QT interval and arrhythmic safety of hydroxychloroquine monotherapy in coronavirus disease 2019

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BACKGROUND Observational studies have suggested increased arrhythmic and cardiovascular risk with the combination use of hydroxychloroquine (HCQ) and azithromycin in patients with coronavirus disease 2019 (COVID-19).

OBJECTIVE The arrhythmic safety profile of HCQ monotherapy, which remains under investigation as a therapeutic and prophylactic agent in COVID-19, is less established and we sought to evaluate this.

METHODS In 245 consecutive patients with COVID-19 admitted to the University of Washington hospital system between March 9, 2020, and May 10, 2020, we identified 111 treated with HCQ monotherapy. Patients treated with HCQ underwent a systematic arrhythmia and QT interval surveillance protocol including serial electrocardiograms (ECG) (baseline, following second HCQ dose). The primary endpoint was in-hospital sustained ventricular arrhythmia or arrhythmic cardiac arrest. Secondary endpoints included clinically significant QTc prolongation.

RESULTS A total of 111 patients with COVID-19 underwent treatment with HCQ monotherapy (mean age 62 ± 16 years, 44 women [39%], serum creatinine 0.9 [interquartile range 0.4] mg/dL). There were no instances of sustained ventricular arrythmia or arrhythmic cardiac arrest. In 75 patients with serial ECGs, clinically significant corrected QT (QTc) prolongation was observed in a minority (n = 5 [7%]). In patients with serial ECGs, there was no significant change in the QTc interval in prespecified subgroups of interest, including those with prevalent cardiovascular disease or baseline use of renin-angiotensin-aldosterone axis inhibitors.

CONCLUSIONS In the context of a systematic monitoring protocol, HCQ monotherapy in hospitalized COVID-19 patients was not associated with malignant ventricular arrhythmia. A minority of patients demonstrated clinically significant QTc prolongation during HCQ therapy.

KEYWORDS Coronavirus; Electrocardiogram; Hydroxychloroquine; QT interval; Ventricular arrhythmia

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogenic cause of coronavirus disease 2019 (COVID-19), which is an ongoing global pandemic.[1] Given its immunomodulatory and antiviral effects against SARS-CoV-2 in vitro, hydroxychloroquine (HCQ) is being evaluated in multiple randomized clinical trials as a therapeutic and prophylactic strategy for COVID-19.[2] Recent observational cohort data have suggested a neutral effect of HCQ on overall in-hospital mortality for patients with COVID-19,[3] although there remain concerns regarding its cardiovascular risk profile. HCQ can block the *KCNH2*-encoded hERG/Kv11.1 potassium channel and thereby carries a risk of drug-induced QT prolongation and cardiac arrest.[4,5] Recent single-center studies evaluating the electrical effects of HCQ in combination with azithromycin (AZM) have identified clinically significant QT prolongation in up to 20% of patients[6,7] and combination therapy was associated with an increased risk of in-hospital cardiac arrest in 1 observational study.[8] The majority of these data, however, have focused on combination HCQ/AZM therapy and thus may not generalize to HCQ monotherapy, which remains a point of active investigation in several ongoing clinical trials.[9] Therefore, in this study, we sought to evaluate the arrhythmic safety profile of HCQ monotherapy in patients with COVID-19.

Methods

We identified 245 patients admitted to the University of Washington medical system with SARS-CoV-2 infection

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KEY FINDINGS

- In 111 patients hospitalized with coronavirus disease 2019 (COVID-19), a 5-day treatment regimen of hydroxychloroquine (HCQ) monotherapy was not associated with in-hospital malignant ventricular arrhythmia over 982 days of person-time follow-up.
- HCQ use was not associated with clinically significant QTc prolongation in the majority of patients (93%). This finding was robust when using different QT correction methods (Bazett, Hodges) and consistent across several subgroups of interest (prevalent cardiovascular disease, baseline renin-angiotensin-aldosterone system inhibitor use, and elevated admission serum creatinine).
- Using a standardized arrhythmic and QT surveillance protocol that includes discontinuation of QT-prolonging medications and correction of electrolyte abnormalities, HCQ monotherapy demonstrated a reasonable arrhythmic safety profile with a low incidence of clinically significant QT prolongation.

on the basis of quantitative reverse transcriptase polymerase chain reaction testing between March 9, 2020, and May 10, 2020. After excluding 134 patients who were not treated with HCQ, the final study cohort included 111 patients. The study was approved by the Institutional Review Board of the University of Washington, and adhered to the guidelines set forth by the Office of Human Research Protection that is supported by U.S. Department of Health & Human Services. Informed consent was not obtained from the patients in accordance with the University of Washington Institutional Review Board, as this was a retrospective chart review study.

HCQ was administered in accordance with a prespecified protocol developed by the University of Washington COVID-19 Task Force (400 mg twice a day for 1 day followed by 200 mg twice a day for 4 days). All QT-prolonging medications were discontinued prior to initiation of HCQ therapy. Corrected QT (QTc) monitoring was prespecified (Figure 1) with a baseline (pre-HCQ) 12-lead electrocardiogram (ECG) and follow-up on-treatment QT assessment after the second dose as captured by 12-lead ECG or telemetry. On-treatment ECG timing was selected based on physiologically based pharmacokinetic modeling of the dosing regimen, which identified steady-state concentrations of HCQ following the initial loading dose (ie, after the second dose of 400 mg).[2] For patients with clinically significant prolongation of the QTc (>500 ms or absolute increase >50 ms), caution was advised regarding continued HCQ therapy.

Detailed retrospective chart review of patient demographics, baseline cardiovascular and pulmonary comorbidities, and ECG parameters was performed. QTc interval was manually adjudicated and defined using the Bazett correction ($QTc = QT / \sqrt{RR}$) employing the longest measured QT (lead II, V_5, or V_6). The primary outcome was the incidence of sustained ventricular arrhythmia and/or arrhythmic cardiac arrest (ie, ventricular tachycardia and/or fibrillation). The primary outcome was evaluated from the date of admission to the first occurrence of death, in-hospital cardiac arrest, or hospital discharge, or May 10, 2020. Secondary outcomes included clinically significant QTc prolongation (absolute on-treatment QTc >500 ms or increase in QTc >50 ms following HCQ therapy). Clinical outcomes were adjudicated until May 10, 2020. Changes in electrical parameters were compared using a paired *t* test. QTc change was evaluated in prespecified subgroups of interest, including patients with baseline cardiovascular disease, elevated serum creatinine on admission, baseline use of renin-angiotensin-aldosterone system (RAAS) blockade pharmacotherapy, and initial admission to an intensive care unit. As the Bazett correction may overestimate QT intervals at faster heart rates (HR),[10] a sensitivity analysis was performed using the Hodges correction ($QTcH = QT + 1.75 [HR - 60] = QT + 105 * [1/RR - 1]$), which is the least sensitive to HR among QT correction methods.[11] All probability values were 2-sided, and a *P* value cutoff of $\leq .05$ was used to determine statistical significance. All statistical analysis was performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Study cohort

The study cohort was composed of 111 patients with COVID-19 treated with HCQ (mean age 62 ± 16 years, 44 women [39%], serum creatinine 0.9 [interquartile range 0.4] mg/dL) (Table 1). Median follow-up for the cohort was 6 (3.5–11) days. Forty percent of patients were initially admitted to an intensive care unit (n = 48 [43%]). Baseline comorbidities included hypertension (n = 57 [51%]), diabetes mellitus (n = 26 [23%]), atrial fibrillation (n = 11 [10%]), heart failure (n = 18 [16%]), and coronary artery disease (n = 14 [13%]). Baseline medication use included RAAS blockade (n = 35 [32%]) and β-blockers (n = 28 [25%]). In one-third of patients (n = 36 [32%]), a QT-prolonging medication was discontinued prior to HCQ initiation (most commonly a macrolide or fluoroquinolone being used for empiric treatment of community-acquired pneumonia [27 of 36 patients]).

Clinical outcomes and incident arrhythmias during hydroxychloroquine treatment

Over 982 days of person-time follow-up in 111 patients treated with HCQ, there were 11 deaths (14%), of which none was attributable to ventricular arrhythmia. Incident arrhythmia was observed in 19 patients (17%), including premature ventricular ectopy (n = 9 [7%]) and atrial tachycardia or atrial fibrillation (n = 10 [9%]). There was 1 instance of sinus bradycardia with an accelerated idioventricular rhythm

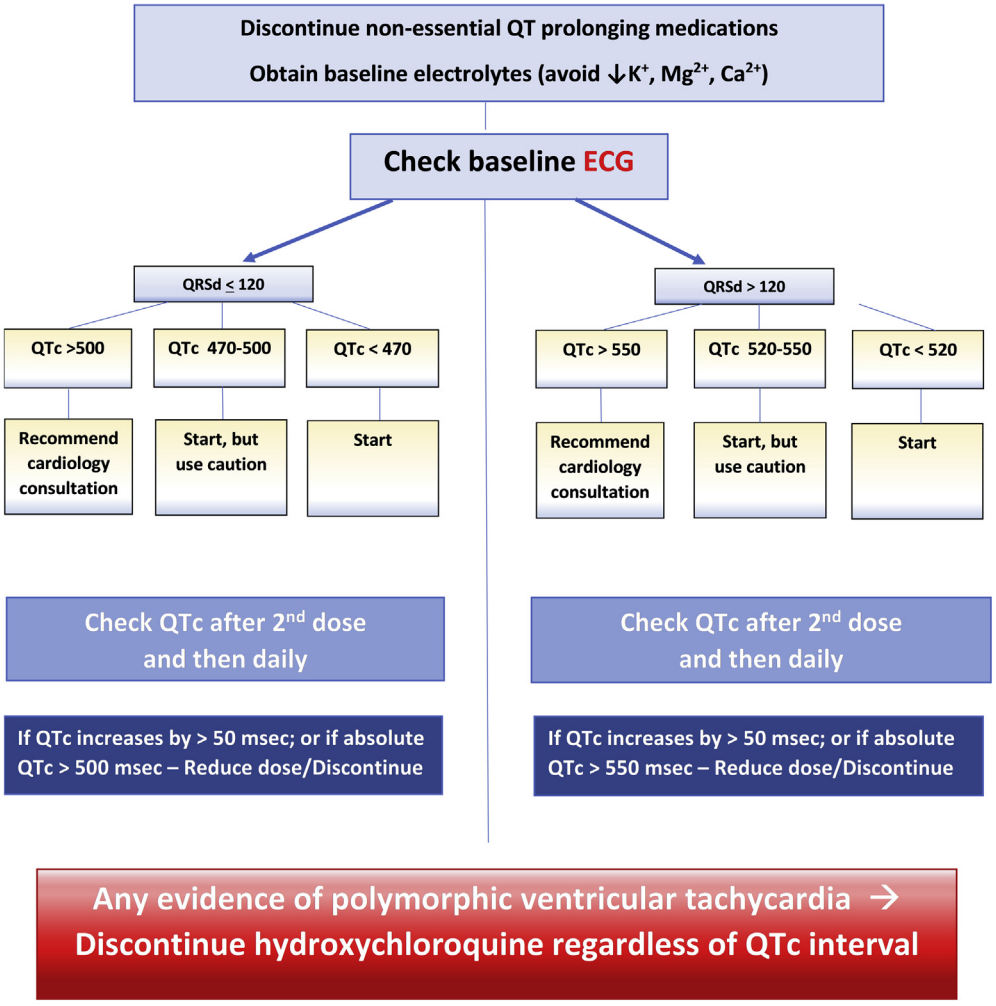

Figure 1 Standardized protocol for QT interval monitoring during hydroxychloroquine therapy for coronavirus disease 2019 (COVID-19). Shown is the standardized protocol employed for QT interval monitoring as guided by baseline QRS duration (QRSd) and QT interval. Corrected QT (QTc) was defined by the Bazett formula. ECG = electrocardiogram.

in a critically ill patient. There were no instances of high-grade atrioventricular block (Mobitz II, complete heart block) or sustained ventricular tachyarrhythmia (either monomorphic or polymorphic).

Impact of hydroxychloroquine on electrocardiographic parameters

Of 111 patients with COVID-19 treated with HCQ, 75 patients had serial ECGs including baseline and follow-up after the second dose of HCQ (Figure 2). In this subset, the mean change in QTc was -2 ± 24 ms (range -65 to +67 ms; *P* for Δ QTc = .53). The mean relative change in QTc was 3% ± 9%. In subgroup analysis, there was no significant change in QTc in patients with prevalent cardiovascular disease (n = 52; ΔQTc = -4 ± 24 ms; *P* = .23), baseline RAAS inhibitor use (n = 24; ΔQTc -7 ± 22 ms; *P* = .16), admission serum creatinine ≥1.5 mg/dL (n = 17; ΔQTc -2 ± 22 ms; *P* = .76), or intensive care unit location on admission (n = 29; ΔQTc -4 ± 21; *P* = .38). A minority of patients demonstrated clinically significant lengthening of the QTc (n = 5 [7%]), reflected by either on-treatment QTc ≥500 ms (n = 3) or increment in absolute QTc of greater than 50 ms (n = 2). The 3 patients with on-treatment QTc of ≥500 ms (501, 500, 500 ms) had baseline QTc prolongation (QTc 511, 504, 504 ms, respectively), whereas the 2 patients with an increment in QTc >50 ms had on-treatment QTc intervals that were within a normal range (425 and 435 ms). There were no instances of discontinuation of HCQ on the basis of QT or arrhythmic monitoring.

Given the risk of QT interval overestimation with the use of the Bazett correction,[10] and the observed decline in HR from baseline to follow-up ECG in our study (-8 ± 17 beats per minute), we performed a sensitivity analysis employing the Hodges correction for QT interval (QTcH), which is the least sensitive to HR compared to other QT correction methods.[11] Similar to the findings using the Bazett correction, the mean change in QTcH in patients with paired ECGs was not significant (2 ± 26 ms, range -46 to +70 ms; *P* for ΔQTc = .52). Subgroup analysis similarly demonstrated nonsignificant changes in QTcH in patients with prevalent cardiovascular disease (ΔQTcH = -2 ± 21 ms; *P* = .51), baseline RAAS inhibitor use (ΔQTcH = -2 ± 26

Table 1 Baseline characteristics of 111 patients with COVID-19 treated with hydroxychloroquine

Baseline characteristic	
Age, years	62 ± 16
Male sex, n (%)	67 (60)
Serum creatinine, admission (mg/dL)	0.9 [0.5]
Hypertension, n (%)	57 (51)
Diabetes mellitus, n (%)	26 (23)
Atrial fibrillation, n (%)	11 (10)
Heart failure, n (%)	18 (16)
Coronary artery disease, n (%)	14 (13)
Smoking, n (%)	
None	92 (83)
Current	12 (11)
Former	7 (6)
Medication use, n (%)	
β-blocker	28 (25)
RAAS inhibitor	35 (32)
Admission location	
Intensive care unit	48 (43)
Non–intensive care unit	63 (57)
QT-prolonging medication stopped prior to HCQ, n (%)	
Amiodarone	1 (<1)
Azithromycin or fluoroquinolone	27 (24)
Antipsychotic, antidepressant*	7 (6)
Other†	1 (<1)

Continuous variables are expressed as mean ± standard deviation or median [interquartile range], as appropriate.

HCQ = hydroxychloroquine; RAAS = renin-angiotensin-aldosterone system.

*Antipsychotics or antidepressants discontinued included mirtazapine, olanzapine, sertraline, venlafaxine, and aripiprazole.

†Tacrolimus.

ms; $P = .77$), admission serum creatinine ≥1.5 mg/dL (ΔQTcH = 1.6 ± 26 ms; $P = .83$), or intensive care unit admission (ΔQTcH = 1 ± 21 ms; $P = .89$). The incidence of clinically significant QTcH lengthening was similarly rare (n = 3 [4%]), reflecting on-treatment QTcH ≥500 ms (n = 1) or increment of absolute QTcH of greater than 50 ms (n = 2).

Discussion

In this multihospital retrospective cohort study of COVID-19 patients, HCQ monotherapy was not associated with malignant ventricular arrhythmias or arrhythmic cardiac arrest. In patients with paired ECG evaluation, there was no significant increment in the QT interval in the majority of patients. These findings extended to patients with elevated admission serum creatinine, baseline RAAS inhibitor use, prevalent cardiovascular disease, and initial admission to an intensive care unit. Importantly, nearly one-third of patients were treated with a concomitant QT-prolonging pharmacotherapy prior to initiation of HCQ. Taken together, in patients with COVID-19 treated with HCQ monotherapy, implementation of a systematic QT monitoring protocol demonstrated a low rate of clinically actionable QT prolongation and no instances of malignant arrhythmias or arrhythmic death.

In the ever-changing landscape of COVID-19 pharmacotherapy, there are several agents under active investigation that have the potential for QT prolongation, including hydroxychloroquine, chloroquine, azithromycin, lopinavir-ritonavir, and fingolimod. Recent cohort studies have demonstrated variable impact of HCQ with or without AZM on QT prolongation and electrical risk in patients with COVID-19. Rosenberg and colleagues[8] identified an increased risk of in-hospital cardiac arrest in patients treated with HCQ/AZM, but not HCQ monotherapy, when compared to those treated without either. In 233 patients treated with HCQ alone, they observed a 17% incidence of QT prolongation, although ECG assessment was not protocolized or adjudicated, HCQ dosing was heterogeneous, detailed information regarding quantitative QT measures were lacking, candidate ECGs were considered at any point during hospitalization, and QT prolongation was defined broadly. Mercuro and colleagues[7] evaluated 90 patients treated with HCQ (maintenance dose 400 mg daily), in whom 53 were additionally treated with AZM, and noted that 19% of patients treated with HCQ monotherapy and 21% of those treated with HCQ and AZM demonstrated a QTc interval longer than 500 ms. Of note, the majority of these patients were taking 2 or more QTc-prolonging medications. In a smaller study of 40 patients with COVID-19 admitted to the intensive care unit, Bessiere and colleagues[6] observed a prolonged QTc (>500 ms or increase >60 ms) in 36% of patients treated with HCQ monotherapy (18 patients) or HCQ + AZM (22 patients). Finally, Saleh and colleagues[12] evaluated 82 patients with COVID-19 treated with HCQ or chloroquine monotherapy and 119 patients treated with HCQ + AZM. In patients treated with HCQ or chloroquine monotherapy, on-treatment QTc >500 ms was observed in 7%, although given the potential differential effects of chloroquine vs HCQ on QT prolongation,[13] the specific risk of HCQ monotherapy was less certain.

Our study adds to this evidence base in several meaningful ways. First, these data represent the largest series to date of adjudicated arrhythmic and electrical safety of HCQ monotherapy in COVID-19. In keeping with previously published work,[6,7,12] our data highlight the low rate of malignant ventricular arrhythmias—specifically torsades de pointes—in COVID-19 patients treated with a delimited course of HCQ. Our finding of clinically actionable QTc prolongation in 7% of our cohort is closely aligned with the findings of Saleh and colleagues,[12] whose study employed a similar HCQ dosing protocol, but substantially lower than other series with higher absolute daily drug dosage of HCQ, higher rates of concomitant QT-prolonging medication use, and higher rates of intensive care unit status.[6,7] In contrast to discrete QTc safety thresholds (ie, absolute increment >500 ms, on-treatment Δ >50–60 ms), previous data evaluating the presence of *any* QT prolongation associated with HCQ monotherapy are likely to overestimate arrhythmic risk. Larger cohorts will be necessary to better delineate the continuous relationship between QT interval and malignant arrhythmia.[14] Second, nearly one-third of patients in our cohort were treated with a QT-prolonging medication prior to initiation of HCQ. Given the overlap in clinical

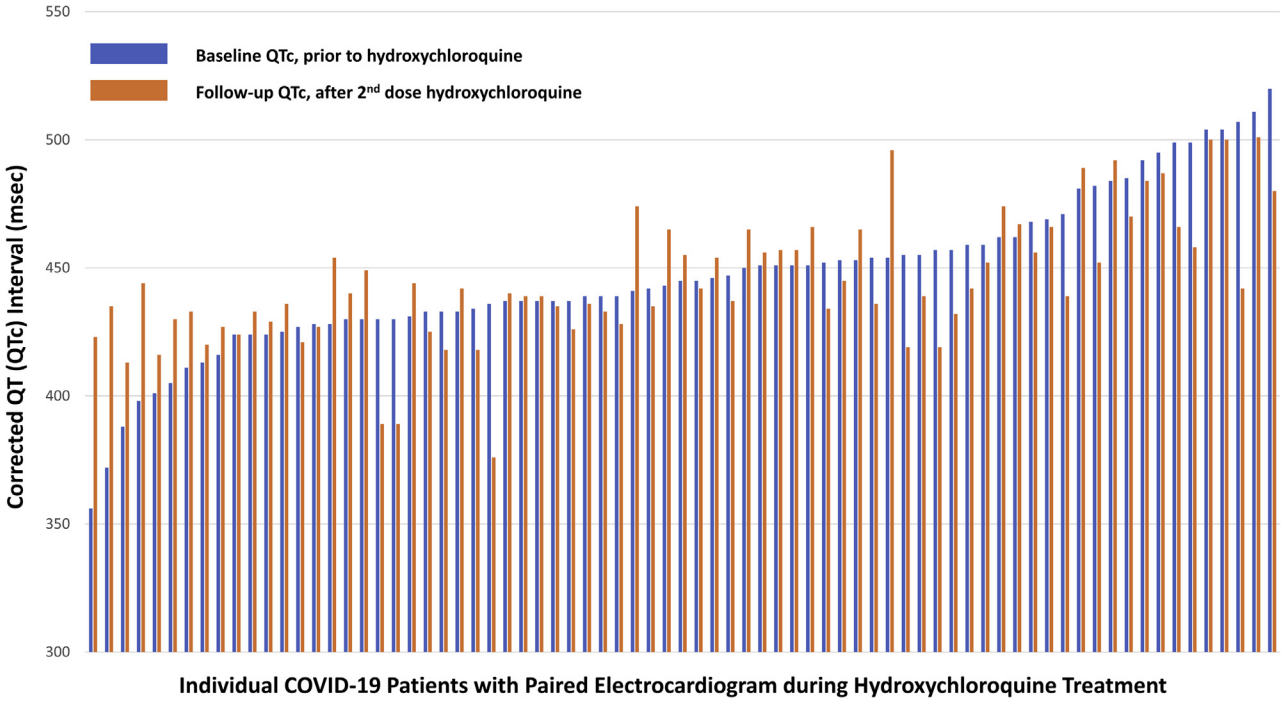

Figure 2 Baseline and on-treatment corrected QT (QTc) intervals in coronavirus disease 2019 (COVID-19) patients treated with hydroxychloroquine. Shown are the baseline and on-treatment (following the second dose) QTc intervals for patients with COVID-19 undergoing serial electrocardiograms during hydroxychloroquine therapy. QT correction was performed using the Bazett correction.

presentation of COVID-19 and community-acquired pneumonia, the most common QT-prolonging drug therapy was either fluoroquinolone or azithromycin. The discontinuation of concomitant QT-prolonging drug therapy and correction of underlying electrolyte abnormalities is a critical feature of the systematic protocol employed in this study and important context for the identified electrical and arrhythmic safety profile identified here. We would hypothesize that at least some of the decrease in QT interval observed in some patients in this study was related to discontinuation of QT-prolonging drugs and correction of electrolyte abnormalities. Third, we did not identify any specific subgroups at increased risk of malignant arrhythmia or excessive QT prolongation. While a previous study[7] suggested that baseline use of loop diuretics and baseline QTc >450 ms may be risk factors for subsequent electrical risk with HCQ, those findings were exploratory given the limited sample size within which they were evaluated. Of note, other groups[12]—similar to our study—have found no specific risk factors for arrhythmic risk following HCQ monotherapy in COVID-19. There are, nonetheless, specific subgroups including those with genetic long QT syndrome, in whom the risk-benefit of HCQ use should be carefully considered.

Clinical implications

There are presently more than 100 clinical trials evaluating the safety and efficacy of HCQ as either treatment or prophylaxis for patients with COVID-19.[15] Our study, in concert with previously published cohort data regarding the arrhythmic safety profile of HCQ monotherapy,[6,7,12] provides meaningful information for patients and clinical investigators. We would highlight that these data are specific to the dosing regimen employed in this study and may not generalize to higher-dose protocols. These safety data are also of particular relevance to patients and healthcare providers practicing in resource-limited healthcare settings, where availability of serial ECGs may be limited.[9] Important ancillary features of the systematic protocol employed here include systematic discontinuation of concomitant QTc-prolonging medications and correction of electrolyte abnormalities. While our study was not specifically designed to evaluate the timing of HCQ initiation following discontinuation of QTc-prolonging medication, this decision would likely be guided by the half-life of the QTc-prolonging medication in question and the clinical implications of delaying HCQ therapy.

Practically, acquisition of a 12-lead ECG or use of routine cardiac telemetry to evaluate the QT interval in COVID-19 patients may be challenging given broader attempts to minimize caregiver exposure and maximize personal protective equipment supplies. Use of continuous telemetry in patients treated with HCQ may be reasonable during the initial loading dose of the protocol, during which time QT monitoring accrues. While our study cannot specifically guide the duration of continuous telemetry monitoring in HCQ-treated COVID-19 patients, our data would suggest that the risk of *de novo* arrhythmias during HCQ therapy is low. Future work identifying other risk factors for in-hospital arrhythmias is warranted to guide the indication for both in-hospital and posthospital arrhythmia surveillance in COVID-19.

Looking ahead, novel technology—including the use of ambulatory event monitors (mobile continuous telemetry)

or smartphone-based applications[4]—will be important to integrate into workflows for arrhythmic safety monitoring in these patients. As pharmacokinetic simulation data indicate that HCQ drug concentrations may exceed the 50% effective concentration (EC_{50}) for several days following completion of a delimited HCQ dosing protocol (eg, HCQ concentrations $>EC_{50}$ on day 10 following a 5-day treatment course),[2] there may be rationale to continue to avoid QT-prolonging medications during this period, though further study is warranted. To the extent that HCQ concentrations are anticipated to reach steady state following the loading dose used in this study (400 mg twice a day $\times$ 1 day),[2] the residual arrhythmic risk attributable to HCQ following the dosing protocol would be anticipated to be captured by on-treatment QT monitoring.

Limitations

Strengths of our study include the implementation of a systematic protocol including serial ECG assessment, adjudication of electrical parameters including QT interval, and evaluation of arrhythmic risk within prespecified subgroups at increased potential risk. There are, however, limitations. First, not all patients receiving HCQ underwent baseline ECG. We do not anticipate that these patients would have had systematically different baseline or follow-up electrical responses to HCQ, though we cannot rule this out. Second, ascertainment of in-hospital arrhythmia was contingent on clinical documentation and availability of surveillance (ECG, telemetry). Although the overall incidence of arrhythmia may be underestimated, we believe our findings related to clinically actionable and malignant arrhythmias (cardiac arrest, torsades de pointes) are less likely to be impacted by this limitation. Second, given the low incidence of QT prolongation and incident arrhythmia, our study was not able to specifically comment on the relationship between QT prolongation and incident arrhythmia. Third, in order to maximize the generalizability and applicability of our study to real-world applications of QT monitoring, we employed the Bazett correction of the QT interval for baseline and follow-up ECG. As the Bazett correction may overestimate the QT interval at faster HR,[10] given the overall decline in HR from baseline to follow-up ECG in our study, the magnitude of QTc prolongation may have been biased toward the null. Importantly, we demonstrate that the findings of the study were robust in a sensitivity analysis using a QT correction method (Hodges) that is the least sensitive to HR when compared to other methods (Bazett, Fridericia, Framingham). Finally, given the overall low incidence of QT prolongation and malignant arrhythmia, our study may have been underpowered for these endpoints within prespecified subgroups.

Conclusion

In this retrospective cohort study of COVID-19 patients treated with HCQ monotherapy, there were no instances of malignant ventricular arrhythmias or arrhythmic cardiac arrest. A minority of patients (7%) demonstrated clinically significant on-treatment QTc prolongation (>50 ms increment) or long QTc (>500 ms). Future studies should focus on identification of those at highest arrhythmic risk with HCQ therapy to more optimally guide arrhythmia surveillance and prevention in patients with COVID-19.

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Disclosures

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