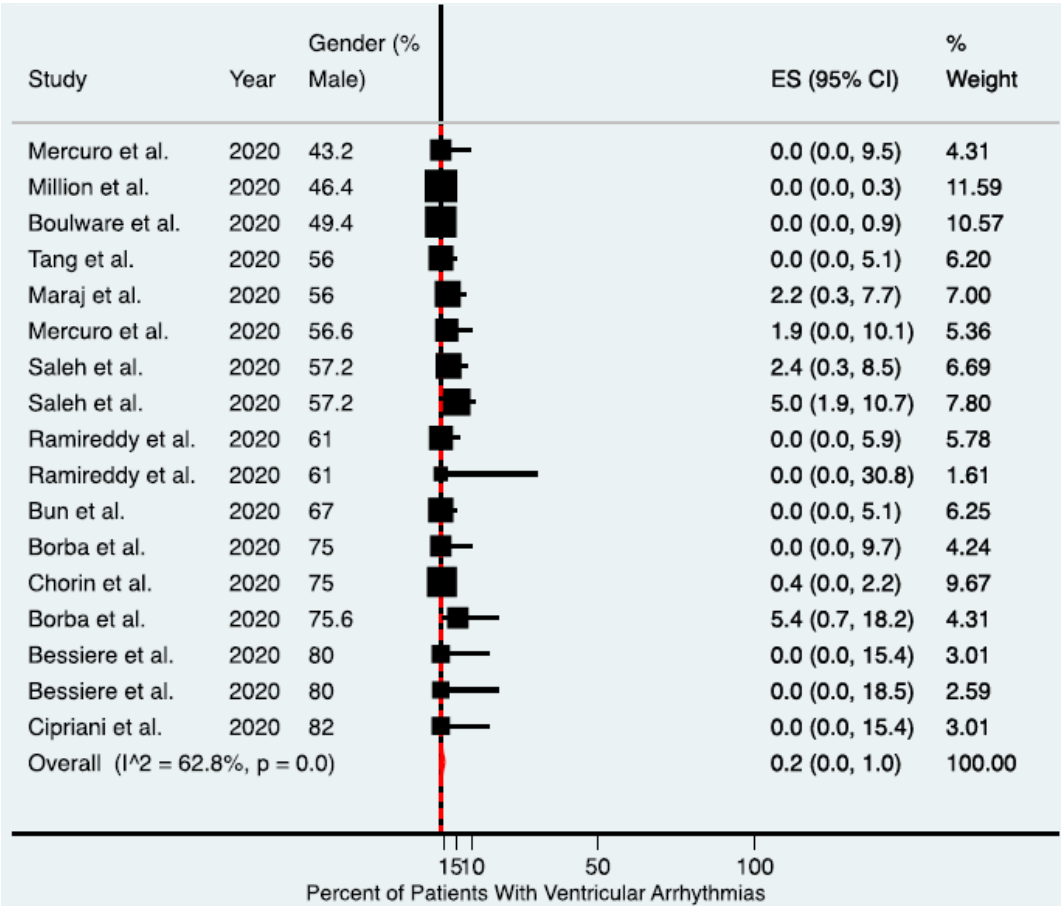
There was a trend towards higher rate of QTc prolongation in studies enrolling more male patients (P = 0.1) but there was no significant relationship between gender and incidence of VA (P = 0.99) (Supplemental Appendix 2) (Figure 7 and Figure 8).

***COVID-19 Disease Severity and the Rate of QTc Prolongation/VA***

All studies were grouped according to COVID-19 disease severity (see Methods for definitions of mild-moderate *vs.* severe disease). A higher rate of QTc prolongation was observed in patients with severe 13.1% (8.6% - 18.3%) *vs.* mild-moderate disease 4.3% (0.3% - 11.6%) (P = 0.013) (Figure 4 and Figure 5). There was also an increase in the rate of VA in severe disease (1.2% *vs.* 0%) (P <0.001) (Supplemental appendix 2, Figure 9).




**Supp Figure 7:** Gender and the rate of significant QTc prolongation.




**Supp Figure 8:** Gender and rate of ventricular arrhythmia.

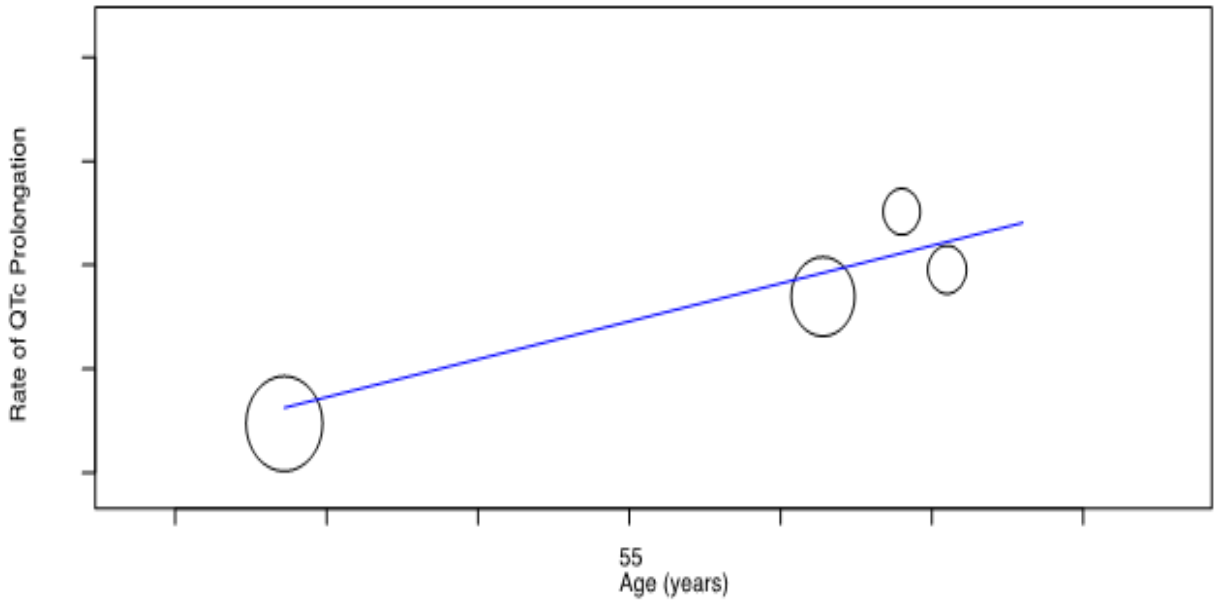



**Figure 4:** The effect of the average age of study population on the rate of significant QTc prolongation (rates were first transformed using Freeman-Tukey Double Arcsine method).

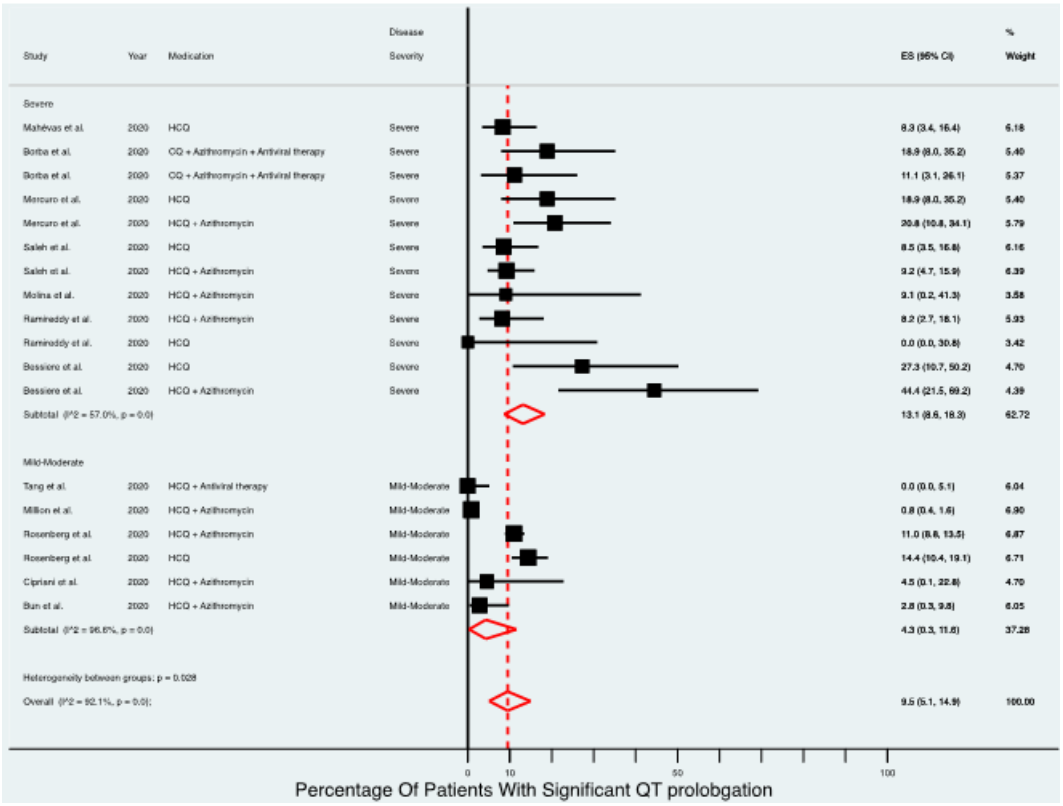
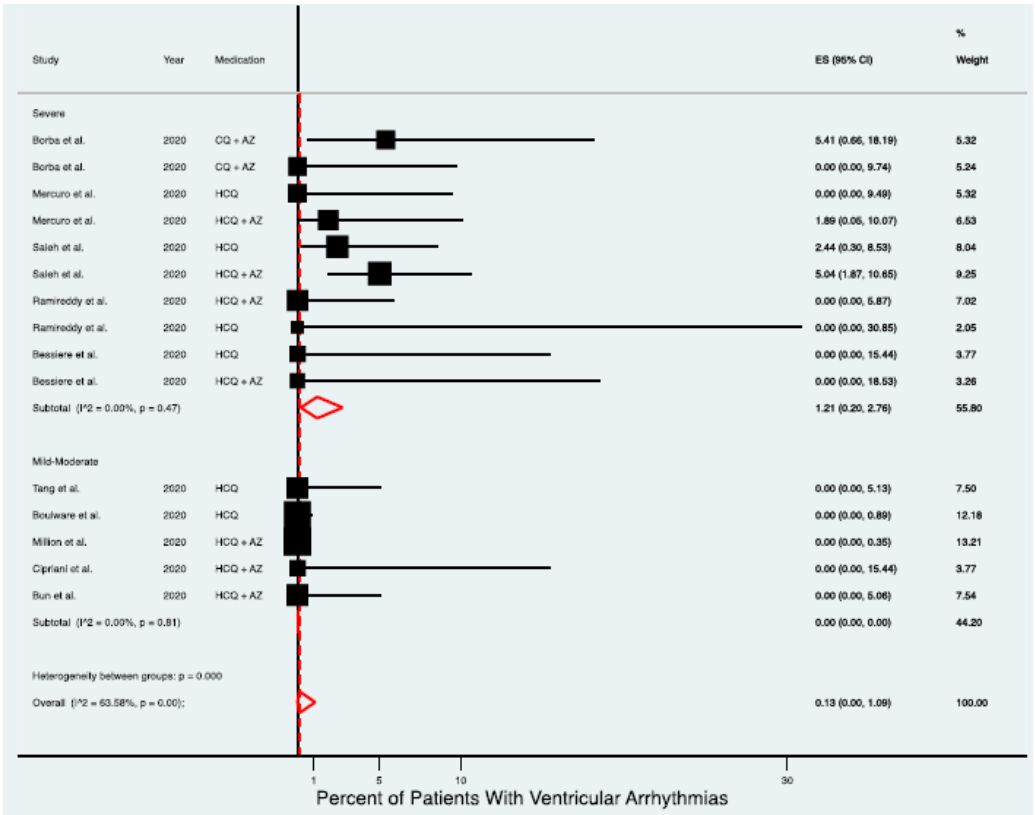


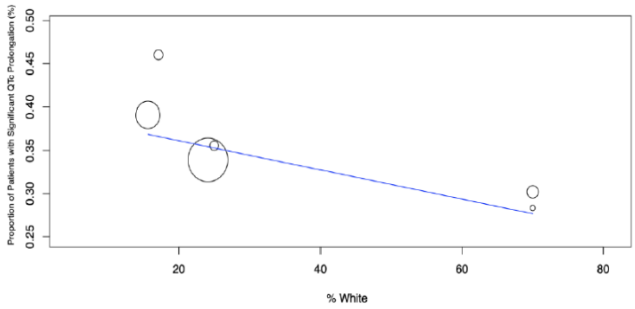

**Figure 5:** COVID-19 severity and the rate of significant QTc prolongation.



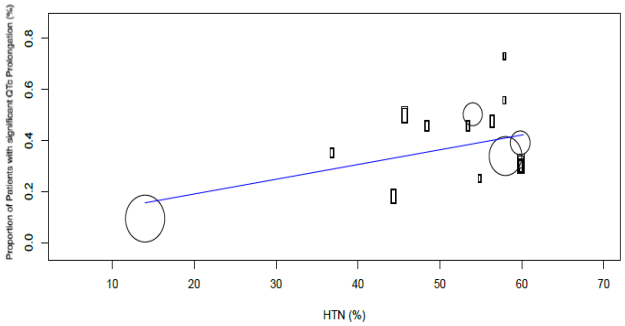

**Supp Figure 9:** COVID-19 severity and the rate of ventricular arrhythmia.

***Race and the Rate QTc Prolongation/VA***

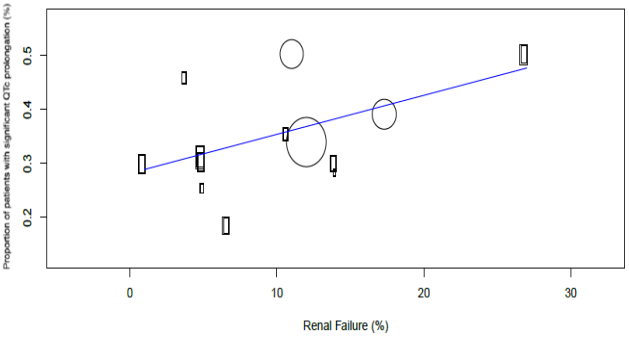
Only 3 studies reported data regarding race that could be used for analysis of the rate of QTc prolongation [22-24]. Using meta-regression, a higher percentage of patients identified as white was associated with a trend towards lower rates of QTc prolongation (P = 0.09) (Supplemental appendix 2, Figure 10).



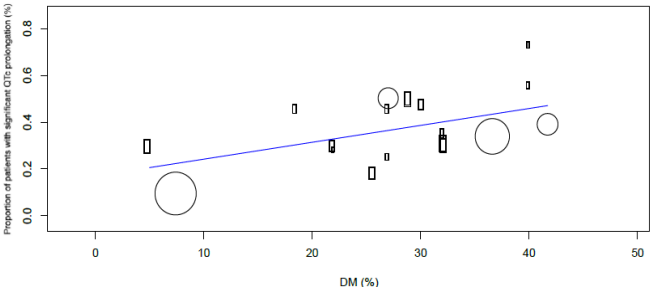

**Supp Figure 10:** Race and the rate of QTc prolongation. Rates were transformed using Freeman-Tukey double arcsine methods. Prevalence of white race was expressed as percentage of the study population.




**Supp Figure 11:** Prevalence of hypertension and the rate of significant QTc prolongation. Rates were transformed using Freeman-Tukey double arcsine methods. Prevalence of hypertension was expressed as percentage of the study population.




**Supp Figure 12:** Prevalence of renal failure and the rate of significant QTc prolongation. Rates were transformed using Freeman-Tukey double arcsine methods. Prevalence of renal failure was expressed as percentage of the study population.




**Supp Figure 13:** Prevalence of diabetes and the rate of significant QTc prolongation. Rates were transformed using Freeman-Tukey double arcsine methods. Prevalence of diabetes was expressed as percentage of the study population.

A subgroup analysis using the country where the study was conducted was performed. Although the racial composition was not available to correlate with country of origin, this analysis did not show any difference in the rate of QTc prolongation between the 6 countries (P = 0.66).

***Effect of Co-Morbidities on QTc Prolongation and VA***

A higher prevalence of hypertension (P <0.001), diabetes (P = 0.003), and renal failure (P = 0.035) were directly related to higher rates of QTc prolongation (Supplemental Appendix 2, Figure 11 - Figure 13). Coronary artery disease (P = 0.26) and heart failure (P = 0.31) did not correlate with the rate of QTc prolongation.

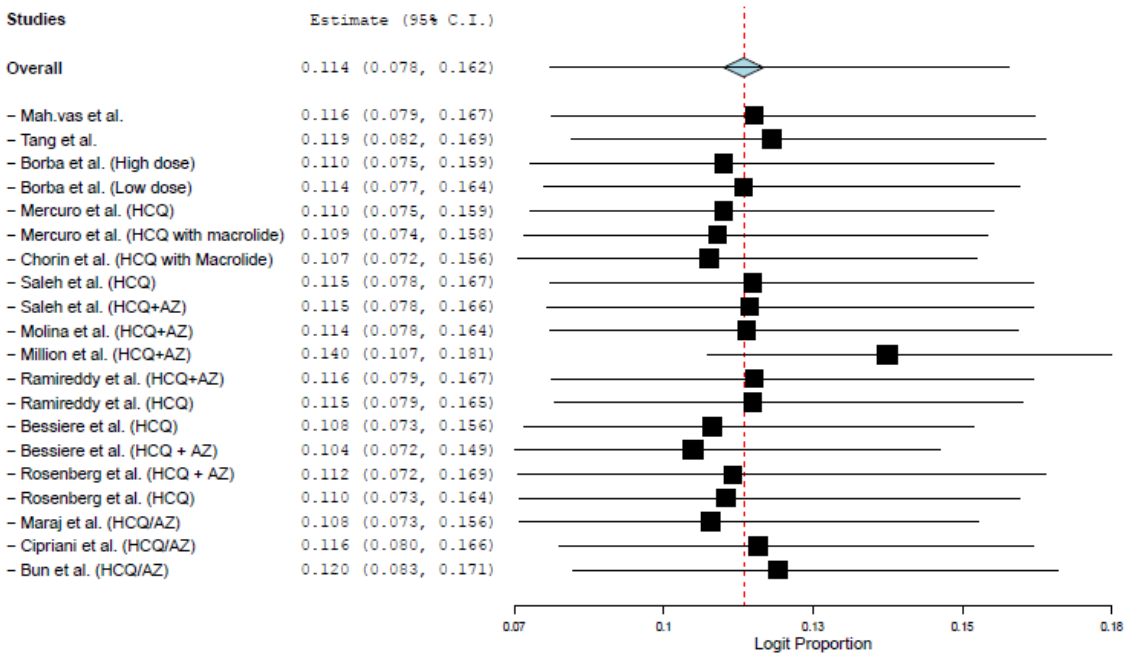
***Sensitivity Analysis***

To investigate the effect of individual studies on the estimated pooled-effect, a "leave-one-out" analysis was performed using sequential meta-analyses on each subset of the studies. By removing individual studies, the estimated rates of QTc prolongation varied from 10.4% to 14%; this did not affect the overall conclusion. (Supplemental appendix 2, Figure 14).

***Quality of Studies***

Studies were assessed using the modified New Castle-Ottawa Scoring (NOS) system (Table 2). To assess a correlation between quality of studies and estimated effect size, meta-regression of the logit transformed rate of QTc

prolongation over the NOS was performed; no correlation existed (P = 0.36).



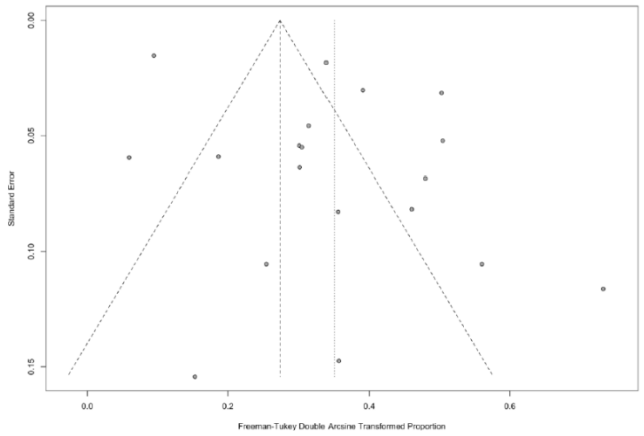

**Supp Figure 14:** Sensitivity analysis using "leave-one-out" analysis. The estimated rates of QTc prolongation varied from 10.4% to 14%.

| # | Study | Selection | | | | Comparability | Outcomes | | Total Score | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Representative Sample | Non-Exposed Control | Ascertainment of Exposure | Absence of Outcome Prior to Exposure | Outcome(s) Compared with Control | Unbiased Assessment of Outcome(s) | Adequate Follow-up | | |
| 1 | Mahévas et al. | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 6 | ECG parameters were not assessed in the control arm. |
| 2 | Tang et al. | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 | |
| 3 | Gautret et al. | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 3 | No control arm. |
| 4 | Borba et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | Comparator groups were low vs high dose CQ. |
| 5 | Mercuro et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | |
| 6 | Boulware et al. | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 6 | No electrocardiographic outcomes were measured. |
| 7 | Chorin et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | |
| 8 | Saleh et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | |
| 9 | Molina et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | |
| 10 | Million et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | |
| 11 | Ramireddy et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | No unexposed patient in the control arm. |
| 12 | Bessiere et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | |
| 13 | Rosenberg et al. | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 | VA were not classified. |
| 14 | Maraj et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | |
| 15 | Cipriani et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | Control arm included healthy patients only. |
| 16 | Bun et al. | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 5 | |

**Table 2:** Modified New Castle Ottawa scoring of included studies.

***Publication Bias***

To investigate presence of publication bias, a funnel plot of each study's standard error *vs*. Freeman-Tukey Double Arcsine Transformed rates of QTc prolongation was constructed. No significant publication bias was observed (Supplemental Appendix 2, Figure 15). Linear regression testing of funnel plot asymmetry was not statistically significant (P = 0.06).




**Supp Figure 15:** Funnel plot of the effect sizes *vs.* study specific standard errors did not show any evidence of publication bias.

## DISCUSSION

In this meta-analysis, the most complete and detailed of its kind in the COVID-19 population to-date, we show a robust and consistent relationship between HCQ/CQ and the rate of clinically significant QTc interval prolongation of about 11%. This increase was more pronounced in studies that included older patients with more severe disease and those with co-morbidities of hypertension, renal failure and diabetes. The higher rate of QTc interval prolongation did not result in a clinically significant greater prevalence of VA that were observed in only 0.2% of patients. Furthermore, no direct evidence suggested that VA resulted from administration of HCQ/CQ or secondary to QTc prolongation. Indeed, some VA occurred independent of QTc prolongation. When they occurred, they rarely resulted in cardiac arrest or death as most end-of-life rhythms were non-shockable [25].

HCQ and CQ are widely used antimalarial drugs. The incidence of QT prolongation in pre-COVID era was extremely low being described mostly in isolated case reports [26]. The unique etiology of QTc prolongation observed with HCQ/CQ in the context of COVID-19 is unknown. Possible hypotheses include direct viral action on cellular depolarization, interaction of HCQ/CQ with other concurrently administered medications, electrolyte imbalance, or increased susceptibility to HCQ/CQ effects on QTc in COVID-infected critically-ill patients.

Special characteristics of patients infected with COVID-19 may predispose to QT interval prolongation. In prior studies, multiple co-morbidities in ICU patients have been associated with QT interval prolongation at a level of approximately 30% irrespective of COVID or use of QT prolonging medications [27]. COVID-19 infected patients are also at risk for myocarditis and ventricular dysfunction and this may be also associated with higher rates of VA.

COVID-19 may affect electrical conductive properties of myocardial cells directly. Alteration of ion channel recycling in myocardial cells may affect QT prolongation during severe SARS-CoV-2 infections; this may be exacerbated by HCQ. SARS-CoV-2 proteins bind to multiple human proteins with the sigma receptor (SIGMAR1) being of particular importance [28]. SIGMAR1 is an ion channel chaperone found in many tissues, including the heart. It is therefore possible that SARS-CoV-2 could alter endosomal trafficking of myocardial ion channels through SIGMAR1 interaction with viral proteins [28,29]. This may explain a higher incidence of QTc prolongation in patients with COVID-19 or their higher susceptibility to it. SIGMAR1 is bound by HCQ, suggesting HCQ can also additively alter this process [28].

An important finding of this study is disconnected between the rate of QT interval prolongation and the risk for VAs. A few explanations could be speculated. One possibility is that azithromycin, for example, and, perhaps, the other drugs lengthen the QT by a mechanism different than $IK_r$ blockade. Recent data indicate that azithromycin can lengthen the QT by other mechanisms including $IK_s$ (less likely to cause torsade de pointes) and Ina [30-38]. Additionally, the QT interval was not prolonged as much in patients who were less critically ill suggesting a lower level of concern in those with early and mild infections. Further, the length of treatment was short thus reducing the chance of VA.

This study has several limitations. No patient-level data were available to allow for more accurate analysis of potential confounders including concomitant use of QT prolonging medications or electrolyte imbalance. Therefore, establishment of any causal relationship would require further randomized studies. Furthermore, the extremely low rate of VA was inconsistent between studies, not allowing for comparison of a potential relationship between development QT prolongation and occurrence of VA. Several studies reported occurrence of VA without QT prolongation suggesting that other arrhythmia mechanisms may be at play.

Finally, we need to consider the "big picture". Any drug therapy that can cause potential harm is of concern but risks need to be considered along with benefits. At present, it is uncertain what the benefits of these drugs are and, if no benefit exists, only harm can ensue. However, considering the potential level of harm, the risk of VA in the entire group is only 0.2% with 64% of studies showing no VA despite evidence for QT interval prolongation. Patients at lowest risk and with less co-morbidities had lowest risk of VA. We recommend caution in drawing conclusions about implications of QT interval prolongation in this population as the risk of malignant VA may not be increased in parallel.

## CONCLUSION

In the largest meta-analysis on the topic to date, HCQ and CQ can prolong the QTc interval in patients infected with COVID-19 but the risk of VA remains extremely low.

## CONFLICT OF INTEREST

None of the author declare any conflict.

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