REVIEW

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QTc prolongation in COVID-19 patients treated with hydroxychloroquine, chloroquine, azithromycin, or lopinavir/ritonavir: A systematic review and meta-analysis

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Abstract

Purpose: Hydroxychloroquine, chloroquine, azithromycin, and lopinavir/ritonavir are drugs that were used for the treatment of coronavirus disease 2019 (COVID-19) during the early pandemic period. It is well-known that these agents can prolong the QTc interval and potentially induce Torsades de Pointes (TdP). We aim to assess the prevalence and risk of QTc prolongation and arrhythmic events in COVID-19 patients treated with these drugs.

Methods: We searched electronic databases from inception to September 30, 2020 for studies reporting peak QTc ≥500 ms, peak QTc change ≥60 ms, peak QTc interval, peak change of QTc interval, ventricular arrhythmias, TdP, sudden cardiac death, or atrioventricular block (AVB). All meta-analyses were conducted using a random-effects model.

Results: Forty-seven studies (three case series, 35 cohorts, and nine randomized controlled trials [RCTs]) involving 13 087 patients were included. The pooled prevalence of peak QTc ≥500 ms was 9% (95% confidence interval [95%CI], 3%–18%) and 8% (95%CI, 3%–14%) in patients who received hydroxychloroquine/chloroquine alone or in combination with azithromycin, respectively. Likewise, the use of hydroxychloroquine (risk ratio [RR], 2.68; 95%CI, 1.56–4.60) and hydroxychloroquine + azithromycin (RR, 3.28; 95%CI, 1.16–9.30) was associated with an increased risk of QTc prolongation compared to no treatment. Ventricular arrhythmias, TdP, sudden cardiac death, and AVB were reported in <1% of patients across treatment groups. The only two studies that reported individual data of lopinavir/ritonavir found no cases of QTc prolongation.

Conclusions: COVID-19 patients treated with hydroxychloroquine/chloroquine with or without azithromycin had a relatively high prevalence and risk of QTc prolongation. However, the prevalence of arrhythmic events was very low, probably due to underreporting. The limited information about lopinavir/ritonavir showed that it does not prolong the QTc interval.

KEYWORDS
COVID-19, QTc interval, sudden cardiac death, Torsades de Pointes, ventricular arrhythmias

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic that affects over 34 million people worldwide.[1] This disease began in Wuhan, China and has spread rapidly across the globe causing significant morbidity and mortality.[2]

Currently, there is evidence that only a few drugs such as dexamethasone[3] and remdesivir[4] have shown a beneficial effect in patients with COVID-19, although several clinical trials for other therapies are still ongoing.[5,6] It was reported that hydroxychloroquine and chloroquine possess antiviral properties in vitro against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[7,8] Thus, has been initially hypothesized that these drugs could be useful for the management of COVID-19.

An early open-label non-randomized clinical trial suggested a potential benefit with the use of hydroxychloroquine with or without azithromycin in COVID-19 patients.[9] On March 28, 2020, the Food and Drug Administration authorized the emergency use of hydroxychloroquine and chloroquine in hospitalized COVID-19 patients.[10] Although this authorization was posteriorly withdrawn (June 15, 2020) for use in the United States of America,[11] it was a treatment option in many countries where they were administered alone or in combination with azithromycin.[12,13] Lopinavir/ritonavir is another class of drug which, based on his in vitro activity against other coronaviruses, has also been used in COVID-19 patients.[14,15] As a result, these agents were widely used off-label for COVID-19 treatment worldwide during the early pandemic period. However, it is previously recognized that these drugs can prolong the corrected QT (QTc) interval which, in turn, can trigger life-threatening arrhythmias, particularly Torsades de Pointes (TdP).[16] Thus, there is an increasing concern about these serious adverse events in the current COVID-19 pandemic.

Recently, several studies that assessed the cardiac safety profile of these drugs have been published. Therefore, we conducted a systematic review and meta-analysis to evaluate the prevalence and risk of QTc prolongation and arrhythmic events in COVID-19 patients treated with hydroxychloroquine, chloroquine, azithromycin, or lopinavir/ritonavir.

2 | METHODS

This review was reported according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement[17] and was registered in the PROSPERO database (CRD42020185226).

2.1 | Search strategy

2.1.1 | Database search

We searched in the following electronic databases: PubMed, Embase, Scopus, Web of Science, and Cochrane Central Register of

Key Points

- Our systematic review and meta-analysis showed that the prevalence of QTc prolongation was relatively high in COVID-19 patients treated with hydroxychloroquine/chloroquine alone or in combination with azithromycin.
- The use of hydroxychloroquine or hydroxychloroquine + azithromycin was associated with three times higher risk of QTc prolongation in comparison to no treatment.
- The prevalence of ventricular arrhythmic events was very low across treatment groups, probably due to underreporting.
- The scarce published data about lopinavir/ritonavir showed that it does not prolong the QTc interval.
- Hydroxychloroquine, chloroquine, azithromycin and lopinavir/ritonavir should be used under adequate clinical and electrocardiographic monitoring.

Controlled Trials (CENTRAL). The search was conducted from database inception until May 7, 2020, with an update on September 30, 2020. We extended the date of database search to September 30 because the evidence was published rapidly and we wanted to keep the search as up to date as possible in order to reduce the publication bias. There were no restrictions on language or publication date. The complete search strategy is available in Table S1 in Data S1.

2.1.2 | Other study sources

We conducted a hand-searching of reference lists of all included articles and relevant reviews to identify further studies. We also searched the articles citing the selected studies (retrieve through Google Scholar), the clinicaltrials.gov registry, and the preprint servers medRxiv (https://www.medrxiv.org/) and SSRN (https://www.ssrn.com/).

2.2 | Eligibility criteria

The inclusion criteria were the following: (i) studies that included adult patients (≥18 years of age) with COVID-19 confirmed by reverse transcription-polymerase chain reaction; (ii) studies that evaluated any dose, timing, and duration of hydroxychloroquine, chloroquine, azithromycin, or lopinavir/ritonavir treatment; (iii) studies that reported at least one of the primary or secondary outcomes; (iv) case series, cross-sectional, case–control, cohort studies, and randomized controlled trials (RCTs). Case reports, abstracts, editorials, commentaries, systematic reviews, and narrative reviews were excluded.

2.3 | Study selection

Two review authors (CDA and ABC) downloaded all articles from electronic search to EndNote X8 and duplicate records were removed. All unique articles were uploaded to Rayyan QCRI (https://rayyan.qcri.org/). Titles and abstracts were independently screened by two review authors (CDA and ABC) to identify relevant studies. Likewise, two review authors (CDA and ABC) independently examined the full-text of all selected studies and registered the reasons for exclusion. Any disagreement on title/abstract and full-text selection was resolved by consensus through face-to-face discussion.

2.4 | Outcomes

The primary outcome was peak QTc interval ≥ 500 ms (maximum QTc during or after treatment – baseline QTc ≥500 ms). Secondary outcomes were peak QTc interval (maximum QTc during or after treatment), peak change of QTc interval (maximum QTc during or after treatment – baseline QTc), peak QTc change ≥60 ms (maximum QTc during or after treatment – baseline QTc ≥60 ms), ventricular arrhythmias, TdP, sudden cardiac death, and atrioventricular block

(atrioventricular block). Author-reported definitions were used for all outcomes. We decided to change the primary outcome to peak QTc interval ≥500 ms due to its higher reporting across included studies in comparison to the outcome described in the protocol.

2.5 | Data extraction

The information from each selected study was independently extracted by two review authors (CDA and ABC) using a standardized data extraction form in an Excel spreadsheet that was previously piloted. Any disagreement was resolved by consensus. If additional data was needed, we contacted the corresponding author through email to request further information. The following data were extracted: first author name, publication year, country, study design, sample size, eligibility criteria, age, sex, comorbidities, use of hydroxychloroquine, chloroquine, azithromycin, and lopinavir/ritonavir (dose, timing, and duration), use of other QT-prolonging drugs, timing of electrocardiogram (ECG) assessment, QT interval correction formula, peak QTc interval ≥500 ms, peak QTc change ≥60 ms, peak QTc interval, peak change of QTc interval, ventricular arrhythmias, TdP, sudden cardiac death, and atrioventricular block.
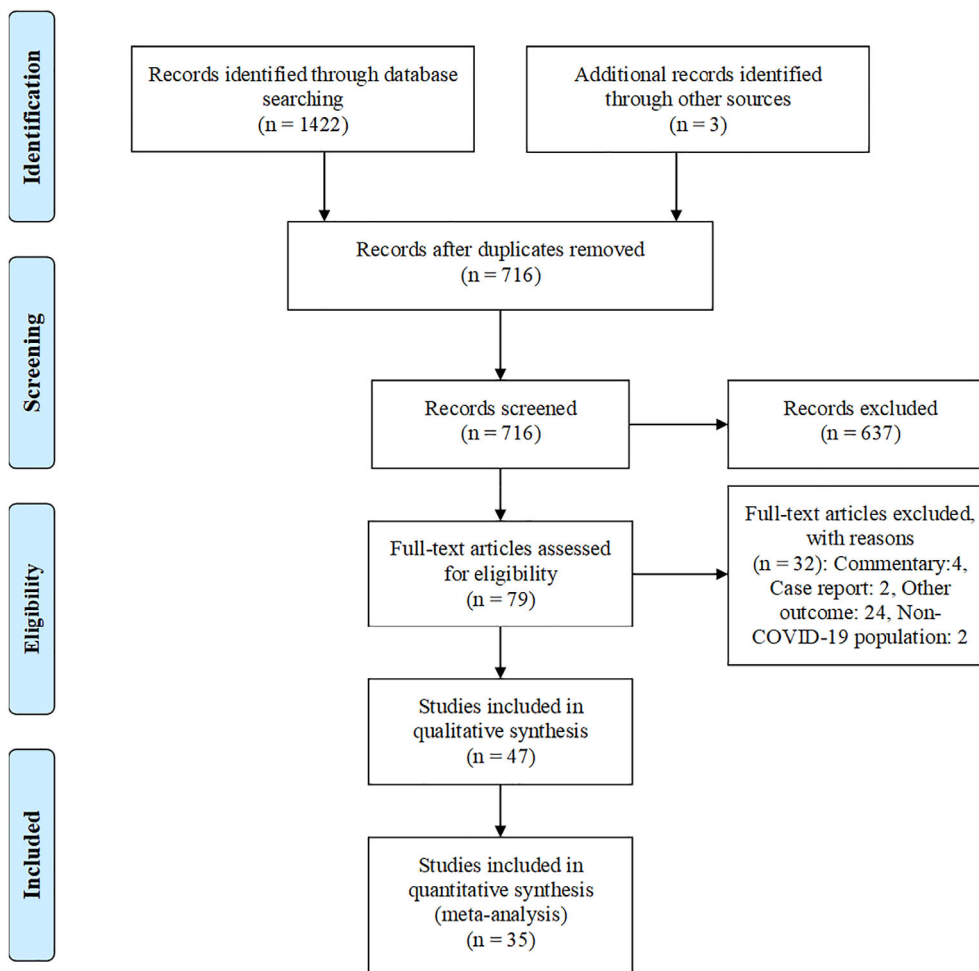

FIGURE 1 Flow diagram of study selection [Colour figure can be viewed at wileyonlinelibrary.com]

2.6 | Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the risk of bias for cohort studies.[18] Each study was classified in the following groups: high risk of bias (0–4 points), moderate risk of bias (5–7 points), and low risk of bias (8–9 points). RCTs were evaluated using the Cochrane Risk of Bias 2.0 tool.[19] Overall, each RCT was judged as having a low, some concerns, or a high risk of bias. The risk of bias of case series studies was not possible to assess given these studies do not have control groups by definition. Two review authors (CDA and ABC) independently assessed the risk of bias for each study and any disagreement was resolved by consensus.

2.7 | Statistical analysis

All meta-analyses were conducted using a random-effects model. The between-study variance (tau^2) was estimated using the DerSimonian-Laird estimator. We pooled the prevalence of patients with peak QTc interval ≥500 ms and peak QTc change ≥60 ms with their 95% confidence interval (95%CI) using the inverse variance method and the Freeman-Tukey double arcsine transformation. For combining studies with a control group and data on QTc prolongation, we use risk ratio (RR) with their 95%CI. The means of peak QTc interval and peak change of QTc interval with their 95%CI were also pooled. Also, we estimate point-prevalence with their 95%CI for ventricular arrhythmias, TdP, sudden cardiac death, and atrioventricular block. All meta-analyses were performed according to the treatment groups (hydroxychloroquine/chloroquine and hydroxychloroquine/chloroquine + azithromycin) and only studies with 10 or more patients were combined. In the case of studies have only reported median and interquartile range, the mean and standard deviation were calculated using the method proposed by Wan et al.[20] We evaluated statistical heterogeneity using the chi-squared test (threshold $p < 0.10$) and the I^2 statistic. Statistical heterogeneity was defined as low if I^2 < 30%, moderate if I^2 is 30%–60%, and high if I^2 > 60%. Funnel plots were used to
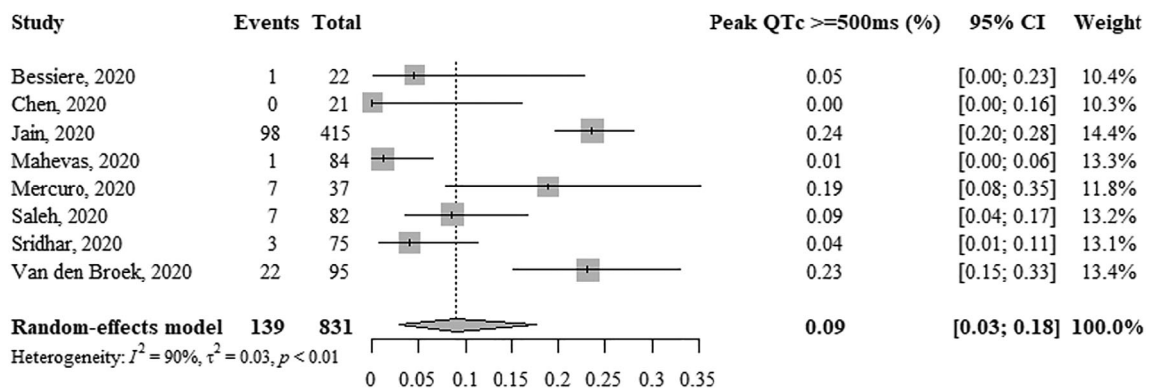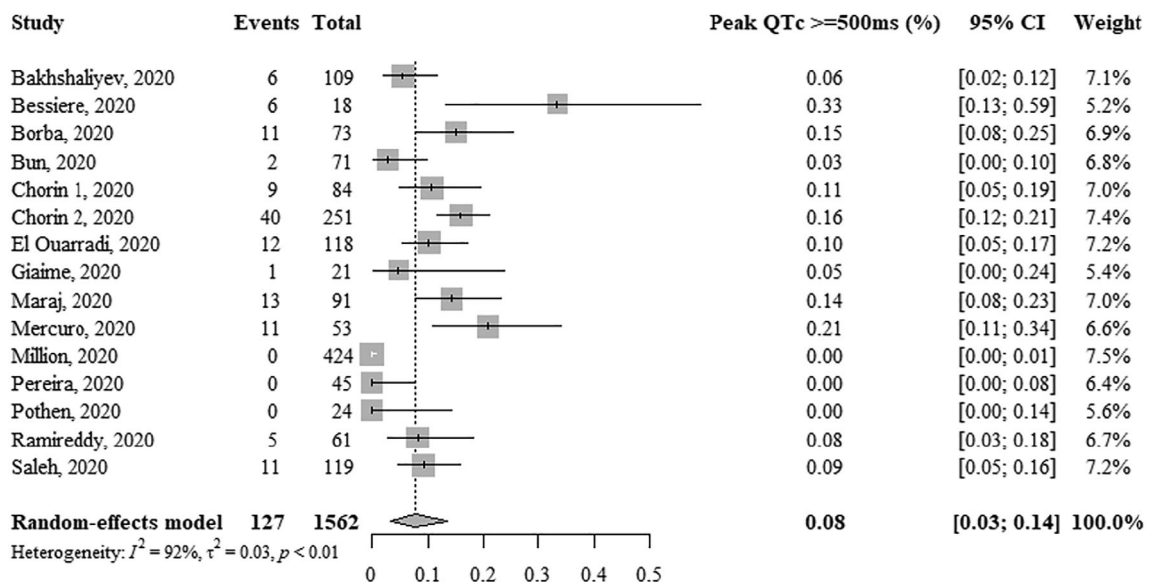

FIGURE 2 Prevalence of peak QTc interval ≥500 ms in COVID-19 patients

evaluate publication bias and the Egger's test was performed to measure asymmetry of funnel plots only if 10 or more studies were included.[21] We performed all meta-analyses using the "meta" package from R 3.6.3 (http://www.r-project.org/). A two-tailed $p < 0.05$ was considered as statistically significant.

3 | RESULTS

3.1 | Study selection

Our search strategy identified initially 1425 articles. After the removal of duplicates, 716 unique articles remained. After screening of studies by title and abstract, 637 articles were excluded. After full-text revision of 79 articles, 32 articles were excluded: four commentaries, two case reports, 24 for other outcomes, and two for non-COVID-19 population (Figure 1). Of the 47 selected studies, 35 studies were included in the meta-analyses because other studies did not have enough information for the evaluated outcomes or assessed other drug combinations.

3.2 | Study characteristics

The main characteristics of the 47 included studies[22-68] (three case series, 35 cohorts, and nine RCTs, n = 13 087) are summarized in Table S2 in Data S1. Fifty-eight percent of the study population was composed of men. The mean age in 24 studies was 58.1 years (range 33 to 68) and the range of median ages was 52 to 69 years across 11 studies. Fifteen out of 47 included studies were conducted in the United States of America. In seven studies, patients with baseline QTc interval > 500 ms at baseline were excluded.

Hydroxychloroquine was evaluated in 42 studies; however, only 15 studies used the same dosage regimen (400 mg BID first day, then 200 mg BID for 4 days). Azithromycin was assessed in 34 studies and its most common dosage regimen was 500 mg QD first day, then 250 mg QD for 4 days, which was reported in 13 studies. There were only three studies[36,48,49] that assessed the individual effect of azithromycin on the QTc interval, although none the these compared it with non-azithromycin users. Only a few studies evaluated the use of chloroquine (five studies) and lopinavir/ritonavir (eight studies) with non-uniform dosages. Given that only three studies,[24,51,54] which reported different outcomes, evaluated the individual effect of chloroquine on the QTc interval; it was not possible to compare, separately, the effect of chloroquine and hydroxychloroquine. The mean proportion of the use of other QT-prolonging drugs was 16 ± 15% which was reported in 16 studies (Table S2 in Data S1).

The timing of ECG evaluation was most frequently performed before and after initiation of treatment in 25 out of 35 studies, while the daily evaluation was only conducted in four studies. The most common method (27 studies) for heart rate
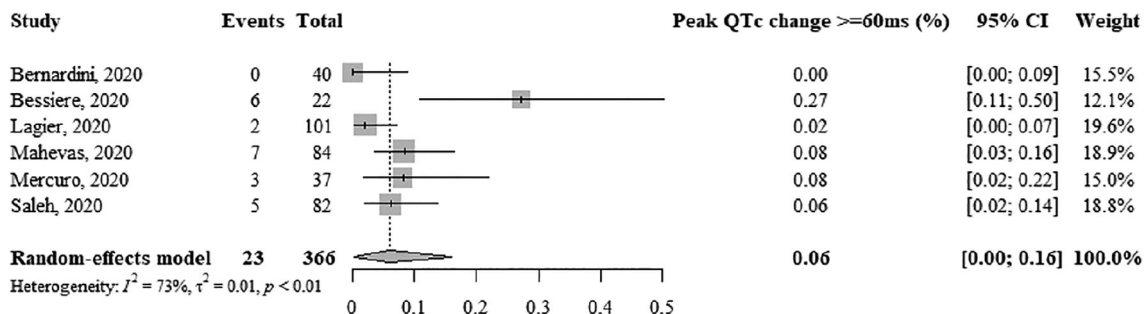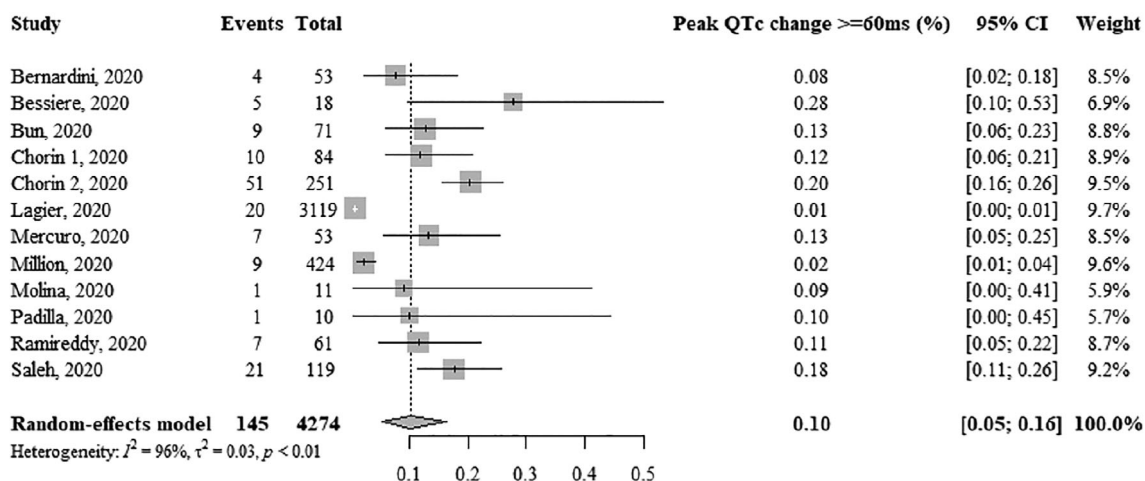

FIGURE 3 Prevalence of peak QTc change ≥60 ms in COVID-19 patients

correction of the QT interval was the Bazett's formula. In 19 of 23 studies, the QT interval was measured by a cardiologist (Table S2 in Data S1).

3.3 | Risk of bias assessment

Thirty-four out of 35 cohort studies were at moderate risk of bias while the remaining one cohort study was at low risk of bias (Table S3 in Data S1). Four RCTs were scored as high risk of bias, two RCTs as some concerns, and three studies as low risk of bias (Figure S1 in Data S1).
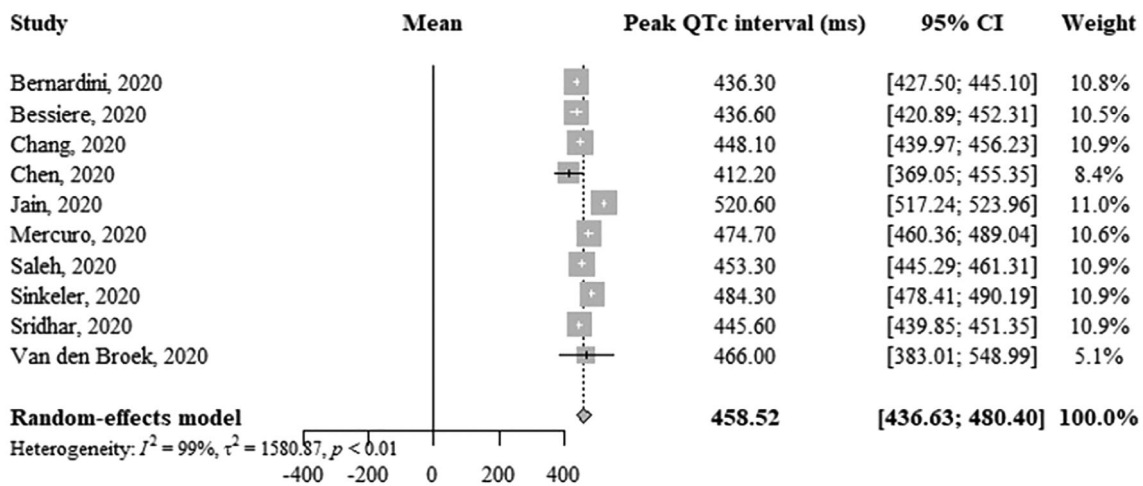
3.4 | Hydroxychloroquine/chloroquine with or without azithromycin

3.4.1 | Peak QTc interval ≥500 ms

In eight studies (seven cohorts and one RCT, n = 831), the pooled prevalence of patients with peak QTc interval ≥500 ms was 9% (95% CI, 3%–18%; I^2 = 90%) in the hydroxychloroquine/chloroquine group (Figure 2).

In 15 studies (one case series, 13 cohorts, and one RCT, n = 1562), the pooled prevalence of patients with peak QTc interval

Hydroxychloroquine/Chloroquine

Study	Mean	Peak QTc interval (ms)	95% CI	Weight
Bernardini, 2020		436.30	[427.50; 445.10]	10.8%
Bessiere, 2020		436.60	[420.89; 452.31]	10.5%
Chang, 2020		448.10	[439.97; 456.23]	10.9%
Chen, 2020		412.20	[369.05; 455.35]	8.4%
Jain, 2020		520.60	[517.24; 523.96]	11.0%
Mercuro, 2020		474.70	[460.36; 489.04]	10.6%
Saleh, 2020		453.30	[445.29; 461.31]	10.9%
Sinkeler, 2020		484.30	[478.41; 490.19]	10.9%
Sridhar, 2020		445.60	[439.85; 451.35]	10.9%
Van den Broek, 2020		466.00	[383.01; 548.99]	5.1%
Random-effects model		**458.52**	**[436.63; 480.40]**	**100.0%**

Heterogeneity: I^2 = 99%, τ^2 = 1580.87, p < 0.01
-400 -200   0   200   400

Hydroxychloroquine/Chloroquine + Azithromycin

Study	Mean	Peak QTc interval (ms)	95% CI	Weight
Bakhshaliyev, 2020		459.70	[452.49; 466.91]	6.2%
Bernardini, 2020		452.80	[445.69; 459.91]	6.2%
Bessiere, 2020		475.00	[457.77; 492.23]	4.2%
Bun, 2020		436.00	[425.77; 446.23]	5.6%
Chang, 2020		451.90	[443.89; 459.91]	6.0%
Chorin 1, 2020		463.00	[456.16; 469.84]	6.3%
Chorin 2, 2020		474.00	[469.42; 478.58]	6.6%
Cipriani, 2020		447.30	[427.45; 467.15]	3.7%
El Ouarradi, 2020		443.70	[435.69; 451.71]	6.0%
Farre, 2020		465.00	[459.32; 470.68]	6.4%
Giaime, 2020		446.90	[433.60; 460.20]	5.0%
Maraj, 2020		473.00	[466.63; 479.37]	6.3%
Mercuro, 2020		466.30	[457.47; 475.13]	5.9%
Moschini, 2020		444.00	[436.55; 451.45]	6.1%
Peng, 2020		445.90	[420.76; 471.04]	2.9%
Ramireddy, 2020		457.00	[447.46; 466.54]	5.8%
Saleh, 2020		470.40	[462.31; 478.49]	6.0%
Torres, 2020		449.90	[434.50; 465.30]	4.6%
Random-effects model		**457.43**	**[451.50; 463.37]**	**100.0%**

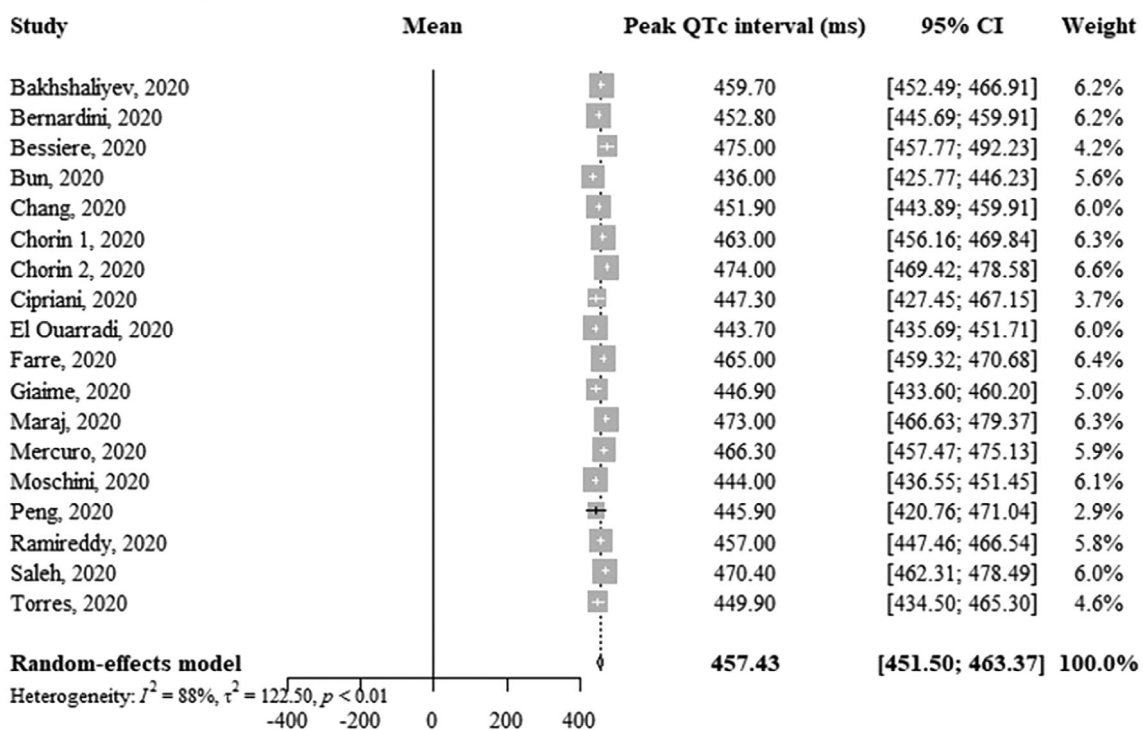Heterogeneity: I^2 = 88%, τ^2 = 122.50, p < 0.01
-400 -200   0   200   400

FIGURE 4 Mean peak QTc interval in COVID-19 patients

≥500 ms was 8% (95%CI, 3%–14%; I² = 92%) in the hydroxychloroquine/chloroquine + azithromycin group (Figure 2). The funnel plot did not show asymmetry and Egger's test was not significant (p = 0.12) (Figure S2 in Data S1).

3.4.2 | Peak QTc change ≥60 ms

In six cohort studies (n = 366), the pooled prevalence of patients with peak QTc change ≥60 ms was 6% (95%CI, 0%–16%; I² = 73) in the hydroxychloroquine/chloroquine group (Figure 3).

In 12 studies (two case series and 10 cohorts, n = 4274), the pooled prevalence of patients with peak QTc change ≥60 ms was 10% (95%CI, 5%–16%; I² = 96%) in the hydroxychloroquine/chloroquine + azithromycin group (Figure 3). The funnel plot showed asymmetry which was significant on Egger's test (p < 0.01) (Figure S3 in Data S1).

3.4.3 | Peak QTc interval

In 10 cohort studies (n = 1052), the pooled mean peak QTc interval was 458.5 ms (95%CI, 436.6–480.4 ms; I² = 99%) in the hydroxychloroquine/chloroquine group (Figure 4). The funnel plot did not show asymmetry and Egger's test was not significant (p = 0.08) (Figure S4 in Data S1).

In 18 studies (two case series and 16 cohorts, n = 1449), the pooled mean peak QTc interval was 457.4 ms (95%CI, 451.5–463.4 ms; I² = 88%) in the hydroxychloroquine/chloroquine + azithromycin group (Figure 4). The funnel plot showed asymmetry which was significant on Egger's test (p = 0.04) (Figure S5 in Data S1).

3.4.4 | Peak QTc change

In seven studies (one case series and six cohorts, n = 505), the pooled mean peak QTc change was 24.8 ms (95%CI, 9.6–40.1 ms; I² = 95%) in the hydroxychloroquine/chloroquine group (Figure 5).

In 11 studies (one case series and 10 cohorts, n = 1168), the pooled mean peak QTc change was 29.6 ms (95%CI, 22.5–36.7 ms; I² = 89%) in the hydroxychloroquine/chloroquine + azithromycin group (Figure 5). The funnel plot did not show asymmetry and Egger's test was not significant (p = 0.14) (Figure S6 in Data S1).
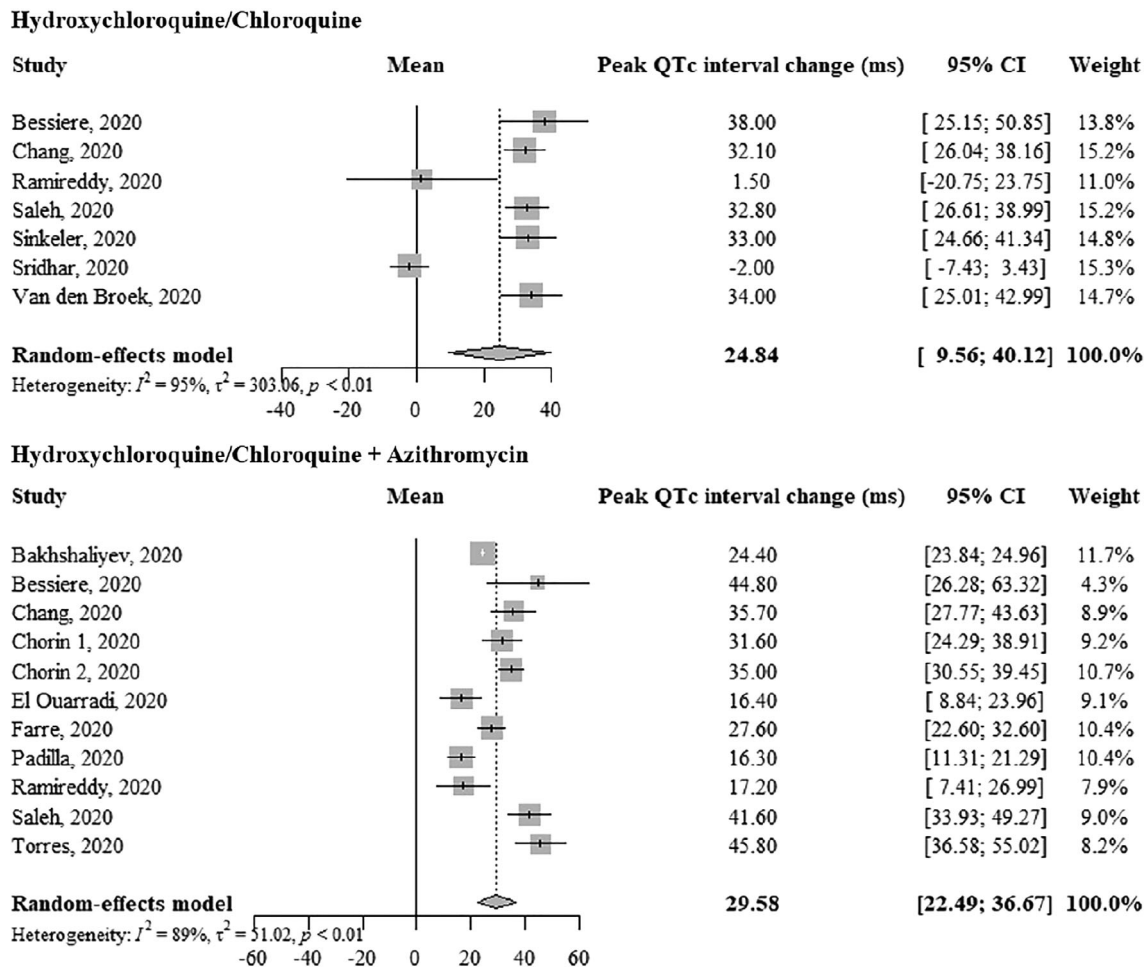

FIGURE 5 Mean peak QTc change in COVID-19 patients

3.4.5 | Ventricular arrhythmias

In 15 studies (one case series, 11 cohorts, and three RCTs, n = 2340), 16 episodes (0.68%; 95%CI, 0.39%–0.11%) of ventricular arrhythmias were reported in patients treated with hydroxychloroquine/chloroquine (Table S2 in Data S1).

In 24 studies (two case series, 19 cohorts, and three RCTs, n = 6368), 25 episodes (0.39%; 95%CI, 0.25%–0.58%) of ventricular arrhythmias were reported in patients treated with hydroxychloroquine/chloroquine + azithromycin (Table S2 in Data S1).

3.4.6 | Torsades de Pointes

In nine studies (one case series, seven cohorts, and one RCT, n = 1500), one episode (0.07%; 95%CI, 0%–0.37%) of TdP were reported in patients who received hydroxychloroquine/chloroquine (Table S2 in Data S1).

In 14 studies (one case series and 13 cohorts, n = 5338), three episodes (0.06%; 95%CI, 0.01%–0.16%) of TdP were reported in patients who received hydroxychloroquine/chloroquine + azithromycin (Table S2 in Data S1).

3.4.7 | Sudden cardiac death

In seven studies (six cohorts and one RCT, n = 660), no episodes of sudden cardiac death were reported in patients treated with hydroxychloroquine/chloroquine (Table S2 in Data S1).

In 15 studies (13 cohorts and two RCTs, n = 5199), two episodes (0.04%; 95%CI, 0%–0.14%) of sudden cardiac death were reported in patients treated with hydroxychloroquine/chloroquine + azithromycin (Table S2 in Data S1).

3.4.8 | Atrioventricular block

In six studies (five cohorts and one RCT, n = 1207), a total of 12 episodes (0.99%; 95%CI, 0.52%–1.73%) of atrioventricular block were reported. Eleven episodes of first-degree atrioventricular block and one episode of atrioventricular block requiring intervention were founded (Table S2 in Data S1). These patients received hydroxychloroquine with or without azithromycin.

3.4.9 | QTc prolongation in studies with a control group

Eight studies with data on QTc prolongation reported a control group (five cohorts and three RCTs). All studies defined the control group without treatment. The dosage of hydroxychloroquine and azithromycin was heterogeneous across studies. Also, only four studies reported the cut-off for the definition of QTc prolongation (range 450–500 ms) and five studies did not describe the timing of ECG assessment.

In seven studies (four cohorts and three RCTs, n = 1139), the use of hydroxychloroquine was associated with a higher risk of QTc prolongation (RR, 2.68; 95%CI, 1.56–4.60; $p < 0.01$; I^2 = 0%) (Figure 6).
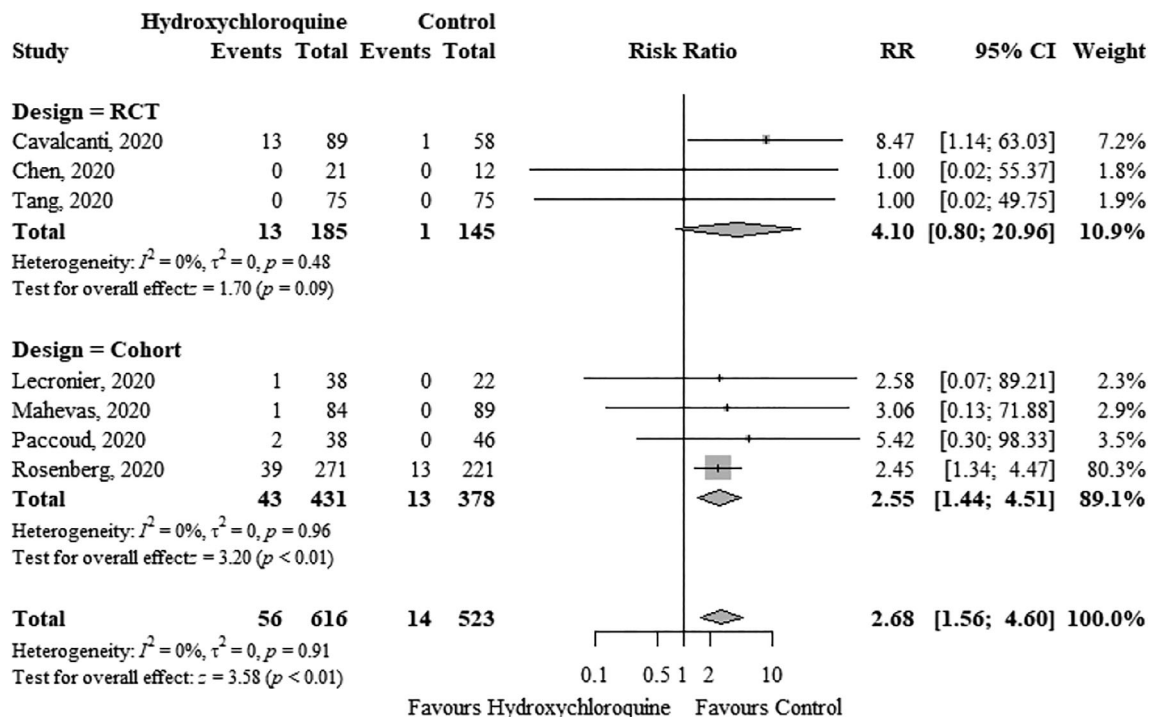

FIGURE 6 Forest plot showing risk ratio and 95% confidence intervals for the effect of hydroxychloroquine on QTc prolongation in COVID-19 patients
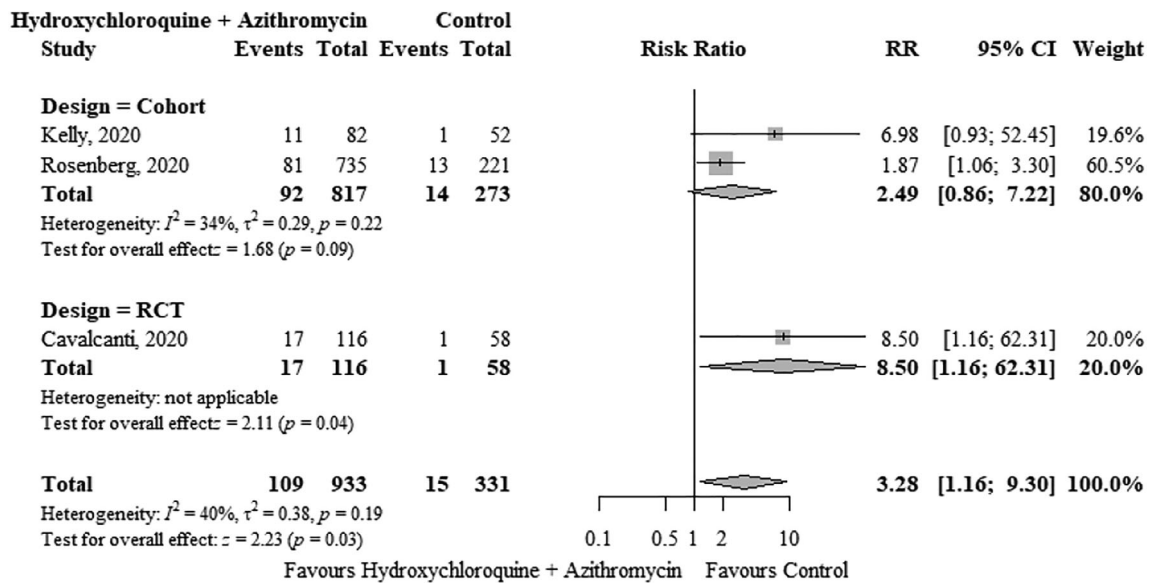
FIGURE 7 Forest plot showing risk ratio and 95% confidence intervals for the effect of hydroxychloroquine + azithromycin on QTc prolongation in COVID-19 patients

In three studies (two cohorts and one RCT, n = 1264), the use of hydroxychloroquine + azithromycin was also associated with a higher risk of QTc prolongation (RR, 3.28; 95%CI, 1.16–9.30; p = 0.03; I^2 = 40%) (Figure 7).

3.5 | Lopinavir/ritonavir

The individual effect of lopinavir/ritonavir on cardiac safety outcomes was only evaluated in three studies (n = 156). Two studies reported no cases of QTc prolongation and one study reported one episode of third-degree atrioventricular block (Table S2 in Data S1).

3.6 | Sensitivity analyses

A sensitivity analyses were performed excluding studies that used the Fridericia formula as the only method for the correction of the QT interval and excluding the case series. No significant differences were found compared to the main analysis (Tables S4 and S5 in Data S1).

4 | DISCUSSION

In our review, we found that the pooled prevalence of peak QTc interval ≥500 ms and peak QTc change ≥60 ms ranged from 6% to 10% in patients treated with hydroxychloroquine/chloroquine with or without azithromycin. The use of hydroxychloroquine and hydroxychloroquine + azithromycin was associated with three times higher risk of QTc prolongation compared with no treatment. The pooled mean peak QTc change varied between 24.8 and 29.6 ms across treatment groups. In contrast, the prevalence of ventricular arrhythmias, TdP, sudden cardiac death, and atrioventricular block was <1%.

Two studies that reported individual data about cardiac safety of lopinavir/ritonavir found no patients with QTc prolongation. The only two studies that reported individual data of lopinavir/ritonavir on QTc prolongation found no cases.

Given the urgent need for useful drugs for COVID-19 management, many repurposed drugs were prescribed in a compassionate manner until more robust data was available.[14] However, two recent systematic reviews have shown that there is insufficient and conflicting evidence of the benefit of treatment with hydroxychloroquine, chloroquine, azithromycin, and lopinavir/ritonavir in COVID-19.[5,69] It is important to remark that repurposing medications for new diseases does not come without the medications known adverse effects and these need to be considered when using them outside of their primary indication. Hydroxychloroquine and chloroquine are drugs commonly used for the treatment of malaria and rheumatological conditions. Although both drugs are generally well-tolerated, they have been associated with an increased risk of QTc prolongation and TdP through blockage of HERG/Kv11.1 potassium channel.[16] The torsadogenic potential of these drugs could be amplified if other QTc-prolonging drugs such as azithromycin and lopinavir/ritonavir are additionally used. Moreover, it is possible that the arrhythmic risk can be even worse in patients with COVID-19 due to the high prevalence of pre-existing heart diseases, electrolyte imbalance, systemic inflammatory process, and myocardial injury observed in COVID-19 patients.[16]

In a large pre-pandemic study of 41 649 hospitalized patients, QTc prolongation was present in the 0.7%, but only 3.8% of those with prolonged QTc interval experienced life-threatening arrhythmias.[70] Other agents (such as procainamide, sotalol, and dofetilide) with known QTc-prolonging effect appears to have a TdP incidence of 1% to 10%.[71] In comparison, our study found a prevalence of about 10% of QTc prolongation in COVID-19 patients who were treated with hydroxychloroquine with or without azithromycin. Furthermore,

it has been reported that up to 38% of critically ill COVID-19 patients presented mild QTc prolongation (>460 ms) at hospital admission, before starting any potentially QT-prolonging drug.[72] This suggests that additional mechanisms responsible for QTc prolongation exist in patients with COVID-19. However, when studies with a control group were pooled, we found that the risk of QTc prolongation was higher in patients who received hydroxychloroquine or hydroxychloroquine + azithromycin compared to those who did not. In addition, many other factors (such as the use of other QT-prolonging drugs and frequency of ECG evaluation) could have influenced the prolongation of QT interval. Therefore, it seems clear that the use of these drugs in COVID-19 patients increases the risk of QTc prolongation, but the relatively high estimated proportion could be overestimated. Our review also shows that ventricular arrhythmias, TdP, and sudden cardiac death were rare events. The very low proportion of these arrhythmic complications can be explained by the short-course duration of COVID-19 therapy, underreporting of arrhythmias, and close ECG monitoring in high-risk cases which allows early discontinuation of QTc-prolonging drugs.

In a recent pharmacovigilance study involving more than 10 million patients, the hydroxychloroquine use was associated with higher reporting of complete atrioventricular block (odds ratio: 2.30, 95%CI 1.55–3.41).[73] Has been found that in nearly half of COVID-19 patients, the PR interval showed paradoxical prolongation or lack of shortening with increasing heart rate.[74] This abnormal PR interval behavior could be explained by the action of anticardiolipin antibodies (reported in COVID-19 patients) on the cardiac conduction system.[74] Although we found a low prevalence (1%) of atrioventricular block in COVID-19 patients, only one case of atrioventricular block requiring intervention was documented.

Lopinavir/ritonavir is a combination of protease inhibitor with nucleoside analog that is commonly used for the treatment of human immunodeficiency virus. This drug has shown a favorable clinical response in patients with severe acute respiratory syndrome caused by a previous coronavirus, thus it has been used in the current COVID-19 pandemic.[14] However, recent studies have reported no clinical benefits in COVID-19.[26,75] Although lopinavir/ritonavir is included in the group of agents that can prolong the QTc interval, the limited information about their pro-arrhythmic effect in COVID-19 patients showed no cases with QTc prolongation.[76] However, there is still insufficient evidence about the cardiac safety profile of this drug.

In the absence of strong efficacy data, all treatments should be individualized in each patient. Our study raises important cardiac safety concerns about the "off-label" use of these repurposed drugs in COVID-19. Although the proportion of individuals at risk for lethal arrhythmias is very small, given the rapid global spreading of COVID-19, the absolute number of potentially affected people is large. Several scientific societies such as the European Society of Cardiology,[77] Heart Rhythm Society,[78] and Canadian Heart Rhythm Society[79] have issued recommendations to minimize the risk of QTc prolongation and arrhythmic events during COVID-19 treatment. These recommendations are focused on the identification of patients at high risk for drug-induced ventricular arrhythmias through baseline and follow-up ECG monitoring, discontinuation of unnecessary drugs that can prolong the QTc interval, and correction of electrolyte disturbances (e.g., hypocalcemia, hypokalemia, and hypomagnesemia).

There is only one published systematic review examining the effect of hydroxychloroquine or chloroquine on QTc interval and its related arrhythmic events in COVID-19.[80] However, this review only conducted a narrative synthesis of 11 studies without risk of bias assessment. In comparison, our review included more studies (n = 47), performed the meta-analyses for relevant cardiac safety outcomes, and evaluated the risk of bias for all studies.

Our study has some limitations. First, given that most of the included studies were observational, causality cannot be concluded. Second, heterogeneity in most studies was high. Possible reasons include sample size, the variable dosage of drugs, heterogeneous population (varying comorbidities and COVID-19 severity), among others. Third, there is a wide range of reported timing of measurement of the QT interval. This could have influenced the rate of detection of QTc prolongation due to more frequent ECG performance. Finally, most studies did not have a control group. However, our analysis of the few studies with a control group shows that the use of hydroxychloroquine for the treatment of COVID-19 increased the risk of QTc prolongation.

5 | CONCLUSIONS

Our meta-analysis shows evidence that COVID-19 patients treated with hydroxychloroquine/chloroquine with or without azithromycin had a relatively high prevalence of peak QTc interval ≥500 ms and peak QTc change ≥60 ms. Likewise, the risk of QTc prolongation was higher in patients who received hydroxychloroquine and hydroxychloroquine + azithromycin compared to no treatment. In contrast, the prevalence of reported arrhythmic events was very low, probably due to underreporting. The limited data about lopinavir/ritonavir showed that it does not prolong the QTc interval. Therefore, these drugs should be used under adequate clinical and electrocardiographic monitoring.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
All authors contributed to the study conception and design. Articles selection, data extraction, and data analysis were performed by Carlos Diaz-Arocutipa and Ana Brañez-Condorena. The first draft of the manuscript was written by Carlos Diaz-Arocutipa and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ETHICS STATEMENT
The authors state no ethical approval was needed.

PATIENT CONSENT

Not applicable.

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SUPPORTING INFORMATION

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