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Frequency of Long QT in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine: A Meta-analysis

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ABSTRACT

Introduction Hydroxychloroquine (HCQ) has been proposed as a SARS-CoV-2 treatment but the frequency of long QT (LQT) during use is unknown.

Objective To conduct a meta-analysis of the frequency of LQT in patients with SARS-CoV-2 infection treated with HCQ.

Data Sources PubMed, EMBASE, Google Scholar, the Cochrane Database of Systematic Reviews and preprint servers (medRxiv, Research Square) were searched for studies published between December 2019 and June 30, 2020.

Methods Effect statistics were pooled using random effects. The quality of observational studies and randomized controlled trials was appraised with STROBE and the Cochrane Risk of Bias Assessment tools, respectively.

Outcomes Critical LQT was defined as: (1) maximum QT corrected (QTc)≥500 ms (if QRS<120 ms) or QTc≥550 ms (if QRS≥120 ms), and (2) QTc increase ≥60 ms.

Results In the 28 studies included (n=9124), the frequency of LQT during HCQ treatment was 6.7% (95% confidence interval [CI]: 3.7-10.2). In 20 studies (n=7825), patients were also taking other QT-prolonging drugs. The frequency of LQT in the other 8 studies (n=1299) was 1.7% (95% CI: 0.3-3.9). Twenty studies (n=6869) reported HCQ discontinuation due to LQT, with a frequency of 3.7% (95% CI: 1.5-6.6). The frequency of ventricular arrhythmias during HCQ treatment was 1.68% (127/7539) and that of arrhythmogenic death was 0.69% (39/5648). *Torsades de Pointes* occurred in 0.06% (3/5066). Patients aged >60 years were at highest risk of HCQ-associated LQT (P<0.001).

Conclusions HCQ-associated cardiotoxicity in SARS-CoV-2 patients is uncommon but requires ECG monitoring, particularly in those aged >60 years and/or taking other QT-prolonging drugs.

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1. Introduction

Hydroxychloroquine (HCQ) is one of the drugs in the still limited therapeutic armamentarium used during the SARS-CoV-2 pandemic. HCQ may block virus infection by increasing the endosomal pH required for virus/cell fusion, and by interfering with the glycosylation of cellular receptors of SARS-CoV [1]. HCQ is a safe drug in rheumatoid arthritis and systemic lupus erythematosus; however, adverse reactions in patients with SARS-CoV-2 are currently under scrutiny. Amid the pandemic, controversy has arisen regarding the cardiotoxicity of HCQ, particularly HCQ-induced long QT (LQT) [2]. The QT interval on an electrocardiogram (ECG) is the time between the start of the QRS complex and the end of the T wave. Physiologically, it represents the sum of the action potential (AP) of ventricular myocytes, and the total duration of the depolarization phase and cardiac repolarization [3]. The clinical reading of the QT interval normally takes into account a correction for the heart rate (QTc).

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The mechanism of HCQ-induced LQT comprises blocking of the rapidly activating delayed rectifier K^+ current encoded by the human ether-a-go-go-related gene (hERG) and blocking of sodium, calcium and other potassium channels. Inhibition of the hERG channel can prolong the action potential duration and, consequently, the QT interval [2]. When QT prolongation occurs, there is a potential risk of causing one-way block, recurrent extrasystoles, re-entry, and *Torsades de pointes* ("twisting of the points", TdP). TdP is a form of ventricular tachycardia that presents clinically as reversible syncope or may degenerate into ventricular fibrillation, cardiac arrest, and sudden death [4]. Drugs used in the treatment of SARS-CoV-2 infection that are associated with drug-induced LQT include chloroquine (CQ), HCQ, azithromycin (AZI), and lopinavir/ritonavir. A criterion for the diagnosis of drug-induced LQT is a QT prolongation ≥500 milliseconds (ms) [5].

The association between HCQ use and drug-induced LQT in patients with SARS-CoV-2 infection is unknown. The objective of the present meta-analysis was to evaluate the frequency of LQT in patients with SARS-CoV-2 infection treated with HCQ. Data were also collected on discontinuation of HCQ, simultaneous use of other QT-prolonging medications, frequency of arrhythmias during HCQ treatment, and arrhythmogenic death.

2. Methods

This study was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [6].

2.1. Search strategy

Two independent investigators performed a systematic search in PubMed, EMBASE, Google Scholar, preprint servers (medRxiv, Research Square) and the Cochrane Database of Systematic Reviews for studies published between December 2019 and June 30, 2020. In addition, a secondary search was conducted based on the references lists of retrieved articles. The PubMed search strategy is detailed in Supplementary Table A.

2.2. Eligibility criteria

We searched for randomized controlled trials (RCTs) or observational studies reporting data on LQT in patients with SARS-CoV-2 infection taking HCQ. We included studies in English or other languages (all ages) meeting the following criteria: a) COVID-19 patients were diagnosed according to the interim guidance of the World Health Organization [7]; b) studies assessing the risk of HCQ-associated LQT in SARS-CoV-2 infection in which ECGs were recorded at documented timepoints before and after drug administration; c) critical QTc prolongation was defined as: (1) maximum QTc ≥500 ms (if QRS <120 ms) or QTc ≥550 ms (if QRS ≥120 ms) and (2) QTc increase ≥60 ms [8]; d) sufficient data were reported to calculate frequency of HCQ-induced LQT, arrhythmias during treatment, arrhythmogenic death, discontinuation of HCQ, and simultaneous use of other QT-prolonging agents.

2.3. Quality assessment

The quality of observational studies (cohort, case-control and cross-sectional studies) and randomized controlled trials (RCTs) were appraised according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [9] and the Cochrane Risk of Bias Assessment Tool [10], respectively. Two investigators independently evaluated the quality of the studies. Conflicting results were resolved by discussion and involvement of a third reviewer if necessary.

2.4. Data extraction

The following data were extracted from each study: authors, study location, year of publication, study design, number of participants, sex, age at baseline, outcome definition, exposure definition, follow-up, effect estimates and 95% CIs. Also collected were: a) anti-COVID-19 treatment indication, participant inclusion and exclusion criteria, and number of study participants who had ECG monitoring; b) ECG measurement methodology (e.g. centralized or study site-based, manual or automated, cardiologist or other physician reader, intermittent or continuous, any other relevant details); and c) cardiovascular adverse events: sudden cardiac death, life-threatening ventricular tachyarrhythmias (ventricular fibrillation, ventricular tachycardia, TdP), any other clinically significant arrhythmias or cardiovascular adverse events.

2.5. Statistical analyses

The frequency of LQT during HCQ treatment, arrhythmogenic death, discontinuation of HCQ, frequency of simultaneous use of other QT-prolonging agents and frequency of arrhythmias during treatment were calculated. Random effects with an inverse variance method was used to calculate the pooled risk ratios (RRs) and 95% confidence intervals (CI) according to the heterogeneity between studies [11]. The overall estimates in the pooled analysis were obtained using Stata 13 software (Stata Corp LP, College Station, TX).

3. Results

After screening 833 citations, 28 studies (27 observational and 1 RCT) [8,12–38] were included (Figure 1), with a total sample of 9124 participants. The characteristics of included studies are summarized in Table 1. Eleven studies were from the USA, with the other 17 from France (6), China (1), India (1), Tunisia (1) Brunei (1), Italy (2), Malaysia (1), Cameroon (1) and Spain (2); one study included patients from USA and Italy. Overall, mean (standard deviation [SD]) age was 59.0 (9.1) years and 63.1% were men. In 25 studies, the proportion of men was more than 50%. In the 24 studies (7646 patients) where the dose of HCQ administered and the duration of treatment were reported, the mean (SD) total cumulative dose of HCQ was 3458 (2521) mg with a mean exposure duration of 7 (3) days. The three most frequent comorbidities were hypertension (73%), diabetes mellitus (49%) and chronic obstructive pulmonary disease (20%) (Table 1). The mean STROBE score of included studies was 85.6 (SD 8.3).

In the 28 studies included (n=9124), the frequency of LQT during HCQ treatment was 6.7% (95% CI: 3.7-10.2) (Figure 2). In 20 studies (n=7825), patients were taking other QT-prolonging drugs as well as HCQ. In 18 studies (n=7399), patients were reported to be taking AZI and in 8 of those 18 studies, patients were also on other QT-prolonging drugs, with lopinavir/ritonavir, propofol and amiodarone the three most common [12,15,19–21,23,32,33]. The frequency of LQT in the 8 studies where HCQ was taken without other QT-prolonging drugs (n=1299) was 1.7% (95% CI:0.3-3.9). (Figure A, Supplementary file). Twenty studies (n=6869) reported HCQ discontinuation due to LQT, with an overall frequency of 3.7% (95% CI: 1.5-6.6) (Figure B, Supplementary file).

Overall, the frequency of ventricular arrhythmias during HCQ treatment was 1.69% (127/7539, reported in 22/28 studies) and that of arrhythmogenic death was 0.69% (39/5648, reported in 22/28 studies). TdP occurred in 0.06% (3/5066, reported in 21/28 studies).

In the subgroup analyses (Table 2), patients aged over 60 years had a higher risk of HCQ-associated LQT ($P<0.001$). The frequency of LQT also seemed higher in the studies that reported HCQ combination with AZI and/or other QT-prolonging agents ($P=0.002$). No

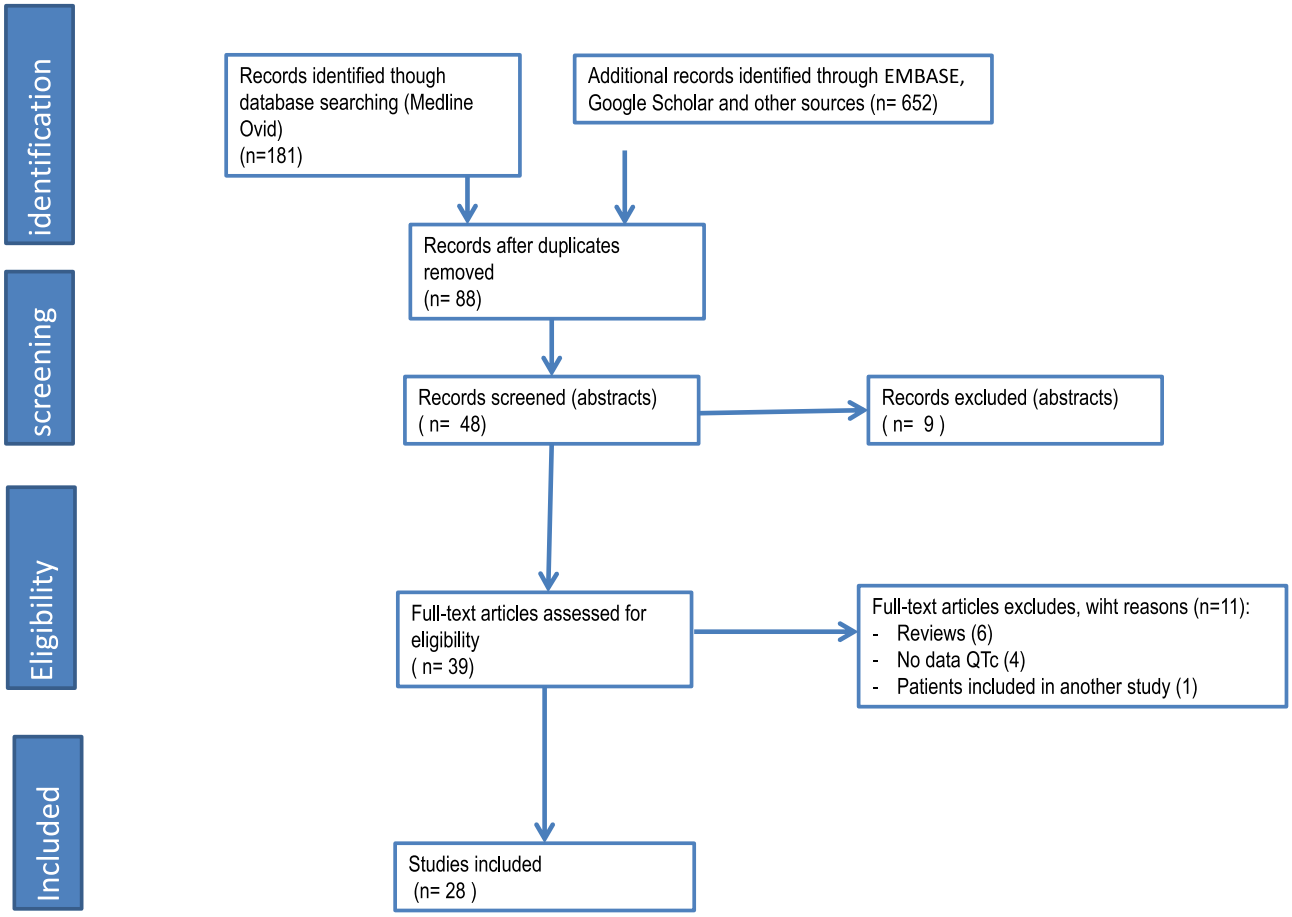

Figure 1. Flowchart of included studies.

significant difference was observed when the total HCQ dose was greater than 3000 mg.

In 5/28 studies, a subgroup analysis was performed that indicated several risk factors related to the frequency of HCQ-associated LQT. The main risk factor was simultaneously taking other QT-prolonging agents, among which were propofol and amiodarone [8,19,32,33]. Other statistically significant risk factors were renal failure or increased creatinine [33,37], structural heart disease [8] and ≥2 points in Systemic Inflammatory Response Syndrome score [32].

4. Discussion

The frequency of LQT in SARS-CoV-2 patients treated with HCQ was 6.7%. However, most patients were also taking other QT-prolonging drugs. In the minority of studies where HCQ was the only QT-prolonging drug, the frequency of LQT was lower (1.7%). Overall, the frequency of HCQ discontinuation due to LQT was 3.7%. During HCQ treatment, the frequency of TdP, ventricular arrhythmias and arrhythmogenic death was very low. The risk of LQT in COVID-19 patients treated with HCQ seemed higher in patients aged over 60 years.

These findings can be compared with those of four related types of study, namely: similar systematic reviews in SARS-CoV-2 infection, studies with HCQ used for short periods against malaria, studies of HCQ used chronically for rheumatologic diseases, and studies with other drugs that cause LQT. Three meta-analytic studies on cardiotoxicity of antimalarials used in SARS-CoV-2 infection have been published [39–41] and the differences with the present study (which reports lower risk frequencies) may be because the present study had the largest numbers of subjects and only included studies with HCQ. Indeed, studies with CQ [42,43] were purposefully excluded after the Borba et al. study [43] was prematurely discontinued due to high mortality associated with high doses of CQ. Since then, clinical guidelines for treatment of SARS-CoV-2 include HCQ and not CQ, and there is evidence that the cardiotoxicity of CQ is greater than HCQ in patients with SARS-CoV-2 infection [44].

Other than drugs, risk factors that cause repolarization reserve reduction and increase the risk of TdP include drug interactions affecting drug serum levels, sex, structural heart disease, genetic polymorphisms, electrolyte disturbances, bradycardia, and hepatic disease [12]. In the present study, the majority of patients were simultaneously taking other QT-prolonging agents, including AZI, lopinavir/ritonavir, propofol or amiodarone. AZI is known to be associated with QT interval prolongation [45–47], TdP [48] and polymorphic ventricular tachycardia in the absence of QT interval prolongation [49]. The proarrhythmic mechanism of AZI is that it potentiates cardiac Na+ current to promote intracellular Na+ loading [50]; however, the frequency of this is low, as AZI has been calculated to cause 47 additional cardiovascular deaths per million treatments [51].

Antimalarials, particularly quinidine and halofantrine, are also associated with LQT [52–54]. In the pre-COVID-19 era, sudden cardiac death with CQ was reported only following rapid intravenous administration or by self-inflicted overdose, causing hypotension due to vasodilation and negative inotropy [55]. Mortality associated with the administration of CQ (not HCQ) in the treatment of plasmodium falciparum and vivax malaria has been reported to be 0.07% (10/23773) and 0% (0/11 848), respectively [52]. HCQ is

Table 1
Characteristics of the 28 studies included in the meta-analysis.

Author (year)	Country	Study design	Total sample size	Mean age (years)	Male sex (%)	Total dose of HCQ (mg)	HCQ length of administration (days)	HCQ alone	HCQ + AZI	Other QT drugs taken	Other QT drugs taken (detail)	Reported HCQ discontinuation	Comorbidities	ECG monitoring	Strobe score
Saleh et al. (2020)	USA	CC	201	59	57	1400	4	No	Yes	Yes	Amiodarone, Haloperidol, Clozapine, Dronedarone, Pantoprazole	Yes	Chronic kidney disease ≥ stage III (5%), Hypertension (60%), Heart failure (8%), Diabetes mellitus (32%), Atrial fibrillation (7%), Coronary artery disease	Baseline ECG then twice daily ECG or mobile cardiac monitoring (Telemetry)	88.5
Bessière et al. (2020)	France	CC	40	68	80	4000	10	No	Yes	Yes	Propofol, amiodarone, ciprofloxacin, ondansetron	Yes	Diabetes (40%), Hypertension (58%), Structural heart disease (20%)	Daily ECG Continuous cardiac monitor	71.4
Mercuro et al. (2020)	USA	Cohort	90	60	51	2400	5	No	Yes	Yes	Propofol	Yes	Hypertension (53%), Congestive heart failure (10%), Diabetes mellitus (29%), Coronary artery disease (11%), Atrial fibrillation (13%), COPD/asthma (20%)	ECG in electronic medical records	96.2
Chorin et al. (2020)	USA and Italy	CC	251	64	75	2400	5	No	Yes	Yes	Amiodarone, Antimicrobials, Psychiatric medications	Yes	Coronary artery disease (12%), Hypertension (54%), Chronic kidney disease (11%), Diabetes mellitus (27%), COPD (7%), Congestive heart failure (3%).	ECG tracings from baseline and until 3 days after drug administration	96.0
Mahevas et al. (2020)	France	CC	84	59	78	600	2	Yes	No	No	NR	Yes	Chronic kidney failure (5%), COPD (11%), Chronic heart failure (3.3%), Cardiovasc diseases (incl. hypertension) (51.9%), Diabetes (8.3%), Liver cirrhosis (0.6%)	Daily ECG until 3-5 days after drug discontinuation	76.0
Molina et al. (2020)	France	O	11	59	64	6000	10	No	Yes	No	NR	Yes	Obesity (18%); solid cancer (28%, haematological cancer (18%) HIV-infection: (9%).	NR	77.2
Perinel et al. (2020)	France	O	13	68	85	3600	8	Yes	No	No	NR	Yes	Severe renal failure (31%)	ECG monitoring in ICU	77.0
Rosenberg et al. (2020)	USA	Cohort	1006	63	60	1200	3	No	Yes	No	NR	No	Hypertension (58%), Coronary artery disease (13%), Congestive heart failure (6%), Diabetes (37%), Any chronic lung conditions (18%), Any kidney disease (12%)	ECG in medical records	90
Ramireddy et al. (2020)	USA	O	61	62	61	2400	5	No	Yes	No	NR	No	Hypertension (60%), Heart failure (20%), Diabetes mellitus (22%), Chronic kidney disease (14%), COPD (26%)	Basal ECG and after drug administration	92.0
Louhaichi et al. (2020)	Tunisia	O	15	61	45	6000	10	No	Yes	No	NR	No	hypertension (73%), diabetes (40%), coronary arterial disease (20%), Chronic kidney disease (7%), COPD (7%).	NR	81.0
Tang et al (2020)	China	RCT	75	46	55	12400	14	Yes	No	No	NR	No	Diabetes (16%), Hypertension (8%).	NR	Missing

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Country	Study design	Total sample size	Mean age (years)	Male sex (%)	Total dose of HCQ (mg)	HCQ length of administration (days)	HCQ alone	HCQ + AZI	Other QT drugs taken	Other QT drugs taken (detail)	Reported HCQ discontinuation	Comorbidities	ECG monitoring	Strobe score
Ip et al. (2020)	USA	Cohort	1914	64	78	2400	5	No	Yes	No	NR	Yes	hypertension (55%), obesity (41%), diabetes (32%), coronary arterial disease (16%), COPD/asthma (15%), cancer (12%)	ECG in electronic health records	88.0
Singh et al. (2020)	USA	CC	910	62	54	NR	NR	Yes	No	No	NR	No	Hypertension (63%), Diabetes mellitus (37%), Ischemic heart disease (29%), Chronic kidney disease (23%), Heart failure (19%), COPD (15%), Atrial fibrillation (17%)	NR	74.0
Jain et al. (2020)	USA	O	415	68	62	NR	NR	No	No	Yes	Amiodarone, Proton Pump Inhibitor, Propofol, Sedative, Anti-Psychotic	Yes	Hypertension (59%), Diabetes mellitus (49%), Chronic kidney disease /End stage renal disease (31%), Lung Disease (18%), Heart Failure (16%), cardiac implantable devices (11%)	ECG or telemetry monitoring	87.0
Sharma et al (2020)	India	O	234	35	59	2800	7	No	Yes	No	NR	Yes	Hypertension (5%), Diabetes (5%), COPD/Asthma (5%)	NR	91.0
Rhodes et al. (2020)	USA	O	62	62	51	NR	NR	Yes	No	No	NR	Yes	COPD (13%), Heart failure (15%), Hypertension (49%), CKD (13%), Diabetes (37%), Obesity (31%), History of cerebrovascular accident (12%), Cancer (6%), Transplant (3%)	ECG in electronic health records	92..0
Hor et al. (2020)	Malaysia	O	13	52	54	1400	5	No	Yes	No	NR	Yes	Hypertension, (31%), diabetes (15%), end-stage renal failure on dialysis (15%), coronary artery diseases (8%), gout (8%)	daily ECG up to 3 days post-treatment	82.0
Maraj et al. (2020)	USA	O	91	63	56	NR	NR	No	Yes	Yes	propofol	No	Hypertension (46%), Diabetes (29%), Coronary Artery Disease (14%), Chronic Lung Disease (7%)	ECG before HCQ and continuous telemetry	92.0
Chong et al (2020)	Brunei	O	11	52	64	2400	5	No	No	Yes	lopinavir/ ritonavir	Yes	hypertension (54%), dyslipidaemia (27%), diabetes mellitus (9%), overweight (73%)	ECG before HCQ, day-2, day-4, and when indicated	62.5
Mazzanti et al. (2020)	Italy	O	150	69	63	4400	11	No	Yes	Yes	lopinavir/ ritonavir	Yes	hypertension (46%), diabetes (19%)	ECG after HQC administration (median of 5 days)	83.0
Oteo et al. (2020)	Spain	O	80	52	47	1600	5	No	Yes	No	NR	Yes	Hypertension (10%), diabetes mellitus (5%), cardiovascular disease (4%); chronic pulmonary disease (4%), immunosuppression or active neoplastic disease (4%)	ECG after HCQ administration	92.0

(*continued on next page*)

Table 1 (*continued*)

Author (year)	Country	Study design	Total sample size	Mean age (years)	Male sex (%)	Total dose of HCQ (mg)	HCQ length of administration (days)	HCQ alone	HCQ + AZI	Other QT drugs taken	Other QT drugs taken (detail)	Reported HCQ discontinuation	Comorbidities	ECG monitoring	Strobe score
Sridhar et al. (2020)	USA	O	75	62	61	2400	5	Yes	No	No	NR	No	Hypertension, (51%), Diabetes mellitus (23%), Atrial fibrillation (10%), Heart failure (16%), Coronary artery disease (13%)	ECG baseline, following second HCQ dose or telemetry	92.0
Voisin et al. (2020)	France	O	50	68	55	6000	10	No	Yes	No	NR	Yes	hypertension (37%), diabetes (17%).	ECG before HCQ, at Day 3, 5 and at discharge	88.0
Cipriani et al. (2020)	Italy	CC	22	64	82	1200	3	No	Yes	No	NR	No	Hypertension (55%), Diabetes Mellitus (27%), Hypercholesterolemia (23%), Chronic pulmonary disease (5%), Chronic kidney disease (5%)	24-h Holter ECG monitoring: 12h before and after HCQ and day 3.	88.0
Pereira et al. (2020)	USA	O	62	57	83	2800	5	Yes	No	No	NR	Yes	solid organ transplant recipients (100%), Hypertension (64%), diabetes (46%), chronic kidney disease (63%), Chronic lung disease (19%)	Baseline ECG and on days 2 or 3 of HCQ	83.0
Fernandez-Ruiz et al (2020)	Spain.	O	18	71	78	4400	10	Yes	No	No	NR	Yes	solid organ transplant recipients	ECG from electronic medical records	91.3
Lagier et al. (2020)	France	O	3119	45	45	6000	10	No	Yes	No	NR	Yes	Cancer disease (5%), Diabetes (8), Chronic heart diseases (6), Hypertension (15), Chronic respiratory diseases (9%), Obesity (2)	ECG before and after HCQ administration	96.0
Mfeukeu-Kuate et al. (2020)	Cameroon	O	51	39	51	2800	7	No	Yes	No	NR	Yes	hypertension (5.9%)	ECG before and after HCQ (Day 3 and 7)	84.6

HCQ: Hydroxychloroquine; CC: case control study; RCT: randomized controlled trial; O: observational study; NR: Not reported. AZI: Azithromycin.

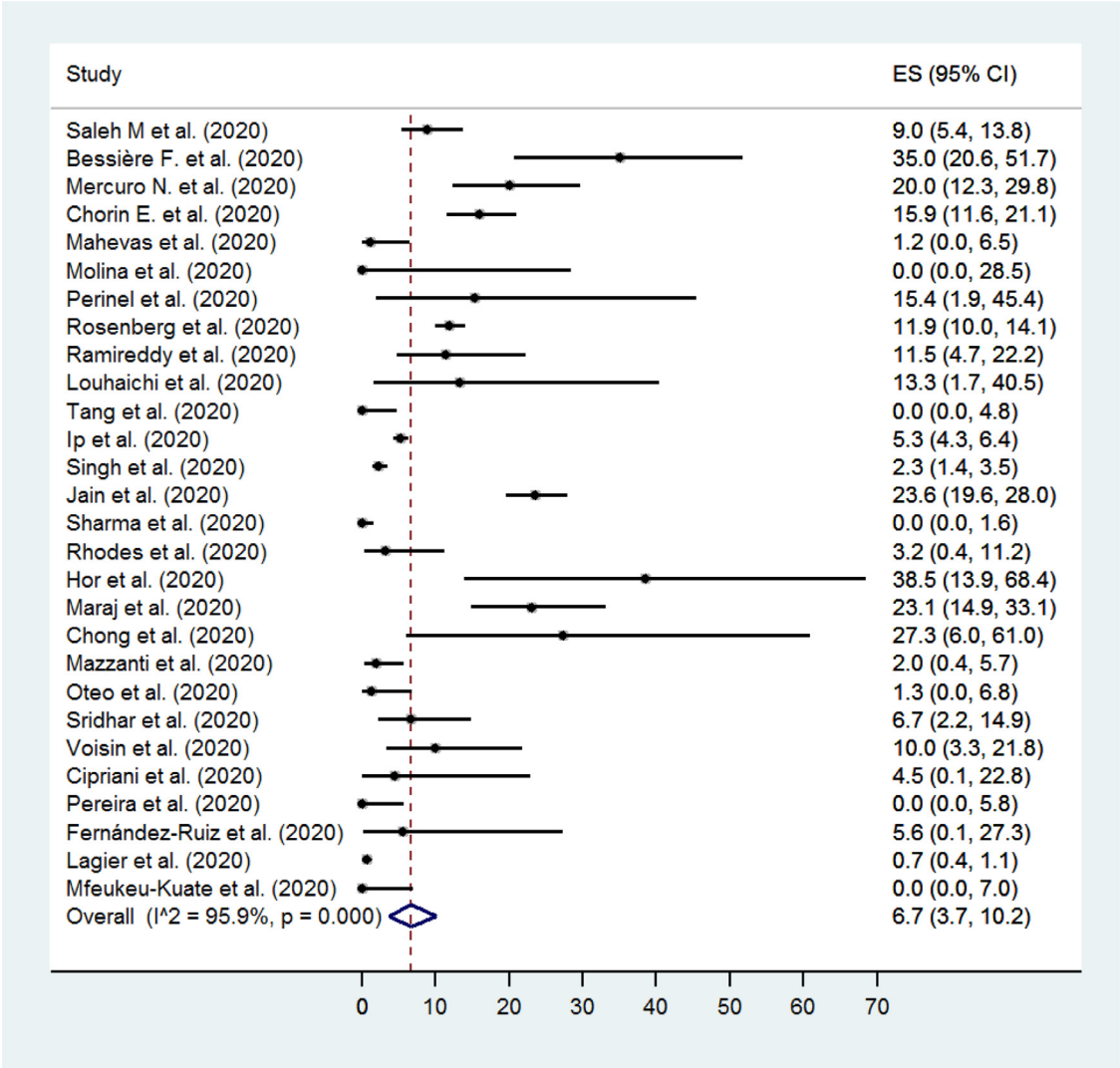

Figure 2. Forest plot of the meta-analysis of the frequency of HCQ-associated QT prolongation in patients with SARS-CoV-2 infection (28 studies, n=9124). Analysis model: random effect. CI: confidence interval.

Table 2
Hydroxychloroquine-associated QT prolongation in Patients with SARS-CoV-2 Infection: Summary of subgroup analyses.

Subgroup	Studies (n)	Proportion (%) (95% CI)	*P*
Mean age (years)			<0.001
<60	11	2 (1–5)	
≥60	17	11 (7–16)	
Presence of other QT-prolonging drugs			0.002
HCQ alone	8	1.7 (0.3–3.9)	
HCQ + other QT-prolonging drugs (including AZI)	20	9.0 (4.8–14.1)	
Total HCQ dose (mg)			1.00
Not reported	4	-	
<3000	15	6.1 (3.0–9.9)	
≥3000	9	5.9 (3.0–9.4)	

HCQ: Hydroxychloroquine.

used in the treatment of rheumatoid arthritis and systemic lupus erythematosus. In one study [56], HCQ-induced LQT in rheumatoid arthritis and systemic lupus erythematosus patients who received 200-400 mg/day HCQ for a mean of 3.6 years was 15.8%; although these patients were simultaneously taking more than one medication that could prolong the QT interval. Chatre et al. investigated 127 cases published until 2017 of CQ and HCQ-induced cardiac adverse reactions and found 3 cases of HCQ-induced LQT (2.4%) [57]. In a study of a cohort of 453 systemic lupus erythematosus patients on antimalarial-induced ECG abnormalities, HCQ-induced LQT was 0.7% and ventricular bigeminy was 0.4% [58]. Hooks et al. recently studied patients with rheumatologic diseases and HCQ-induced LQT was 1.5% [59]. In addition, they found that chronic kidney disease (CKD), history of atrial fibrillation (AF), and heart

failure were independent risk factors for LQT. The median dosage of HCQ was 400 mg daily and duration of HCQ therapy was 1006 (471–2075) days in the study.

The detection of drug-induced LQT is important because it increases the risk of TdP, which in turn can degenerate into ventricular fibrillation in 10% of cases [60,61]. Medications that increase QTc >500 ms are generally discontinued because they increase the risk of TdP by 3- to 4-fold [62,63]. Of all the drugs that are associated with LQT, antiarrhythmic drugs are those that have the highest risk of TdP with an incidence of 1 to 5%, whereas in non-cardiovascular drugs, the incidence is much lower (0.001%) [61]. According to *CredibleMeds* (www.Crediblemeds.org), there are currently 63 drugs marketed with known risk of TdP. Many healthcare organizations have attempted to increase awareness of QT-prolonging drugs and recognition of LQT through educational strategies [64].

The present study has limitations, among which is the design of the included studies (mostly observational) and the strategies used to detect HCQ-induced LQT in these studies. Many studies where HCQ has been used for COVID-19 infection have not been able to measure QTc because this requires special devices (e.g. mobile cardiac outpatient telemetry) to avoid exposure to the virus, or the use of special personal protective equipment (PPE) for its measurement [15]. On the other hand, Cipriani et al. reported 24-h QTc dynamics in COVID-19 patients versus controls and reported that the former had higher QTc values with no significant hourly variability, recommending that there is no need to perform multiple daily ECGs to monitor possible treatment toxicity [26]. Given the very low number of studies including a majority of women, the sex differences between the risk of HCQ-associated LQT warrant further investigation.

In conclusion, HCQ-associated cardiotoxicity in SARS-CoV-2 patients is uncommon but requires ECG monitoring, particularly in those aged over 60 years and/or taking other QT-prolonging drugs.

Declarations

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Competing Interests: No.
Ethical Approval: Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2020.106212.

References

[1] Yousefi B, Valizadeh S, Ghaffari H, Vahedi A, Karbalaei M, Eslami M. A global treatments for coronaviruses including COVID-19. J Cell Physiol 2020. jcp.29785 https://doi.org/10.1002/jcp.29785 .
[2] Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin Proc 2020;95:1213–21. https://doi.org/10.1016/j.mayocp.2020.03.024.
[3] Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. Ther Adv Drug Saf 2012;3:241–53. https://doi.org/10.1177/2042098612454283.
[4] Schwartz PJ, Woosley RL. Predicting the unpredictable. J Am Coll Cardiol 2016;67:1639–50. https://doi.org/10.1016/j.jacc.2015.12.063.
[5] Woosley RL, Schwartz PJ. Drug-induced long QT syndrome and Torsades de Pointes. Card. Repolarization, Cham: Springer International Publishing; 2020. p. 185–200.
[6] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339. b2535–b2535 https://doi.org/10.1136/bmj.b2535 .
[7] World Health Organization Clinical management of COVID-19: interim guidance; 27 may 2020. https://www.who.int/publications/i/item/clinical-management-of-covid-19.
[8] Ramireddy A, Chugh H, Reinier K, Ebinger J, Park E, Thompson M, et al. Experience with hydroxychloroquine and azithromycin in the coronavirus disease 2019 pandemic: Implications for QT Interval monitoring. J Am Heart Assoc 2020;9. https://doi.org/10.1161/JAHA.120.017144.
[9] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. Int J Surg 2014;12:1495–9. https://doi.org/10.1016/j.ijsu.2014.07.013.
[10] Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. https://doi.org/10.1136/bmj.d5928.
[11] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88. https://doi.org/10.1016/0197-2456(86)90046-2.
[12] Saleh M, Gabriels J, Chang D, Soo Kim B, Mansoor A, Mahmood E, et al. Effect of Chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Circ Arrhythmia Electrophysiol 2020:13. https://doi.org/10.1161/CIRCEP.120.008662.
[13] Ip A, Berry DA, Hansen E, Goy AH, Pecora AL, Sinclaire BA, et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients-an observational study. medRxiv. 2020 n.d..
[14] Singh S, Khan A, Chowdhry M, Chatterjee A. Outcomes of hydroxychloroquine treatment among hospitalized COVID-19 patients in the United States-real–world evidence from a federated electronic medical record network. medRxiv 2020 n.d..
[15] Jain S, Workman V, Ganeshan R, Obasare ER, Burr A, DeBiasi RM, et al. Enhanced ECG monitoring of COVID-19 patients. Heart Rhythm 2020. https://doi.org/10.1016/j.hrthm.2020.04.047.
[16] Sharma AK, Ahmed A, Baig VN, Dhakad P, Dalela G, Kacker S, et al. Characteristics and outcomes of hospitalized young adults with mild to moderate Covid-19 at a University Hospital in India. medRxiv. 2020 n.d..
[17] Rhodes NJ, Dairem A, Moore W, Shah A, Postelnick MJ, Badowski ME, et al. Multicenter point-prevalence evaluation of the utilization and safety of drug therapies for COVID-19. medRxiv. 2020 n.d..
[18] Hor CP, Hussin N, Nalliah S, Ooi WT, Tang XY, Zachariah S, et al. Experience of short-term hydroxychloroquine and azithromycin in COVID-19 patients and effect on QTc trend. J Infect 2020. https://doi.org/10.1016/j.jinf.2020.05.058.
[19] Maraj I, Hummel JP, Taoutel R, Chamoun R, Workman V, Li C, et al. Incidence and determinants of QT interval prolongation in COVID-19 patients treated with hydroxychloroquine and azithromycin. J Cardiovasc Electrophysiol 2020. jce.14594 https://doi.org/10.1111/jce.14594 .
[20] Chong VH, Chong PL, Metussin D, Asli R, Momin RN, Mani BI, et al. Conduction abnormalities in hydroxychloroquine add on therapy to lopinavir/ritonavir in COVID-19. J Med Virol 2020. jmv.26004 https://doi.org/10.1002/jmv.26004 .
[21] Mazzanti A, Briani M, Kukavica D, Bulian F, Marelli S, Trancuccio A, et al. Association of hydroxychloroquine with QTc interval in patients with COVID-19. Circulation 2020. CIRCULATIONAHA.120.048476 https://doi.org/10.1161/CIRCULATIONAHA.120.048476 .
[22] Oteo JA, Marco P, de León LP, Roncero A, Lobera T, Lisa V. A short therapeutic regimen based on hydroxychloroquine plus azithromycin for the treatment of COVID-19 in patients with non-severe disease. A strategy associated with a reduction in hospital admissions and complications. medRxiv. 2020 n.d..
[23] Bessière F, Roccia H, Delinière A, Charrière R, Chevalier P, Argaud L, et al. Assessment of QT Intervals in a case series of patients with coronavirus disease 2019 (COVID-19) Infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. JAMA Cardiol 2020. https://doi.org/10.1001/jamacardio.2020.1787.
[24] Sridhar AR, Chatterjee NA, Saour B, Nguyen D, Starnes E, Johnston C, et al. QT interval and arrhythmic safety of hydroxychloroquine monotherapy in coronavirus disease 2019. Heart Rhythm O2 2020. https://doi.org/10.1016/j.hroo.2020.06.002.
[25] Voisin O, Lorc'h E le, Mahé A, Azria P, Borie M-F, Hubert S, et al. Acute QT Interval modifications during hydroxychloroquine-azithromycin treatment in the context of COVID-19 infection. Mayo Clin Proc 2020. https://doi.org/10.1016/j.mayocp.2020.05.005.
[26] Cipriani A, Zorzi A, Ceccato D, Capone F, Parolin M, Donato F, et al. Arrhythmic profile and 24-hour QT interval variability in COVID-19 patients treated with hydroxychloroquine and azithromycin. Int J Cardiol 2020. https://doi.org/10.1016/j.ijcard.2020.05.036.
[27] Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. Am J Transplant 2020;20:1800–8. https://doi.org/10.1111/ajt.15941.
[28] Fernández-Ruiz M, Andrés A, Loinaz C, Delgado JF, López-Medrano F, San Juan R, et al. COVID-19 in solid organ transplant recipients: A single-center case series from Spain. Am J Transplant 2020;20:1849–58. https://doi.org/10.1111/ajt.15929.
[29] Lagier J-C, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel Med Infect Dis 2020:101791. https://doi.org/10.1016/j.tmaid.2020.101791.
[30] Mfeukeu-Kuate LM, Ngatchou W, Temgoua MN, Kouanfack C, Lemogoum D, Tochie J, et al. Electrocardiographic safety of daily hydroxychloroquine 400mg plus azithromycin 250mg as an ambulatory treatment for COVID-19 patients in Cameroon. medRxiv.https://doi.org/10.1101/2020.06.24.20139386 n.d.
[31] Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open la-

bel, randomised controlled trial. BMJ 2020:m1849. https://doi.org/10.1136/bmj.m1849.
[32] Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020. https://doi.org/10.1001/jamacardio.2020.1834.
[33] Chorin E, Wadhwani L, Magnani S, Dai M, Shulman E, Nadeau-Routhier C, et al. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Heart Rhythm 2020. https://doi.org/10.1016/j.hrthm.2020.05.014.
[34] Mahevas M, Tran V, Roumier M, Chabrol A, Paule R, Guillard C, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. MedRxiv 2020.
[35] Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Médecine Mal Infect 2020;50:384. https://doi.org/10.1016/j.medmal.2020.03.006.
[36] Perinel S, Launay M, Botelho-Nevers É, Diconne É, Louf-Durier A, Lachand R, et al. Towards optimization of hydroxychloroquine dosing in intensive care unit COVID-19 Patients. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa394.
[37] Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020;323:2493. https://doi.org/10.1001/jama.2020.8630.
[38] Louhaichi S, Allouche A, Baili H, Jrad S, Radhouani A, Greb D, et al. Features of patients with 2019 novel coronavirus admitted in a pneumology department: The first retrospective Tunisian case series. Tunis Med 2020;98:261–5.
[39] Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai M-C. QT prolongation, torsades de pointes, and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: A systematic review. Heart Rhythm 2020. https://doi.org/10.1016/j.hrthm.2020.05.008.
[40] Kim MS, An MH, Kim WJ, Hwang TH. Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis of confounder-adjusted 20212 hospitalized patients. medRxiv. 2020. https://doi.org/10.1101/2020.06.15.2013 n.d..
[41] Tleyjeh I, Kashour Z, AlDosary O, Riaz M, Tlayjeh H, Garbati MA, et al. The cardiac toxicity of chloroquine or hydroxychloroquine in COVID-19 Patients: A systematic review and meta-regression analysis. medRxiv. 2020. https://doi.org/10.1101/2020.06.16.20132878 n.d..
[42] van den Broek MPH, Möhlmann JE, Abeln BGS, Liebregts M, van Dijk VF, van de Garde EMW. Chloroquine-induced QTc prolongation in COVID-19 patients. Netherlands Hear J 2020. https://doi.org/10.1007/s12471-020-01429-7.
[43] Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of High vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. JAMA Netw Open 2020;3:e208857. https://doi.org/10.1001/jamanetworkopen.2020.8857.
[44] Isaksen JL, Holst AG, Pietersen A, Nielsen JB, Graff C, Kanters JK. Chloroquine, but not hydroxychlorquine, prolongs the QT interval in a primary care population. medRxiv 2020.06.19.20135475; doi: https://doi.org/10.1101/2020.06.19.20135475 n.d. https://doi.org/10.1101/2020.06.19.20135475.
[45] Matsunaga N, Oki Y. PA. A case of QT-interval prolongation precipitated by azithromycin. N Z Med J 2003;116:U666.
[46] Samarendra P, Kumari S, Evans SJ, Sacchi TJ, Navarro V. QT Prolongation associated with azithromycin/amiodarone combination. Pacing Clin Electrophysiol 2001;24:1572–4. https://doi.org/10.1046/j.1460-9592.2001.01572.x.
[47] Russo V, Puzio G SN. Azithromycin-induced QT prolongation in elderly patient. Acta Biomed 2006;77:30–2.
[48] Huang B-H, Wu C-H, Hsia C-P, Yin Chen C. Azithromycin-induced Torsade de Pointes. Pacing Clin Electrophysiol 2007;30:1579–82. https://doi.org/10.1111/j.1540-8159.2007.00912.x.
[49] Kim MH, Berkowitz C, Trohman RG. Polymorphic ventricular tachycardia with a normal QT interval following azithromycin. Pacing Clin Electrophysiol 2005;28:1221–2. https://doi.org/10.1111/j.1540-8159.2005.50146.x.
[50] Yang Z, Prinsen JK, Bersell KR, Shen W, Yermalitskaya L, Sidorova T, et al. Azithromycin causes a novel proarrhythmic syndrome. Circ Arrhythmia Electrophysiol 2017:10. https://doi.org/10.1161/CIRCEP.115.003560.
[51] Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881–90. https://doi.org/10.1056/NEJMoa1003833.
[52] Meeting WERG The cardiotoxicity of antimalarials; 2016. https://www.who.int/malaria/mpac/mpac-mar2017-erg-cardiotoxicity-report-session2.pdf.
[53] Bouchaud O, Imbert P, Touze JE, Dodoo AN, Danis M, Legros F. Fatal cardiotoxicity related to halofantrine: a review based on a worldwide safety data base. Malar J 2009;8:289. https://doi.org/10.1186/1475-2875-8-289.
[54] Monlun E, Pillet O, Cochard JF, Favarel Garrigues JC LBM. Prolonged QT interval with halofantrine. Lancet 1993;342:1541–2.
[55] White NJ. Cardiotoxicity of antimalarial drugs. Lancet Infect Dis 2007;7:549–58. https://doi.org/10.1016/S1473-3099(07)70187-1.
[56] Negoescu A, Thornback A, Wong E, Ostor AJ. Long QT and hydroxychloroquine; a poorly recognised problem in rheumatology patients. In ACR/ARHP Annual Meeting; 2013. Abstract number 2045 n.d..
[57] Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers Y-M. Cardiac complications attributed to chloroquine and hydroxychloroquine: A systematic review of the literature. Drug Saf 2018;41:919–31. https://doi.org/10.1007/s40264-018-0689-4.
[58] McGhie TK, Harvey P, Su J, Anderson N, Tomlinson G TZ. Electrocardiogram abnormalities related to anti-malarials in systemic lupus erythematosus. Clin Exp Rheumatol 2018;36:545–51.
[59] Hooks M, Bart B, Vardeny O, Westanmo A, Adabag S. Effects of hydroxychloroquine treatment on QT interval. Hear Rhythm 2020. https://doi.org/10.1016/j.hrthm.2020.06.029.
[60] Sarganas G, Garbe E, Klimpel A, Hering RC, Bronder E, Haverkamp W. Epidemiology of symptomatic drug-induced long QT syndrome and torsade de pointes in Germany. Europace 2014;16:101–8. https://doi.org/10.1093/europace/eut214.
[61] Roden DM. Predicting drug-induced QT prolongation and torsades de pointes. J Physiol 2016;594:2459–68. https://doi.org/10.1113/JP270526.
[62] Wilders R, Verkerk AO, Review Mini. Long QT Syndrome and Sinus Bradycardia–A. Front Cardiovasc Med 2018:5. https://doi.org/10.3389/fcvm.2018.00106.
[63] Khan Q, Ismail M, Haider I. High prevalence of the risk factors for QT interval prolongation and associated drug–drug interactions in coronary care units. Postgrad Med 2018;130:660–5. https://doi.org/10.1080/00325481.2018.1516106.
[64] National Medicines. Information Centre. ST. JAMES'S HOSPITAL D. DRUG-INDUCED QT INTERVAL PROLONGATION. Vol. 21. NUMBER 6. 2015. www.nmic.ie . http://www.stjames.ie/GPsHealthcareProfessionals/Newsletters/NMICBulletins/NMICBulletins2015/NMIC%20Bulletin%20February%202016%20-%20Drug-Induced%20QT%20Interval%20Prolongation% n.d.