Hydroxychloroquine and QTc prolongation in patients with COVID-19: A systematic review and meta-analysis

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Aims: This meta-analysis is planned to study the risk of QTc prolongation and Torsades de pointes (TdP) with hydroxychloroquine (HCQ), by a well-defined criterion for HCQ, CQ alone, and in combination with azithromycin in patients with COVID-19.

Methods: A comprehensive literature search was made in two databases (PubMed, Embase). Three outcomes explored in the included studies were frequency of QTc > 500 ms (Outcome 1), frequency of QTc > 500 ms (Outcome 2) and frequency of TdP (Outcome 3). Random effects method with inverse variance approach was used for computation of pooled summary and risk ratio.

Results: A total of 13 studies comprising of 2138 patients were included in the final analysis. The pooled prevalence of outcome 1, outcome 2 and outcome 3 for HCQ, CQ alone, and in combination with azithromycin were 10.18% (5.59–17.82%, I² = 92%), 10.22% (6.01–16.85%, I² = 79%), and 0.72% (0.34–1.51, I² = 0%) respectively. The prevalence of outcome 2 in subgroup analysis for HCQ and HCQ + Azithromycin was 7.25% (3.22–15.52, I² = 59%) and 8.61% (4.52–15.79, I² = 76%), respectively. The risk ratio (RR) for outcome 1 and outcome 2 between HCQ + Azithromycin and HCQ was 1.22 (0.77–1.93, I² = 0%) & 1.51 (0.79–2.87, I² = 13%), respectively and was not significant. Heterogeneity was noted statistically as well clinically (regimen types, patient numbers, study design, and outcome definition).

Conclusion: The use of HCQ/CQ is associated with a high prevalence of QTc prolongation. However, it is not associated with a high risk of TdP.

Keywords: COVID-19, Coronavirus, SARS-CoV-2, Hydroxychloroquine, Chloroquine, Aminoquinoline, QTc prolongation, Torsades de pointes

1. Introduction

The World Health Organization has declared coronavirus disease 2019 (COVID-19), a pandemic on March 11, 2020 [1]. In the absence of a specific and effective therapy against the disease, currently the treatment remains supportive. COVID-19 is caused by a novel beta coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [2]. Among many proposed antiviral therapies, an anti-malarial Hydroxychloroquine (HCQ) has been suggested to be of potential benefit in patients with COVID-19 based on in-vitro and small clinical studies [3–5]. The most serious adverse event associated with the use of HCQ is QTc prolongation which can lead to fatal polymorphic ventricular tachycardia known as Torsades de pointes (TdP) [6].

The prominent mechanism of QTc prolongation by HCQ is by blocking the delayed rectifier potassium current (I_{Ks}), which is involved in final rapid repolarization phase (phase 3) of the action potential.
potential (Fig. 1) [6]. A human ether-a-go-go related gene (HERG, alpha subunit) potassium channel underlies If, and HCQ specifically inhibits this subunit of If. The blockade of the HERG channel lengthens the ventricular repolarization, and this is reflected on the surface electrocardiogram as a prolonged QTc interval. It may also result in the reactivation of inward, mainly calcium, depolarizing currents, thereby generating early afterdepolarizations and can trigger TdP [7,8]. Macrolides antibiotics such as erythromycin, azithromycin, and antivirals lopinavir/ritonavir [13]. Combination of multiple QTc prolongation drugs can trigger TdP [11]. Chloroquine additionally blocks potassium channel current (IK), which are involved in maintaining phase 4 diastolic depolarization of cardiac myocytes [12]. In addition, HERG channels are also blocked by azithromycin, and antivirals lopinavir/ritonavir [13]. Combination of multiple QTc prolonging drugs, bradyarrhythmia, female sex, dyselectrolytemia (hypokalemia, hypocalcemia, and hypomagnesemia) reduces the repolarization reserve and precipitates TdP [6]. Furthermore, at sinoatrial node (SA node) cells (Inset) HCQ predominantly blocks funny channels, along with potassium channels and long-acting calcium channels in animal studies [10]. Funny channel current (If) is involved in generating phase 4 depolarization, potassium channel current (IK) is involved in generating phase 3 repolarization phase of sinoatrial nodal action potential, and calcium channel current (ICaL) is involved in generating phase 0 rapid depolarization. The blockade of these currents prolongs the action potential of the SA node, reduces automaticity, and causes bradyarrhythmia [14]. The bradyarrhythmia prolongs QT interval [6].

Among the selected studies, studies reporting ECG parameters were taken for data extraction. The studies which reported QTc prolongation, defined as QTc > 500 ms (ms) or increase in QTc >60 ms from baseline (ΔQTc) or TdP were included for final metaanalysis. QT prolongation was taken into account and QRS prolongation was not assessed in the metaanalysis. Both screening and data extraction were conducted by two investigators (SA and AY) and were matched with conflicts resolved by a third investigator (AG). Three outcomes were extracted from the included studies namely,

1. Outcome 1 – Frequency of QTc prolongation defined as QTc > 500 ms or ΔQTc > 60 ms out of total patient evaluated.
2. Outcome 2 - Frequency of QTc prolongation defined as QTc > 500 ms out of total patient evaluated.
3. Outcome 3 - frequency of TdP out of total patient evaluated.

Studies not providing a clear definition of QTc prolongation were omitted. We took the number of patients rather than the number of events when both the information was provided. When the authors did not distinguish between the events and patients, it was presumed to be patients. If a study had taken the patients which were included in the previous study, only the study with the largest sample size was included. Studies including patients with structural heart diseases in which ECG may be influenced by underlying diseases were excluded. Also, the minimum number of patients in a study required for inclusion into the metaanalysis was kept as 10. In case of queries, electronic mail (e-mail) communication was made to the author for clarification.

Besides the study design, the severity of included patients,
dosing regimen, and any special cardiovascular-related information either in terms of monitoring or outcomes were extracted and tabulated.

2.1. Statistical analysis

The analysis was conducted using R (version 3.6.2) and meta-package was used in addition to the base package [15,16]. Logit transformations were made in proportion before computing the summary. Clopper-Pearson confidence interval was used for individual studies. The summary pooled prevalence was computed using a random effect model along with an inverse variance approach. The risk ratio (RR) was computed for the comparison between the frequency between the two interventions.

Fig. 2. PRISMA flowchart showing the flow of study selection.
The reasons for excluding clinical studies reporting ECG parameters for metanalysis for any of the outcomes is shown in Table 1.

### 3. Results

Eighteen studies have evaluated ECG parameters, out of which 13 were included in the metaanalysis and 5 were excluded [17–34]. The flow of study inclusion is shown in Fig. 2. In Saleh et al. study, we took HCQ/CQ as a single group (HCQ) as the author has not reported distinct outcome between HCQ/CQ and the number of patients of CQ was only 10 [28]. The characteristics of the included studies for metanalysis for any of the outcomes is shown in Table 1. The reasons for excluding clinical studies reporting ECG parameters are shown in Table 2.

Out of 11 studies reporting HCQ with or without Azithromycin, 2 followed regimen 1 (HCQ 200 mg twice daily for 10 days and azithromycin 250 mg for 5 days), 4 followed regimen 2 (HCQ 400 mg twice daily for day 1 followed by 200 mg twice daily for next 4 days), 5 followed regimen 3 (HCQ 200 mg three times a day for 10 days, and azithromycin 500 mg single dose followed by 250 mg OD for day 2–5). 2 studies of CQ with or without azithromycin gave either (high dose CQ 600 mg twice daily for 10 days versus low dose 450 mg twice daily on day 1 followed by 450 mg OD for the next 4 days). For analysis, drug-specific outcomes were explored, irrespective of the regimen.

Out of the 13 studies (2138 patients) which evaluated either HCQ or CQ alone or with a combination of Azithromycin for outcome 1 (QTc >500 ms or ΔQTc > 60 ms), the prevalence varied between 0 and 35% with a pooled prevalence of 10.18% (5.59%–17.82%, I² = 92%) (Fig. 3A). Similarly, 10 studies (1926 patients) which explored the same drugs with outcome 2 (QTc >500 ms), the prevalence varied between 0 and 23.16% with a pooled prevalence of 10.22% (6.01%–16.85%, I² = 79%) (Fig. 3B). I² showed heterogenous results for both the QTc prolongation outcome (I² > 50%). For consideration of outcome 3 i.e., frequency of TdP with the same group of drugs, 12 studies reported a prevalence between 0 and 1.11% with a pooled prevalence of 0.72% (0.34%–1.51%, I² = 0%) (Fig. 3C). The results were homogeneous among studies for TdP (I² < 50%).

Exploration of prevalence for HCQ and HCQ + Azithromycin for

### Table 1

Characteristics of included studies.

| Study, Country | Study Design | Number of Patients | Criteria (All values in msec) | Dosing regimen | Treatment Groups (n) | Illness severity |
|----------------|--------------|--------------------|-------------------------------|----------------|----------------------|-----------------|
| Bessiere et al. [17], France | Retrospective study | 40 | QTc >500 ms or ΔQTc 60 ms | Regimen 1 | HCQ (n = 22) vs.HCQ + Azithromycin (n = 18) | Severe, ICU admitted patients |
| Borba et al. [18], Brazil | Randomized double-blind study | 81 | QTc >500 ms | CQ | High dose CQ (600 mg BD x 10 days) vs. low dose (450 mg BD on day 1 followed by 450 mg OD for next 4 days) All azithromycin (n = 51) | Severe, Hospitalized patients |
| Chang et al. [19], USA | Prospective observational study | 117 | QTc >500 ms | Regimen 2 | HCQ (n = 66) vs. HCQ + Azithromycin (n = 51) | Hospitalized, Non-ICU |
| Chorin et al. [20], USA, Italy | Retrospective study | 251 | QTc >500 ms or ΔQTc 60 ms or ΔTc >410 ms | Regimen 2 | HCQ + Azithromycin | Hospitalized patients |
| Ciprani et al. [21], Italy | Prospective observational study | 22 | QTc >500 ms | Regimen 1 | HCQ + Azithromycin (minimum for 3 days) | Hospitalized patients, room air |
| Gautret et al. [22], France | Prospective observational study | 80 | QTc >500 ms | Regimen 3 | HCQ + Azithromycin | Hospitalized patients, mild-moderate illness |
| Mahévas et al. [23], France | Retrospective observational study | 181 | QTc >500 ms or ΔQTc 60 ms | Regimen 3 | HCQ (n = 84) Azithromycin (n = 15) vs.standard of care (n = 89) | Hospitalized patients, requiring oxygen |
| Million et al. [24], France, Mercuro et al. [25], USA | Retrospective observational study | 1061 | QTc >500 ms or ΔQTc 60 ms | Regimen 3 | HCQ | Mild illness |
| Molina et al. [26], France | Prospective observational study | 90 | QTc >500 ms or ΔQTc 60 ms | Regimen 2 | HCQ (n = 37) vs. HCQ + Azithromycin (n = 53) | Hospitalized patients |
| Perin et al. [27], France | Prospective study, cohort study | 11 | QTc >500 ms or ΔQTc 60 ms | Regimen 3 | HCQ + Azithromycin | Hospitalized patients, requiring oxygen |
| Saleh et al. [28], USA | Prospective observational study | 13 | QTc >500 ms | Regimen 3 | HCQ alone | Hospitalized ICU patients |
| Broek et al. [29], Netherlands | Retrospective observational study | 201 | QTc >500 ms | Regimen 2 | CQ (n = 10) HCQ (72) | Hospitalized ICU severe patients |
| | | 95 | QTc >500 ms | CQ (n = 119) QC 600 mg loading dose followed by 300 mg BD for next 5 days started after 12 h of loading dose | Hospitalized ICU patients |
the outcome 1 showed the pooled prevalence of 13.11% (6.9%–
23.52%, I² = 67%) and 8.2% (3.26%–19.13%, I² = 93%), respectively,
with combined prevalence of 9.87% (5.39%–17.40%, I² = 89%) (Fig. 4A).
The number of studies (HCQ + Azithromycin = 10), the maximum (HCQ–
82, HCQ + Azithromycin = 1061) and minimum (HCQ – 13, HCQ + Azithromycin – 11) sample size were different between the two agents, thereby making them directly
not comparable. Similarly, the prevalence of HCQ and
HCQ + Azithromycin for the outcome 2 showed a pooled preva-
lence of 7.25% (3.22%–15.52%, I² = 59%) and 8.61% (4.52%–15.79%, I²
= 76%), respectively, with combined prevalence of 8.25% (5.07%–
13.15%, I² = 71%) (Fig. 4B). Again, the number of studies, the
maximum and minimum sample sizes were different, thereby
making the results, not comparable based on prevalence. The two
studies reporting TdP were from HCQ + Azithromycin arm. Since
the number of studies was less for all outcomes for CQ and
CQ + Azithromycin, its prevalence was not computed.
Five studies had a direct comparison of CQ and
HCQ + Azithromycin for outcome 1 and outcome 2. In those
studies, the RR for outcome 1 and outcome 2 were 1.22 (0.77–1.93,
I² = 0%) & 1.51 (0.79–2.87, I² = 13%) and both were not significant
(Fig. 5A and B).

4. Discussion

Multiple studies on HCQ in COVID 19 patients have focussed
upon the efficacy of the drug without clearly defining the meth-
ology used for QTc prolongation [30–34], 13 studies which laid
down the criteria for QTc prolongation reported a pooled preva-
lence of 10.18% taking either HCQ or CQ alone or in combination
with Azithromycin for outcome 1 and 10.22% for outcome 2. We
had to exclude one of the biggest studies of Rosenberg et al. [32],
consisting of 1438 patients as the criteria for QTc prolongation
was not defined. Another study of 524 patients by Jain et al., had to be
excluded as they had taken the criteria for QTc prolongation dependent
upon the QRS duration (QTc >470 ms for QRS < 120 ms,
QTc > 500 ms for QRS > 120 ms) without mentioning the absolute
numbers in each group [31]. An attempt was made to get the data
via e-mail for the 5 excluded studies, however, the same could not
be obtained (except Louhaichi et al. [33] where QTc criteria were
informed as >480 ms, hence excluded). The pooled prevalence
must be taken in the context of other associated factors causing QTc
prolongation in these patients which include and are not limited to
concomitant medications including various anti-viral drugs, elec-
trolyte disturbances, structural heart disease, channelopathies, and
advanced age. This QTc prolongation prevalence of 10% matches
with the recently published review by Jankelson et al. [35]. The high
prevalence of QTc prolongation with these drugs reiterates that the
clinicians should be proactive in monitoring of QTc interval by
doing daily ECGs in these patient population.
11 out of 13 studies included in our meta-analysis included HCQ
and only 2 studies used CQ. It is commonly believed that the
addition of Azithromycin to HCQ in COVID 19 patients significantly
increases the risk for QTc prolongation [9]. Interestingly, in our
meta-analysis the pooled prevalence in patients taking only HCQ
versus HCQ and Azithromycin for outcome 1 was 13.11% and 8.20%,
respectively and for outcome 2 was 7.25% and 8.61%, respectively.
The RR of QTc prolongation in patients taking both HCQ and Azith-
romycin as compared to HCQ alone was also not significant.
These results are predominantly influenced by the study of Million
et al., who reported significantly lower events (9 out of 1061) in
patients taking both HCQ and Azithromycin and mostly included
patients with mild disease [24]. The heterogeneity among the
included studies for outcome 1 and outcome 2 can be explained by
the variability in the dosing regimen, variability in the severity of
COVID-19 among the included patients, confounding factors such
as associated comorbidity and medications, variability between the
study design, number of patients and study settings.
Another important observation from our meta-analysis was the
relatively low pooled prevalence (0.72%) of TdP which occurred in
only 2 out of 2021 patients taking aminoquinoline with or without
macrolides. The prevalence of TdP must be considered in the
background of the following factors: only 2 studies reported the
events, the number of patients varied between studies, and contin-
uity correction of 0.5 was applied for computing the summary
effect. This may be compared to the risk of around 2.5% of TdP
associated with oral sotalol use [36]. This increased risk with sotalol
may be attributed to the chronic use and the fact that the majority
of the patients had underlying structural heart disease. It is
important to note that the ventricular arrhythmia in TdP is a
polymorphic ventricular tachycardia. The underlying cardiovas-
cular diseases in COVID 19 patients may predispose these patients
to VT which may not be polymorphic and may not be related to HCQ
usage. Therefore, patients in which polymorphic ventricular
tachycardia was not explicitly mentioned were not considered to
have TdP in this meta-analysis. Very low chances of developing TdP

| Study name        | Type of study                | Number of patients | Antiviral regimen                                                                 | Reason for exclusion                                      |
|-------------------|------------------------------|--------------------|----------------------------------------------------------------------------------|----------------------------------------------------------|
| Alberici et al.   | Retrospective observational  | 94                 | Lopinavir/ritonavir with HCQ (dose adjusted according to kidney function)        | QTc not defined for prolonged QT                          |
| Jain et al.       | Observational comparative    | 415                | HCQ dose not defined                                                             | QTc prolongation criteria was not defined                 |
| Rosenberg et al.  | Retrospective Observational  | 1438               | Variable HCQ dose at 4 groups HCQ (n = 211) HCQ + Azithromycin (n = 735)          | QTc not defined for prolonged QT                          |
| Louhaichi et al.  | Retrospective observational  | 15                 | HCQ + Azithromycin                                                               | QTc prolongation criteria was > 480 ms                    |
| Tang et al.       | Open labelled RCT            | 150                | HCQ + standard of care (n = 75) vs. standard of care alone (n = 75)                | QTc not defined for prolonged QT                          |

Tang et al. [34], China
in hospitalized COVID 19 patients with QTc prolongation, which on the contrary should be at a higher risk, suggests that there is a missing link between QTc prolongation and the risk of developing TdP. This is further strengthened by the fact the TdP has been re-reported in COVID 19 patient taking HCQ with a QTc interval of <500 ms [25]. In a malaria-endemic country like ours, HCQ is commonly prescribed and sudden unexpected deaths are unheard of. Even, WHO second this notion [6]. Not all the drugs that prolong QTc interval, significantly increase the risk of TdP. Proarrhythmic potential also depends upon prolongation of transmural dispersion of repolarization across the myocardium as proposed by El-Sherif and co-workers where re-entry causes a short-long-short initiating pattern of TdP [11]. For this, the coupling interval of the initiating premature ventricular contraction is important and needs to be studied in this patient subset. In the presence of many confounders, a clear cause and effect relationship cannot be established between HCQ and TdP, data from large randomized studies are awaited and will make us wiser. Till then, caution is advised and the use of HCQ/CQ can only be recommended in the setting of a clinical trial with close monitoring of QTc.

The greatest limitation of this metanalysis was the marked heterogenicity among the studies. Apart from different dosages of HCQ alone with or without azithromycin for three outcomes are shown: Fig. 3A: Outcome 1 (QTc >500 ms or ΔQTc > 60 ms); Fig. 3B: Outcome 2 (QTc >500 ms); Fig. 3C: Outcome 3 (Torsades de Pointes -TdP). The summary was computed by a random effect. The heterogeneity was assessed by I² and p-value of heterogeneity (p < 0.10). CI stands for confidence interval.

![Fig. 3](image-url)
HCQ used in these studies, there were few studies in which other QTc prolonging drugs like Lopinavir/Ritonavir were used and underlying dyselectrolemia was present. The QTc prolonging effect attributable to HCQ is difficult in the presence of so many confounding factors. For better comprehension, we tabulated the dosage of HCQ into three different regimens. Another important limitation is the difference in the severity of the disease amongst patients in the absence of a well-defined definition of disease severity and admission criteria.

5. Conclusion

The risk of QTc prolongation associated with HCQ/CQ with or without Azithromycin is significant; however, very few patients develop TdP.

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Fig. 4. Subgroup based prevalence of HCQ and HCQ + azithromycin for two outcomes are shown: Fig. 4A: Outcome 1 (QTc >500 ms or ΔQTc >60 ms); Fig. 4B: Outcome 2 (QTc >500 ms). The summary was computed by a random effect method. The heterogeneity was assessed by I² and p-value of heterogeneity (p < 0.10). CI stands for confidence interval.

Fig. 5. Risk ratio (RR) between HCQ + azithromycin and HCQ for two outcomes are shown: Fig. 5A: Outcome 1 (QTc >500 ms or ΔQTc >60 ms); Fig. 5B: Outcome 2 (QTc >500 ms). The summary was computed by a random effect method. The heterogeneity was assessed by I² and p-value of heterogeneity (p < 0.10). CI stands for confidence interval.
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