

Hydroxychloroquine versus hydroxychloroquine-azithromycin combination therapy on QT interval prolongation of COVID-19 patients: a systematic review and meta-analysis

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SOUHRN

Výzkum zaměřený na léčbu onemocnění COVID-19 vedl k použití hydroxychlorochinu (HCQ) jako jedné z možností léčby. Účinnost HCQ lze zvýšit jeho podáváním v kombinaci s azitromycinem (AZM). Hydroxychlorochin však může spouštět arytmiie v podobě prodloužení intervalu QT. Přidání AZM k HCQ by rovněž mohlo zvýšit riziko prodloužení intervalu QT. Protože mechanismus účinku těchto látek stále není přesně znám, je naprosto nezbytné provést systematický přehled výsledků dosavadního výzkumu. Cílem předložené studie bylo porovnat incidenci prodloužení intervalu QT u pacientů s onemocněním COVID-19 léčených podáváním HCQ a pacientů s kombinací HCQ-AZM. Uspořádáním se jednalo o komparativní studii dvou samostatných skupin pacientů. Údaje byly shromažďovány z časopisů publikovaných online v období od ledna do července 2020, v nichž se srovnávala incidence prodloužení intervalu QT u pacientů s onemocněním COVID-19 léčených buď HCQ samotným, nebo kombinací HCQ-AZM; články byly následně zařazeny do systematického přehledu. Bylo nalezeno pět studií splňujících zadaná kritéria; výsledný vzorek zahrnoval 477 osob ve Francii a v USA. Údaje byly následně zpracovány formou deskriptivní a statistické analýzy. Statistická analýza se prováděla pomocí fixního modelu s použitím poolovaných údajů. Analýza nenalezla žádný statisticky významný rozdíl ve výskytu prodloužení intervalu QT mezi skupinami pacientů s onemocněním COVID-19 léčenými podáváním buď pouze HCQ, nebo kombinací HCQ-AZM (OR 1,294; 95% CI 0,707–2,370).

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ABSTRACT

Research related to the treatment of COVID-19 put hydroxychloroquine (HCQ)-based as a treatment option. The effectiveness of HCQ can be increased if combined with azithromycin (AZM). However, HCQ can trigger arrhythmias in the form of QT interval prolongation. Combining AZM to HCQ might also amplify the risk of QT prolongation. Since the mechanism remains elusive, a systematic review study of existing research is absolutely necessary. This study aimed to compare the incidence of QT interval prolongation in COVID-19 patients who received HCQ therapy with those who received HCQ-AZM therapy. The design used is comparative study of two independent groups. Data were collected from journals published online, from January to July 2020, regarding the comparison of QT interval prolongation between COVID-19 patients treated with HCQ only and those treated with HCQ-AZM combination, which had undergone a systematic review. Five studies that met the criteria were obtained, which included a total sample of 477 people in France and the United States. The data were then analysed descriptively and statistically. Statistical analysis was done using the fixed-effects model from the pooling of the research. It was found that there is no significant difference statistically in the QT interval prolongation between HCQ therapy group and HCQ-AZM therapy group (OR 1.294; 95% CI 0.707–2.370).

Keywords:

Azithromycin

COVID-19

Hydroxychloroquine

QT interval prolongation

Introduction

SARS-CoV-2 as the new corona virus has spread throughout the world causing a global pandemic of Coronavirus disease 2019 (COVID-19). This new virus was known to attack multiple organs in the body which was fatal in some cases. The

leading death causes are respiratory failure, cardiac failure and sepsis.¹ Several research to find the definite therapy has been done because of the high mortality rate, though the effective definite therapy for COVID-19 has not yet been found.² Several potential therapies are currently under investigation, including the usage of hydroxychloroquine.

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Hydroxychloroquine is an antimalarial and immunomodulatory agent, also a safer analogue of chloroquine.³ It has demonstrated antiviral activity against SARS-CoV-2 although the mechanism of action has yet to be known. It is believed to disturb the life cycle of the virus in the cell and disturb the glycolysis process of ACE-2 receptor thus disrupting the docking process of the virus.^{4,5} The drug increases intracellular pH resulting in decreased phago-lysosome fusion, impairing viral receptor glycosylation. In addition, it has an immune-modulating effect by inhibiting toll-like receptor signalling, decreasing production of cytokines especially IL-1 and IL-6.³ Although several researches have been conducted to investigate the usage of hydroxychloroquine in decreasing the mortality rate, there are still arguments in its result.⁶

A study conducted in Turkey showed that combining hydroxychloroquine with azithromycin could increase its effectiveness and decrease patients' length of stay in hospital.⁶ Azithromycin, a macrolide antibiotic, has in vitro antiviral properties such as decreasing viral replication, blocking entrance into host cells, and a potential immunomodulating effect.⁷ An in vitro study demonstrated synergistic activity of the combination of hydroxychloroquine and azithromycin against SARS-CoV-2.⁸

Although hydroxychloroquine can be a treatment for COVID-19 patients, it has shown to cause several dangerous side effects including cardiac toxicity which cause arrhythmia, QT interval prolongation, torsade de pointes, and can be fatal. Combining hydroxychloroquine and azithromycin can also increase its cardiac toxicity.^{9,10}

This review and meta-analysis aimed to investigate the prolongation of QT interval in COVID-19 patients who received hydroxychloroquine therapy compared with COVID-19 patients who received hydroxychloroquine-azithromycin combination therapy across recent studies.

Methods

The obtained data were processed with PRISMA (Preferred Reporting Items for Systematic Review and Meta Analysis) method. The search was done between July 18th to 24th 2020 on two online databases: PubMed and Google Scholar. On PubMed, using the PICO system, the keywords were: "COVID-19" (Patient/Problem), "Hydroxychloroquine" (Intervention), "Hydroxychloroquine and Azithromycin" (Comparison), and "QT interval" (Outcome). While on Google Scholar the search term used was "COVID-19 AND Hydroxychloroquine AND combination Hydroxychloroquine and Azithromycin AND prolong QT interval". The search was limited to original free full text articles and articles published from January to July 2020.

The search results were screened based on the title and abstract by seven independent reviewers. Afterwards the selected articles were checked for the full text availability and duplications amongst the selected articles. The inclusion criteria of the studies were RCT, prospective cohort, or retrospective cohort studies performed among adult patients with COVID-19 which compared patients who received hydroxychloroquine and patients who received hydroxychloroquine-azithromycin combination therapy. The outcome investigated in this study was QT interval prolongation. The quality of the study was assessed using the Effective Public Health Practice Project quality assessment tool (EPHPP) and were graded as strong, moderate, and weak. The eligibility and quality of the studies were assessed by four reviewers and the final check was done by another two reviewers.

Extraction of data was conducted independently by two authors using a standardized data collection form from Cochrane library. Extracted data included study characteristics (author, year of publication, region, time of study, study design, sample size, inclusion criteria), population character-

Table 1 – Sample size and limitation of the studies used

Author	QT interval prolongation		Limitation
	HCQ therapy	HCQ+AZT therapy	
Bessière et al., 2020	7 of 22 patients (31.8%)	7 of 18 patients (38.9%)	• There are no baseline clinical factor data related to QT prolongation
Saleh et al., 2020	7 of 82 patients (8.6%) with QTc >500 ms and 5 patients (6.3%) ΔQTc 60 ms	11 of 119 patients (9.2%) with QTc >500 ms and 21 patients (17.9%) ΔQTc 60 ms	• Chloroquine is included in the sample using HCQ • There are no patient data that show patients with QTc >500 ms and ΔQTc ≥60 ms simultaneously
Ramireddy et al., 2020	0 of 10 patients (0%) with QTc >500 ms or ΔQTc 60 ms	7 of 61 patients (11.5%) with QTc >500 ms or ΔQTc 60 ms	• There is no control group • Inconsistency of ECG checking during therapy • Low sample size
Mercuro et al., 2020	8 of 37 patients (21.6%) • 7 patients (18.9%) QTc >500 ms • 3 patients (8.1%) ΔQTc 60 ms • 2 patients (5.4%) have both	13 of 53 patients (24.5%) • 11 patients (20.8%) QTc >500 ms • 7 patients (13.2%) ΔQTc 60 ms • 5 patients (9.4%) have both	• Not all patients experienced repeated ECG to be followed up • Cannot rule out cardiomyopathy and myocarditis due to COVID-19
Enzman et al., 2020	0 of 9 patients (0%)	15 of 66 patients (22.7%) QTc >500 ms	• Limited samples • 10 patients of 66 HCT + AZM patients have concomitant cardiovascular disease
TOTAL	22 of 160 patients (13.8%)	53 of 317 patients (16.7%)	

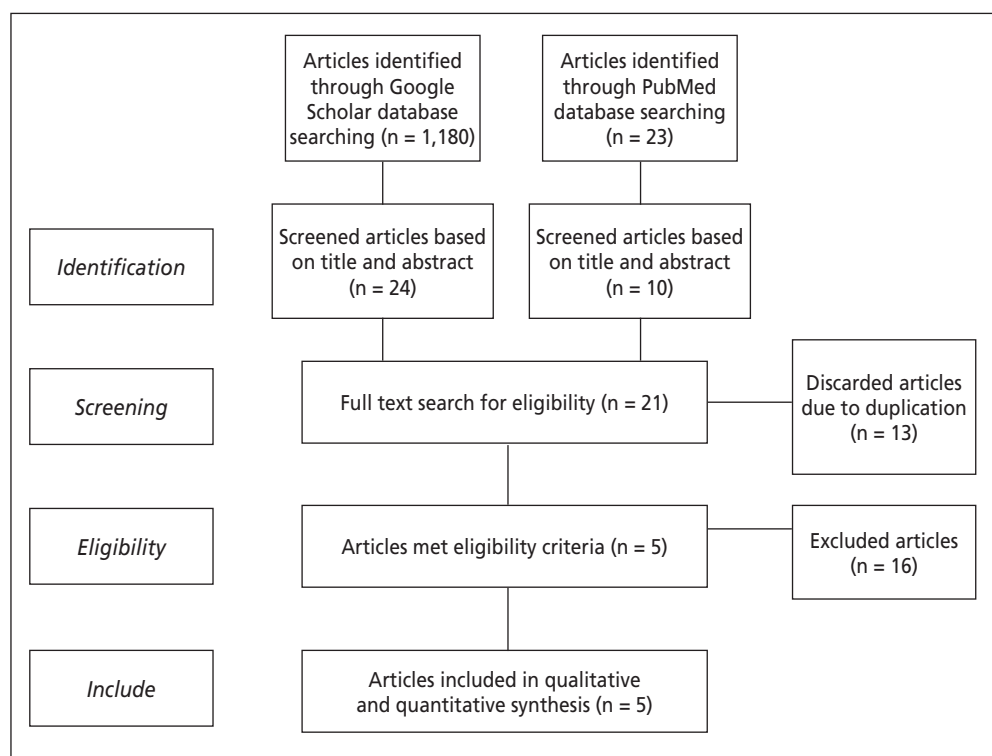


Fig. 1 – Flowchart for study design using PRISMA

istics, intervention characteristics (size of each intervention group, dosage, duration therapy, QT interval assessment) and outcomes (QT interval prolongation, limitation of study).

Statistical analysis was performed using CMA V3 (Comprehensive Meta Analysis V3) software. Odds Ratio (OR) was used for estimating the outcome with 95% confidence Interval (CI). The fixed effects model was used with $I^2 \leq 50\%$ which represents unimportant heterogeneity.

Results

Qualitative synthesis

The initial searches identified 1,203 articles and 1,182 were excluded after the title and abstracts screening process. The 21 potential studies were assessed for its full text eligibility and 16 were excluded. The excluded ones were articles other than the original article (review, trial protocol, etc.), articles which were not relevant to the study objective, and studies assessing the QT interval prolongation side effect of other COVID-19 potential therapy (Fig. 1). In the final result, 5 articles were included with 477 patients

who met the inclusion criteria and could be further statistically analyzed (Table 1).^{11–15}

Based on the EPHPP quality assessment tool, it was unclear regarding the blinding of participants.^{11–15} There were also absent details regarding the combined therapy and the outcome assessors in one of the studies.¹⁴ The EPHPP quality assessment tool showed 2 studies were strong in quality^{8,9} and 3 studies were moderate in quality (Table 2)^{13–15}.

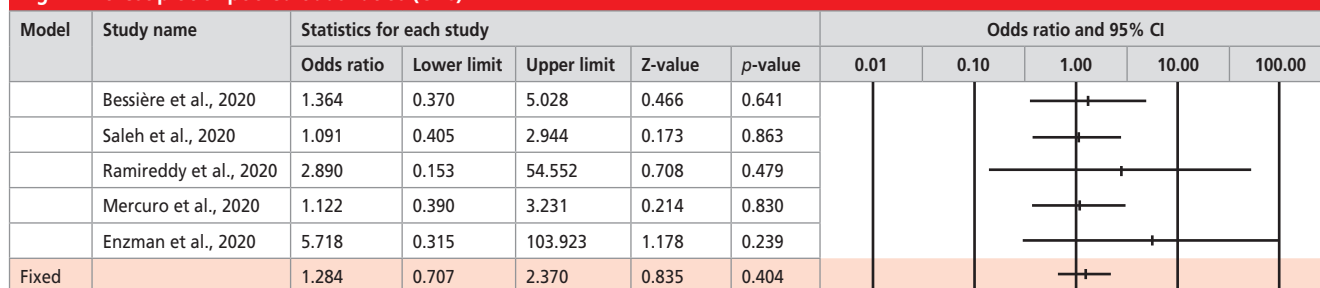
Four of the studies were cohort study^{11,12,14,15} and one was repeated measure study.¹³ Studies were heterogeneous in its design and sample size. Most of the studies had a larger size of sample group which received combined hydroxychloroquine and azithromycin. There was some difference in dosage and duration of the therapy used among the studies. One of the studies did not mention the dosage and duration of the hydroxychloroquine and azithromycin combination therapy.¹⁴ The assessment of QTc interval was carried out once every day before, during, and after the interventional therapy. Only one study did not mention the detailed QTc interval assessment.¹⁴ Characteristics of the selected studies can be seen in Table 3.

Table 2 – Quality assessment of the studies based on EPHPP quality assessment tool

Author	A (Selection bias)	B (Study design)	C (Confounders)	D (Blinding)	E (Data collection method)	F (Withdrawal and dropout)	Global rating
Bessière et al., 2020	Moderate	Moderate	Strong	Moderate	Moderate	Strong	Strong
Saleh et al., 2020	Strong	Moderate	Strong	Moderate	Strong	Moderate	Strong
Ramireddy et al., 2020	Moderate	Moderate	Weak	Moderate	Strong	Strong	Moderate
Mercuro et al., 2020	Moderate	Moderate	Weak	Moderate	Moderate	Strong	Moderate
Enzmann et al., 2020	Moderate	Moderate	Weak	Moderate	Strong	Strong	Moderate

Table 3 – Characteristic of selected studies

Author	Location and time	Study design	Study subject	Comorbidity	Inclusion criteria	Exclusion criteria	Sample size	Statistical outcome	Result
Bessière et al., 2020	France, 15th March–29th March 2020	Retrospective cohort	40 COVID-19 patients with critical illness in ICU	16 patients (40%) with DM, 23 patients (57.5%) with hypertension, and 8 patients (20%) with structural heart disease	COVID-19 patients confirmed with PCR	Patients with QTc more than 460 ms before treatment	N = 40, HCQ = 22, HCQ + AZM = 18	QT interval prolongation in: HCQ therapy: 7 out of 22 patients (31.8%), HCQ + AZM therapy: 7 out of 18 patients (38.9%) $p = 0.03$	There is no significant difference in QT interval prolongation between HCQ therapy and HCQ combination AZM therapy
Saleh et al., 2020	New York, USA, March 2020	Observational	201 COVID-19 patients	60% patients with hypertension, 41.8% with hyperlipidemia, 32.3% with diabetes mellitus, 7% with atrial fibrillation, 11.4% with coronary artery disease, 14.9% with COPD/asthma, 5% with CKD stage >III	COVID-19 patients confirmed with PCR or high suspicious COVID-19 patients with ARDS or SIRS, or patients with at least 6 hours of clinical ARDS symptoms	Patient with long-term HCQ treatment (patients with lupus, or hypersensitivity) and patients who reject therapy	N = 201, CQ = 10, HCQ = 82, HCQ + AZM = 119	QT interval prolongation in: HCQ therapy: 7 out of 82 patients (8.6%), HCQ + AZM therapy: 11 out of 119 patients (9.2%) $p = 1.00$	There is a significant increase in QT interval prolongation in patients with combination therapy
Ramireddy et al., 2020	Cedars-Sinai Medical Center, Los Angeles, CA, date not mentioned	Repeated measure study	COVID-19 confirmed patients hospitalized in Cedars-Sinai Medical Center from 1st February until 4th April 2020 who received hydroxychloroquine, azithromycin, or combination therapy	Not mentioned	Confirmed COVID-19 patients with at least 2 data of 12 lead ECG recorded with MUSE system from 1st January to 5th April 2020	Patients with tachyarrhythmia, atrial fibrillation, atrial flutter, supraventricular tachycardia, and ECG record that is not suitable to determine the QT interval accurately	N = 71, HCQ = 10, HCQ + AZM = 61	QT interval prolongation in: HCQ therapy: 0 out of 10 patients (0%), HCQ + AZM therapy: 7 out of 61 patients (11.5%) $p = 0.07$	Incidence of QT interval prolongation increased in patients who received combination therapy
Mercuro et al., 2020	Boston, Massachusetts, date not mentioned	Observational (cohort)	COVID-19 confirmed patients from 1st May until 7th April 2020 who received at least 1-day therapy of chloroquine	53.3% patients with hypertension, 10% with congestive heart failure, 28.9% with diabetes mellitus, 11.1% with coronary heart disease, 13.3% with atrial fibrillation, 20% with COPD/asthma	Not mentioned	Not mentioned	N = 90, HCQ = 37, HCQ + AZM = 53	QT interval prolongation in: HCQ therapy: 7 out of 37 patients (18.9%), HCQ + AZM therapy: 11 out of 53 patients (20.8%), $p < 0.001$. Adjusted odds ratio 3.38 (95% CI 1.03–11.08)	Patients who received HCQ therapy has higher risk of QT interval prolongation incidence, and patients with combination therapy had even higher risk
Enzmann et al., 2020	Sanford Health hospitals, Dakota, March 2020	Cohort	150 COVID-19 confirmed patients of 3 hospitals in Dakota from 21st March to 20th April 2020	51.3% patients with cardiovascular disease, 28.7% with diabetes mellitus, 18% with asthma, 15.3% with chronic renal disease, 10.7% with COPD	COVID-19 confirmed patients with PCR test in Sanford Health hospital	Not mentioned	N = 75, HCQ = 9, HCQ + AZM = 66	QT interval prolongation in: HCQ therapy: 0 out of 9 patients (0%), HCQ + AZM therapy: 15 out of 66 patients (22.7%)	There is a higher incidence of QT interval prolongation in patients who received combination therapy compared with patients with HCQ therapy

Fig. 2 – Forest plot of pooled odds ratios (ORs)

Quantitative synthesis

We performed a meta-analysis on 5 studies (477 patients) regarding the QT interval prolongation between COVID-19 patients who received hydroxychloroquine and COVID-19 patients who received combined hydroxychloroquine-azithromycin therapy. The meta-analysis showed that there is no statistically significant difference in QT interval prolongation between group of patients which received hydroxychloroquine and group of patients which received combined hydroxychloroquine-azithromycin therapy (OR 1.294; 95% CI 0.707–2.370; *p*-value 0.404) (Table 4, Fig. 2).

Discussion

By the end of 2020, hydroxychloroquine and chloroquine used for COVID-19 treatment, have been prohibited by The United States Food and Drug Administration (FDA) and World Health Organization (WHO) because of its ineffectiveness and inability to reduce mortality.^{16,17} Despite that fact, several studies stated that there are benefits of using hydroxychloroquine and chloroquine in COVID-19 treatment.¹⁸ The American Thoracic Society recommends the use of hydroxychloroquine and chloroquine in hospitalized patients with evidence of pneumonia on a case-by-case basis.¹⁹ Meanwhile, the Indian Medical Research Council is one of the first medical councils worldwide to issue recommendations for hydroxychloroquine prophylaxis among healthcare providers and close contacts involved in COVID-19 treatment or suspected patients, asymptomatic healthcare workers stationed in non-COVID-19 areas and hospitals, asymptomatic front-line personnel such as those involved in surveillance, police, and paramilitary services.²⁰ This shows that there are still potential benefits in using hydroxychloroquine for COVID-19 treatment. For groups which still use hydroxychloroquine

as treatment modalities for COVID-19, its adverse effect shall not be left out, including prolonged QTc.

In this study, three studies stated that there is a relationship between hydroxychloroquine treatment with prolonged QTc although not statistically significant.^{11,12,14} One study only showed clinical results without statistical analysis.¹² Other studies found no relationship between hydroxychloroquine treatment and prolonged QTc.^{13,15} Different results in the studies could be caused by several factors such as small number of study samples, patient's clinical condition, and also existing cardiac disease like cardiomyopathy and myopathy that was hard to be excluded.¹⁴ The use of vasoactive drugs and Simplified Acute Physiology Score (SAPS) II can also significantly influence the presence of a prolonged QT.¹¹ Absence of prolonged QTc interval in several studies could cause bias in determining the adverse event which might result in double counted or uncounted data.¹² Additional drugs used in the treatment like loop diuretic could also prolong QTc interval. Incomplete data regarding patient's symptoms before admitted to the hospital could also create bias in the reviewed studies.¹³

Two of the reviewed studies showed no prolonged QTc interval with hydroxychloroquine therapy. This could be caused by the small number of samples which received hydroxychloroquine therapy in both studies compared to the samples which received hydroxychloroquine-azithromycin combination therapy. Because of that, it couldn't be proved that there were no correlations between hydroxychloroquine therapy and prolonged QTc interval.¹³

In the five studies reviewed by the author, there were almost uniform results in which populations with hydroxychloroquine-azithromycin combination therapy had a QTc interval prolongation >500 ms. As one of COVID-19 choices of antiviral treatment, the combination regimen of hydroxychloroquine and azithromycin has been con-

Table 4 – Odds ratio of QT interval prolongation comparison between patients with HCQ-AZM combination therapy and HCQ therapy

Author	Combination hydroxychloroquine-azithromycin therapy		Hydroxychloroquine therapy		Odds ratio	Lod odds ratio	Std. err
	Interval QTc >500 ms	Interval QTc ≤500 ms	Interval QTc >500 ms	Interval QTc ≤500 ms			
Bessière et al., 2020	7 (38%)	11 (61%)	7 (31.8%)	15 (68.2%)	1.364	0.310	0.666
Saleh et al., 2020	11 (9.2%)	108 (90.7%)	7 (8.5%)	75 (91.5%)	1.091	0.087	0.506
Ramireddy et al., 2020	7 (11.5%)	54 (88.5%)	0 (0%)	10 (100%)	2.890	1.061	1.499
Mercuro et al., 2020	11 (20.8%)	42 (79.2%)	7 (18.9%)	30 (81.1%)	1.122	0.116	0.539
Enzmann et al., 2020	15 (22.7%)	51 (77.3%)	0 (0%)	9 (100%)	5.718	1.744	1.480
Total	51 (16.1%)	266 (83.9%)	21 (13.1%)	139 (86.9%)			

siderably investigated regarding its effectiveness and safety.^{11–15,21,22} Unfortunately, there is still a debatable discussion following that topic since there is not yet any research regarding this treatment with randomized blinded controlled clinical trials design.²³

Theoretically, combining azithromycin with hydroxychloroquine might worsen QT prolongation incidence, compared to single therapy of hydroxychloroquine. However, this study proves that there is no significant difference among both regimens. This may be caused by the study that provides as data a different number of samples, in which there is an unproportioned number between each group, as well as inconsistent total sample between each study.¹³ Jankeson et al.²⁴ suggested that it was hydroxychloroquine which has an important role in causing prolonged QTc interval. Nevertheless, the fact that limited study regarding the difference between hydroxychloroquine and combination of hydroxychloroquine-azithromycin to their effect of QT prolongation should also be anticipated.

This study has several limitations. The fact that there is no data in the reviewed studies about the duration of patient's symptoms before admission to the hospital can cause bias regarding the history and duration of COVID-19 infection. Another thing is that several reviewed studies only gave clinical results without statistically analysing them because of the small number of the study sample and the non-randomized study sample. The reviewed studies had different dosage and duration of the therapy given between each study. There is one study that didn't mention the dosage and the duration of therapy given.

Conclusion

In this study, involving 477 patients in the five publications studied, it can be concluded that there was no significant difference of the QTc prolonged interval in COVID-19 patients who received hydroxychloroquine therapy with those who received hydroxychloroquine-azithromycin combination therapy. However, there are some differences in treatment from each journal studied, namely the dose used, duration of therapy, inconsistencies in ECG measurements during therapy, and other risk factors that can also cause prolongation of the QTc interval.

Conflict of interest

There is no conflict of interest in this study.

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None

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