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Changes in QTc interval after hydroxychloroquine therapy in patients with COVID-19 infection: a large, retrospective, multicentre cohort study

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ABSTRACT

Objective To evaluate the extent of hydroxychloroquine-induced corrected QT (QTc) prolongation and its relation to COVID-19 infection severity and incidence of polymorphic ventricular arrhythmias and sudden arrhythmic deaths.

Design A large-scale cohort study with retrospective analysis of baseline and on-therapy QT interval corrected using Bazett and Fridericia formulas.

Setting A multicentre study involving eight secondary and tertiary care hospitals of the Abu Dhabi Health Services Company (SEHA), United Arab Emirates.

Participants 2014 patients consecutively admitted with PCR-confirmed SARS-CoV-2 infection between 1 March 2020 and 1 June 2020.

Interventions Treatment with hydroxychloroquine alone or in combination with azithromycin for at least 24 hours and with a baseline ECG and at least one ECG after 24 hours of therapy.

Main outcome measures Maximal QTc interval prolongation and its relationship to clinical severity, polymorphic ventricular tachycardia and sudden arrhythmic death while on treatment.

Results The baseline $QTc_{(Bazett)}$ was 427.6±25.4 ms and the maximum $QTc_{(Bazett)}$ during treatment was 439.2±30.4 ms (p<0.001). Severe QTc prolongation (QTc ≥500 ms) was observed in 1.7%–3.3% of patients (Fridericia and Bazett, respectively). There were no cases of polymorphic ventricular arrhythmia or hydroxychloroquine-related arrhythmic death. QTc prolongation was more pronounced in combination therapy compared with hydroxychloroquine alone (22.2 ms vs 11.0 ms, p<0.001) and in patients with higher COVID-19 clinical severity (asymptomatic: 428.4±25.4 ms, severe COVID-19 infection: 452.7±35.7 ms, p<0.001). The overall in-hospital mortality was 3.97% and deceased patients had longer on-therapy $QTc_{(Bazett)}$ than survivors (459.8±21.4 ms vs 438.4±29.9 ms, p<0.001).

Conclusions The incidence of severe QTc prolongation with hydroxychloroquine was low and not associated with ventricular arrhythmia. The safety concerns surrounding the use of hydroxychloroquine may have been overestimated; however, caution should be exercised when using hydroxychloroquine in patients with risk factors for QT prolongation.

Strengths and limitations of this study

- This is the largest multicentre study to date with paired ECG data examining the effects of hydroxychloroquine on QTc prolongation.
- The study explores the link between clinical disease severity and QTc interval prolongation.
- The study population included patients with different clinical severity levels; hence, the effects of hydroxychloroquine on QTc in our study are more applicable to a wider population.
- The retrospective design of the study, the absence of a control group and the strong male preponderance are limitations to this study which was performed during the first wave of the COVID-19 pandemic.

INTRODUCTION

The COVID-19 pandemic brought unprecedented diagnostic and therapeutic challenges to the world. Until a proven disease-specific treatment is available, repurposing of available drugs is among the few options available to reduce mortality and morbidity.[1]

Hydroxychloroquine (HY) is a commonly used antimalarial agent frequently prescribed for rheumatoid arthritis and systemic lupus erythematosus (SLE). Azithromycin (AZ) is a macrolide antibiotic with well-described anti-inflammatory and immunomodulatory properties.[2] The antiviral efficacy of HY against SARS-CoV-2 in some in vitro studies[3 4] along with favourable outcomes observed in few small-scale human studies[5 6] led to wide-scale use of HY/AZ combination early in the pandemic.[7] Several subsequent studies, however, did not corroborate the clinical efficacy of these drugs[8–11]; on the contrary,

possible adverse cardiovascular effects were reported, casting serious doubts on the rationale for using these drugs in patients with COVID-19.[12–14]

Since both HY and AZ are known to prolong QT interval, their use alone or in combination has been the subject of intense debate.[15–17] Such concerns are even more valid in critically ill patients with COVID-19 who often have concomitant myocardial injury.[18 19] While most studies reported QTc prolongation with these drugs, the magnitude of this prolongation and its impact on adverse cardiac outcomes such as sudden cardiac death and torsade de pointes (TdP) were variable between different studies.[20–27] For example, the incidence of extreme QTc prolongation (a marker of sudden cardiac death) varied between 2.7% and 36% depending on the study.[17 25] Small sample size and differences in infection severity are among the plausible explanations for the observed discrepancy between published reports. While the use of HY to treat COVID-19 has largely been abandoned, safety concerns regarding its effect on QTc may potentially affect its use even within traditional indications such as SLE and malaria. This highlights the need for a large clinical study to clarify the effect of these medications on QT interval.[18 19 22 28] This retrospective multicentre study in a large cohort of patients with COVID-19 investigates the effect of HY therapy on QTc prolongation and any related ventricular arrhythmias or sudden arrhythmic deaths.

METHODS

Patients

We identified all patients with confirmed SARS-CoV-2 infection consecutively admitted to eight hospitals of Abu Dhabi Health Services Company (SEHA) between 1 March 2020 and 1 June 2020 who received HY monotherapy or HY/AZ combination therapy as part of their treatment. COVID-19 testing was performed using reverse transcription-PCR assay. A detailed retrospective chart review was performed by a team of cardiologists to assess baseline characteristics, pneumonia clinical severity and adverse events. Only patients with a baseline premedication ECG as well as a postmedication ECG recorded no earlier than 24 hours after commencing treatment were included in the analysis. Patients receiving HY for less than 24 hours or having follow-up ECG recorded within the first 24 hours of therapy or after discontinuation of therapy were excluded from analysis.

Therapy regimen

HY and AZ were given routinely to patients admitted with COVID-19 infection in the early days of the pandemic as part of the local COVID-19 treatment protocol. HY was administered orally at a dose of 400 mg twice for the first day (loading dose), followed by 200 mg two times per day. Patients on HY/AZ therapy also received AZ at a daily dose of 500 mg. As per institution protocol, the duration of therapy was 5–7 days, but the final decision was left to the discretion of the treating physician.

QT measurements

ECG measurements were performed on a computer screen with digital callipers. Uncorrected QT and RR intervals were measured independently by two senior electrophysiologists and any discrepancy was resolved by agreement with a third electrophysiologist. The QT interval was calculated using the tangent method[29] and the longest QT interval of all leads was recorded according to the guidelines.[30] The QT interval was reported daily (where available) for the first 5 days of treatment. The QT interval reported on day 5 was for the maximum QT interval on any ECG performed after day 4 while the patient was still on HY treatment. In patients with wide QRS (>120 ms) due to bundle branch block or paced rhythm, the QT interval was corrected using the formula QT-(QRS-120).[31] QT intervals were rate-corrected with the Bazett formula ($QTc_{(Bazett)}$). We also reported QTc using the Fridericia formula ($QTc_{(Fridericia)}$), since the Bazett formula is prone to overcorrection at higher heart rates.[32]

Outcomes

The primary outcome of interest was maximal QTc interval prolongation while on treatment. Severe QTc prolongation was defined as QTc ≥500 ms or an increase of ≥60 ms in QTc from the baseline value.[33] The main secondary outcomes were TdP/polymorphic ventricular tachycardia (VT) and sudden arrhythmic death.

Statistical analysis

Baseline characteristics were summarised using descriptive statistics, including mean and SD for continuous measures and frequency tables for categorical variables. Categorical variables were compared using the χ^2 or Fisher's exact test and continuous variables using the unpaired t-test or its non-parametric version (Wilcoxon rank-sum test), if the assumption of normality was not met. The paired t-test was used for the main analysis when comparing QTc intervals between baseline and different time points.

We also carried out a series of multiple linear regression models to investigate the association between mortality and severity of COVID-19 from one side and QTc prolongation from another side. In these models, the worst QTc was considered as the dependent variable and was regressed against each of the main independent variables (ie, mortality and severity of COVID-19), adjusting for available potential confounders such as age, body mass index (BMI), gender and comorbidity. All statistical tests were two-sided and $p<0.05$ was considered statistically significant. Statistical analysis was conducted using R V.3.6.1 software (R Core Team, 2013).

Patient and public involvement

Patients and the public were not involved in the design, conduct or reporting of this research in view of its retrospective nature.

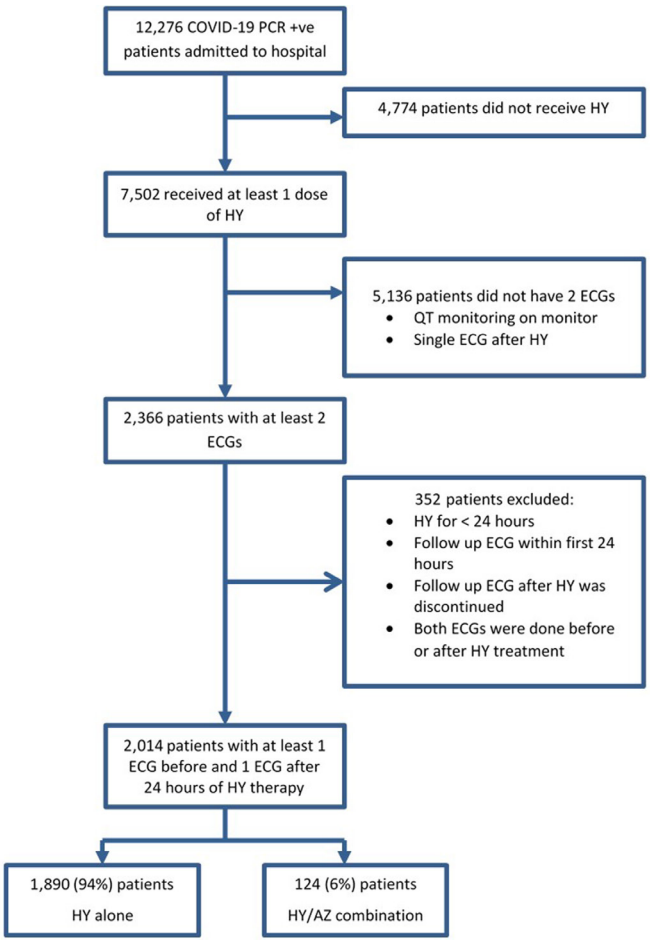

Figure 1 Flow chart of study participants included in the analysis. AZ, azithromycin; HY, hydroxychloroquine.

RESULTS

During the study period, a total of 12 276 patients with COVID-19 were admitted to our medical centres and 7502 of them received at least one dose of HY. Of these, 5136 patients had an ECG performed only after HY therapy or had continuous QTc monitoring. There were 2366 patients with at least two ECGs performed during the admission. We excluded a further 352 patients for not meeting other inclusion criteria, as defined in the Patients section. The final analysis involved 2014 patients, of whom 1890 (94%) received HY monotherapy and 124 (6%) received HY/AZ combination therapy (figure 1).

The average age of patients was 46.8±12.6 years and the majority were male (85.8%). The average length of hospital stay (LOS) was 9.4±8.6 days (six patients were still in hospital at the time of analysis), and the mean duration of HY treatment was 6.4±2.4 days. The LOS and duration of HY treatment were longer in the HY/AZ group than in the HY group. Overall, 36.5% of the patients were diabetic, with no specific preponderance to any group. Patients with hypertension were more likely to be found in the HY group; there was no difference in the prevalence of chronic kidney disease, cancer, lung disease, structural heart disease, dialysis or liver disease in the study groups. In total, 49 (2.4%) patients were immunocompromised and the prevalence of such patients was higher in the HY/AZ group. Of all patients, 50 (2.5%) were asymptomatic, and 772 (38.3%), 736 (36.5%) and 456 (22.6%) had mild, moderate and severe clinical severity, respectively. The HY/AZ group had more severely infected patients compared with the HY group (41.9% vs 21.4%). Patients requiring admission to intensive care unit (ICU), mechanical ventilation, inotropic support or dialysis were also more prevalent in the HY/AZ group (table 1).

The overall in-hospital mortality was 3.97% (80 patients), which was relatively higher in the HY/AZ group (5.65%) than in the HY group (3.86%); however, the difference did not reach statistical significance (p=0.46). Only eight patients (10%) were receiving HY at the time of death. Sudden death was observed in only four patients (5%), all of whom were still receiving HY at the time of death. Cardiac arrest was due to asystole in two patients (2.5%) and pulseless electrical activity (PEA) in the other two patients (2.5%). In all remaining cases, a clear clinical deterioration in the hours preceding cardiorespiratory arrest was observed. Cardiac arrest was commonly caused by bradycardia and asystole (55 of 80 patients, 68.7%). PEA was the cause of cardiac arrest in 23 patients (28.8%), whereas monomorphic VT was observed only in 2 patients (2.5%), neither of whom was on HY at the time of death. There were no cases of polymorphic VT or TdP.

A modest but statistically significant QTc prolongation was observed during treatment. The mean $QTc_{(Bazett)}$ increased by 11.6 ms from 427.6±25.4 ms at baseline to 439.2±30.4 ms during therapy (p<0.001). $QTc_{(Fridericia)}$ had lower absolute numerical values compared with $QTc_{(Bazett)}$; however, the pattern of QTc increase was similar (baseline: 402.8±23.2 ms, HY: 419.5±28.2 ms, p<0.001). The higher values with $QTc_{(Bazett)}$ were largely due to overcorrection during tachycardia since 441 (21.9%) patients had heart rate ≥100 beats per minute at baseline. Almost one-third of the patients had a decrease in QTc while on treatment, primarily due to the resolution of tachycardia with supportive treatment; hence, this effect was more apparent with $QTc_{(Bazett)}$. QTc ≥500 ms and ΔQTc ≥60 ms were observed in 3.3% and 4.5% of patients, respectively, using Bazett formula, and in 1.7% and 5.5% of patients, respectively, using Fridericia formula (figure 2).

The temporal changes in QTc interval during HY therapy revealed a daily increase in both $QTc_{(Bazett)}$ and $QTc_{(Fridericia)}$ until day 3, after which the relative increase in QTc was less prominent (figure 3). In the HY/AZ combination therapy group, $QTc_{(Bazett)}$ increased from 431±25 ms to 451±36 ms, whereas in the HY monotherapy group the value increased only to 438±30 ms from a baseline value of 427±25 ms. A similar trend was observed in $QTc_{(Fridericia)}$, with an increase of 28.8 ms and 16.0 ms in the HY/AZ and HY groups, respectively (figure 4).

Patients with more severe COVID-19 infection had greater QTc prolongation while on HY treatment. The observed $QTc_{(Bazett)}$ was significantly lower in survivors than it was in the deceased (438.4±29.9 ms vs 459.8±21.4 ms, p<0.001). A similar trend was also observed using

Table 1 Baseline characteristics, risk factors and clinical course of patients

	Total 2014 (100%)	HY only 1890 (94%)	HY/AZ 124 (6%)	P value*
Baseline characteristics				
Age, mean (±SD)	46.8 (±12.6)	47.0 (±12.6)	43.8 (±12.2)	0.005
Male sex, n (%)	1727 (85.7)	1619 (85.6)	108 (87.1)	0.756
Ethnicity, n (%)				
African	15 (0.7)	15 (0.8)	0 (0.0)	0.686
Arab	367 (18.2)	342 (18.1)	25 (20.3)	
Asian	1612 (80.2)	1515 (80.3)	97 (78.3)	
Caucasian	11 (0.5)	10 (0.5)	1 (0.8)	
Other	7 (0.4)	6 (0.3)	1 (0.8)	
Length of stay (days), mean (±SD)	9.4 (±8.6)	9.0 (±8.3)	15.2 (±10.7)	<0.001
Length of HY treatment (days), mean (±SD)	6.4 (±2.3)	6.3 (±2.3)	7.6 (±2.7)	<0.001
Clinical risk factors				
BMI, mean (±SD)	27.6 (±5.0)	27.7 (±5.1)	26.4 (±4.6)	0.003
BMI categories, n (%)				
<25	593 (33.3)	549 (32.9)	44 (39.3)	0.057
25–30	711 (39.9)	662 (39.7)	49 (43.7)	
30–40	425 (23.9)	406 (24.3)	19 (17.0)	
>40	51 (2.9)	51 (3.1)	0 (0.0)	
Smoking status, n (%)				
Current smoker	109 (5.4)	107 (5.7)	2 (1.6)	0.028
Former smoker	74 (3.7)	73 (3.9)	1 (0.8)	
Non-smoker	1831 (90.9)	1710 (90.4)	121 (97.6)	
Diabetes, n (%)	736 (36.5)	695 (36.8)	41 (33.1)	0.463
Hypertension, n (%)	786 (39.0)	749 (39.6)	37 (29.8)	0.038
CKD, n (%)	141 (7.0)	132 (6.9)	9 (7.3)	1.000
Cancer, n (%)	49 (2.5)	45 (2.4)	4 (3.2)	0.771
Lung disease, n (%)	118 (5.9)	113 (6.0)	5 (4.0)	0.486
Structural heart disease, n (%)	155 (7.7)	150 (7.9)	5 (4.0)	0.160
Liver disease, n (%)	15 (0.7)	14 (0.7)	1 (0.8)	1.000
Immunosuppression, n (%)	49 (2.4)	42 (2.2)	7 (5.6)	0.036
Clinical course				
Clinical severity, n (%)				
Asymptomatic	50 (2.5)	46 (2.4)	4 (3.2)	<0.001
Mild	772 (38.3)	731 (38.7)	41 (33.1)	
Moderate	736 (36.6)	709 (37.5)	27 (21.8)	
Severe	456 (22.6)	404 (21.4)	52 (41.9)	
CXR findings, n (%)				
Consolidation	1390 (69.0)	1294 (68.5)	96 (77.4)	0.031
No consolidation	251 (12.5)	235 (12.4)	16 (12.9)	
CXR not performed	373 (18.5)	361 (19.1)	12 (9.7)	
Lung CT findings, n (%)				
Normal	80 (4.0)	73 (3.7)	7 (5.6)	<0.001
Mild changes	523 (26.0)	496 (26.3)	27 (21.8)	
Moderate changes	785 (39.0)	758 (40.2)	27 (21.8)	

Continued

Table 1 Continued

	Total 2014 (100%)	HY only 1890 (94%)	HY/AZ 124 (6%)	P value*
Severe changes	209 (10.3)	192 (10.2)	17 (13.7)	
Lung CT not performed	417 (20.7)	371 (19.6)	46 (37.1)	
ICU admission, n (%)	241 (11.2)	209 (11.1)	32 (25.8)	<0.001
Mechanical ventilation, n (%)	190 (9.4)	166 (8.8)	24 (19.3)	<0.001
Inotropes, n (%)	183 (9.0)	160 (8.4)	23 (18.5)	<0.001
Dialysis, n (%)	90 (4.5)	82 (4.3)	8 (6.4)	0.379
Mortality, n (%)	80 (3.97)	73 (3.86)	7 (5.65)	0.455

*Continuous variables were summarised using t-test, while discrete variables were summarised using χ^2 test.
AZ, azithromycin; BMI, body mass index; CKD, chronic kidney disease; CXR, chest X-ray; HY, hydroxychloroquine; ICU, intensive care unit.

$QTc_{(Fridericia)}$. There was a systematic increase in $QTc_{(Bazett)}$ and $QTc_{(Fridericia)}$ values with increasing clinical infection severity. The mean values of $QTc_{(Bazett)}$ in asymptomatic, mild, moderate and severely infected patients were 428.4±25.4 ms, 432.3±27.2 ms, 438.9±27.5 ms and 452.7±35.7 ms, respectively (p<0.001); $QTc_{(Fridericia)}$ also exhibited a similar pattern (figure 5). The associations between $QTc_{(Bazett)}$ and $QTc_{(Fridericia)}$ from one side and mortality and severity of COVID-19 from another side were still statistically significant when multiple linear regression models adjusting for age, gender, BMI and comorbidity were used. The details of these adjusted analyses are reported in online supplemental tables 1–4.

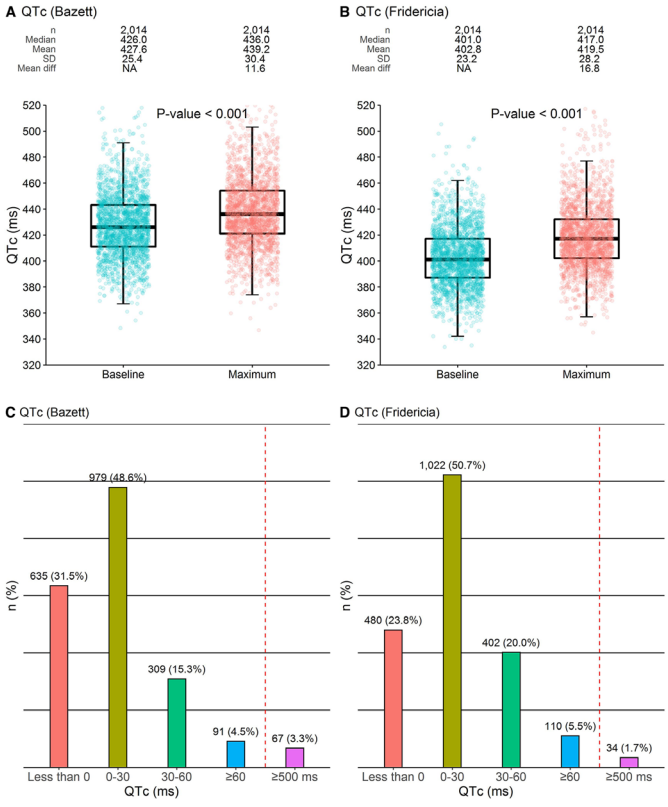

Figure 2 Changes in QTc interval in patients treated with hydroxychloroquine (with or without azithromycin). (A, B) Baseline and peak QTc interval using Bazett and Fridericia formulas, respectively. (C, D) Distribution of patients stratified by degree of QTc change using Bazett and Fridericia formulas, respectively. QTc, corrected QT; NA, not applicable.

DISCUSSION

This large cohort study with paired ECG data suggests a clinically modest but statistically significant QTc prolongation after HY or HY/AZ therapy. Like other studies,[21 34] QTc prolongation was evident from the first day of therapy and showed an increasing daily trend suggestive of a possible cumulative effect. Notably, however, QTc prolongation was less marked than most other studies on patients with COVID-19[17 19] and was more in line with previous large-scale studies in patients with rheumatological diseases.[26 35] Studies on patients with COVID-19 reported a highly variable degree of QTc prolongation, which is unsurprising given the differences in sample size, demographics and clinical severity in these studies. These shortcomings were largely overcome in our study by virtue of its large sample size and covering different clinical severities.

In our cohort, the peak average QTc was higher in HY/AZ combination therapy than in HY monotherapy. This

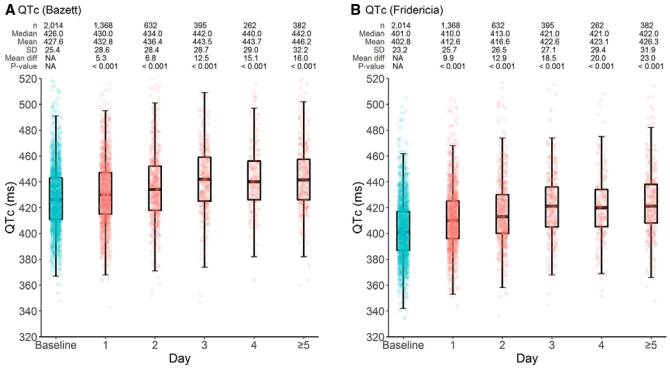

Figure 3 Baseline and daily QTc interval change in patients treated with hydroxychloroquine (with or without azithromycin) using (A) Bazett and (B) Fridericia formulas, respectively. QTc, corrected QT; NA, not applicable.

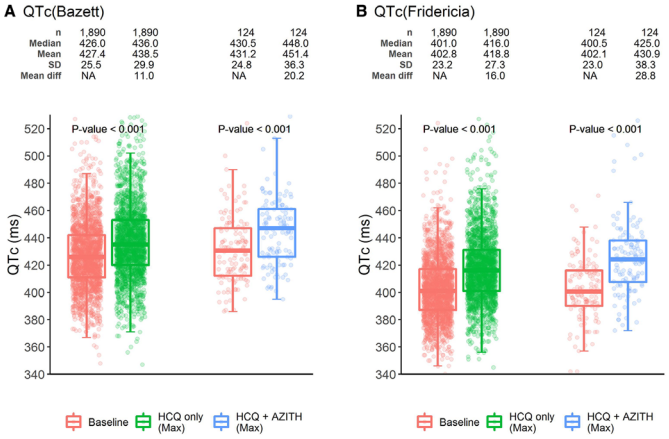

Figure 4 Baseline and maximal QTc measurements in patients treated with hydroxychloroquine (HCQ) alone or in association with azithromycin (AZITH) using (A) Bazett and (B) Fridericia formulas, respectively. QTc, corrected QT; NA, not applicable.

was expected since both drugs are known to prolong QTc interval.[36] In the combination therapy group, there was a 20.2 ms increase in $QTc_{(Bazett)}$ in the HY/AZ group and 11.0 ms in the HY group from their respective baseline values (p<0.001). This QTc prolongation in the combination group is broadly similar to the 20–30 ms increase reported by several other investigators.[17 19 24 34] In our study, patients receiving combination therapy were more likely to have higher clinical COVID-19 severity and longer hospital stay. The need for ICU admission, mechanical ventilation and inotropic support was also more likely in this group, reflecting a more turbulent clinical course. The frequent use of combination therapy in higher severity cases likely reflects the need for a more aggressive therapeutic approach in these patients.

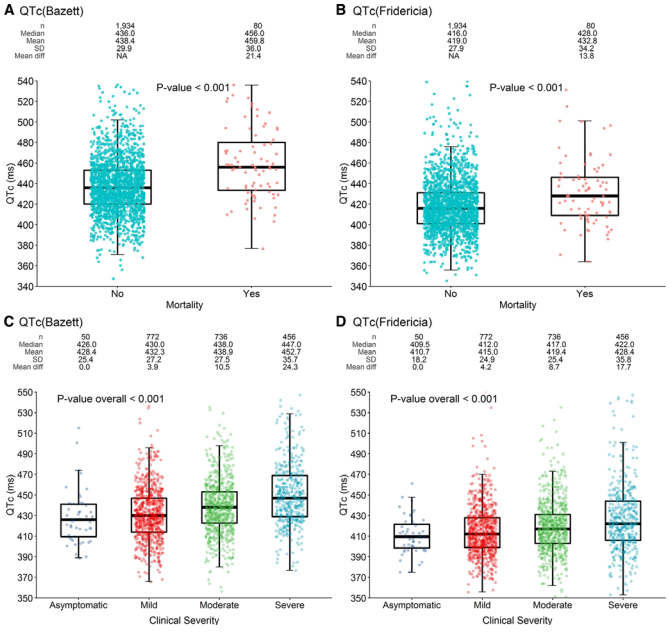

Figure 5 Relationship between QTc and mortality and disease severity. (A, B) Maximal QTc interval in survivors and deceased patients (Bazett and Fridericia formulas, respectively). Distribution of maximal QTc intervals stratified by clinical severity of COVID-19 infection is shown in (C) and (D) using Bazett and Fridericia formulas, respectively. QTc, corrected QT; NA, not applicable.

The incidence of critical QTc prolongation was relatively low in our cohort compared with other studies.[19] Hooks *et al*[26] reported a similar low incidence of 1.5% in rheumatological patients on HY therapy. In contrast, the incidence of severe QTc prolongation in literature from the COVID-19 era ranged between 11% and 36%, with most patients being treated with HY/AZ combination.[17 21 24 36] Such a variance can be attributed to the differences in the clinical severity and the demographics of the patients included in these studies and our younger cohort.[17 21]

The overall mortality in our study was 3.97%, with no cases of polymorphic VT, TdP or sudden death due to ventricular arrhythmia. The mortality rate in our study was significantly lower than the 21%–27% mortality rate reported in other studies.[11 24 37] There are several possible explanations for this observation. In contrast to other studies, our study population was significantly younger and HY was administered liberally irrespective of clinical severity (ie, use not restricted to severe cases). Another favourable factor in our case was that the healthcare system coped well with the pandemic and was never overwhelmed; therefore, optimal care continued to be provided to all admitted patients. Finally, differences in the virulence of the virus strain may have been a contributing factor in explaining the differences in fatality rates observed in different parts of the world, although more research is needed to establish such a factor.

Our study highlights the effects of COVID-19 infection severity on QTc duration. Overall, QTc prolongation during treatment was more pronounced in patients with higher clinical severity. A stepwise increase in QTc interval during HY treatment was proportional to the increase in clinical severity from asymptotic to severe. Indeed, patients with the highest severity leading to fatality had the most prolonged QTc in the whole study (459.8±36.0 ms (Bazett), 432.8±34.2 ms (Fridericia)). Electrolyte abnormalities, myocardial injury, renal impairment and polypharmacy are all more common in patients with severe infection, possibly compounding QTc prolongation.[38 39] Our observations highlight the multifactorial nature of QTc prolongation. The simultaneous presence of several QT-prolonging factors (such as drugs, genetic predisposition, electrolyte imbalance, severe illness) often has a synergistic effect, occasionally leading to marked QTc prolongation.[40]

To account for the impact of tachycardia frequently observed in patients with COVID-19 on QTc calculations, we reported QTc measurements using both Bazett and Fridericia formulas. Indeed, in our study, almost a quarter of the patients were admitted with sinus tachycardia. The Fridericia formula probably offers better rate correction in this setting, a finding also observed by Vandenberk *et al*.[32] Our results suggest that, although

there was a noticeable difference in the calculated QTc values by these two approaches, both showed a similar trend.

The demographics and patient characteristics in our study reflect the social structure and workforce distribution in United Arab Emirates. The majority of patients in this study were Asian men, relatively young, but with a high prevalence of diabetes and hypertension. Many of these expatriate workers live in shared accommodation, possibly explaining the higher representation of Asian men among SARS-CoV-2-infected patients in our study.

The main strength of this study is that it is the largest multicentre study to date with paired ECG data examining the effects of HY on QTc prolongation. Another strength of the study is the inclusion of patients with different clinical severity levels. Therefore, the effects of HY on QTc in our study are more applicable to a wider population compared with previous studies predominantly recruiting Caucasian patients with severe infection. Our study also reports QTc values by two methods and therefore factors in the effect of heart rate on QTc measurements. One of the major limitations of the study is its retrospective design and the absence of a control group. ECG data collection from a drug-free control group was not possible due to the liberal use of HY in most patients with COVID-19 in our hospitals at that time. In addition, it was difficult to justify performing non-clinically indicated ECGs in a control group at a time when healthcare resources were already overstretched and it was vital to protect staff by reducing unnecessary exposure to patients with COVID-19. However, the lack of a control group was compensated for by the paired nature of our measurements reducing the intersubject variability. In addition, since AZ was used only as an additional therapy to HY and not as monotherapy, we do not have an AZ-only group; hence, we cannot comment on its isolated effect on QTc. Furthermore, there may be a degree of selection bias with ECGs potentially being recorded in patients deemed to be at higher risk of QT prolongation. In addition, due to the large sample size and retrospective nature of the study, it was not possible to confirm whether patients were receiving other QT-prolonging drugs during HY therapy. However, the institutional protocol for HY therapy mandated regular monitoring of drug interactions by clinical pharmacists, thereby limiting the impact of this factor. Moreover, our data are mainly from patients with COVID-19 infection, with a strong male preponderance, possibly limiting the generalisability of the study findings to women and patients without COVID-19. Finally, our results may not be relevant anymore to the treatment of patients with COVID-19 given the rapid decline in the use of HY and AZ in this group. However, the fact that our population was younger and with lower clinical severity compared with other studies may make our results more relevant during HY treatment for other conditions such as malaria and SLE.

CONCLUSION

Among patients with COVID-19 prescribed HY alone or in combination with AZ, there was a modest QTc prolongation. The incidence of extreme QTc prolongation was low and not associated with any major drug-induced cardiovascular events. Although the use of HY to treat COVID-19 has largely been abandoned, it remains widely indicated to treat other conditions. Thus, when HY is used appropriately and with adequate cardiac monitoring, it remains a safe drug with only a trivial risk of significant adverse cardiac events. Caution should, however, be exercised with the concomitant use of HY with other QT-prolonging drugs or with very sick patients.

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