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Hydroxychloroquine/azithromycin treatment, QT interval and ventricular arrhythmias in hospitalised patients with COVID-19

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Abstract

Background: Hydroxychloroquine (HCQ) and azithromycin (AZM) are widely used in off-label treatment of novel coronavirus disease (COVID-19). However, cardiac safety of these drugs is still controversial in COVID-19. Therefore, we aimed to evaluate association of HCQ or HCQ + AZM treatment regimens, corrected QT (QTc) interval and malignant ventricular arrhythmias in hospitalized patients.

Methods: This is a single-center, retrospective and observational study. All data were extracted from the electronic medical records. The initial and post-treatment mean QTc intervals were calculated and compared in patients with HCQ alone or HCQ + AZM therapy. Associated factors with QTc prolongation, the incidence of ventricular arrhythmia during treatment and in-hospital mortality because of ventricular arrhythmias were evaluated.

Results: Our cohort comprised 101 hospitalized COVID-19 patients (mean age of 49.60 ± 18 years, 54.4% men). HCQ + AZM combination therapy group (n = 56) was more likely to have comorbidities. After 5-days treatment, 19 (18.8%) patients had QTc prolongation, and significant increase in the QTc interval was observed in both two groups ($P < .001$). However, HCQ + AZM combination group had significantly higher ΔQTc compared to HCQ group (22.5 ± 18.4 vs 7.5 ± 15.3 ms, $P < .001$). All of 101 patients completed the 5-days treatment without interruption. Also, no malignant ventricular arrhythmia or death secondary to ventricular arrhythmia occurred during the treatment in both groups.

Conclusions: The present study revealed that although HCQ + AZM treatment was independently associated with QTc prolongation, none of patients experienced malignant ventricular arrhythmia or death during treatment. Further prospective studies are needed to determine the exact implications of these drugs on arrhythmias in patients with COVID-19.

1 | INTRODUCTION

On December 31st, 2019, the World Health Organization (WHO) China Country Office was informed about several cases of atypical pneumonia in Wuhan City, China.[1] Chinese authorities later identified a new type of coronavirus (novel coronavirus) disease called COVID-19.[2] The WHO declared a global health emergency, and on March 11th, 2020 a pandemic. The medications used against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were mainly based on their effectiveness against earlier strains of coronavirus (SARS-CoV and Middle East Respiratory Syndrome-Coronavirus). The antimalarial drug chloroquine was reported as being successful in the treatment of SARS-CoV-2 infection in China in shortening

the duration of infection in patients.[3] One small scale French study reported that the use of azithromycin (AZM), in combination with hydroxychloroquine (HCQ), was associated with a more rapid clearance of the virus compared to HCQ used alone. This promoted the worldwide use of that combination against COVID-19.[4] Initial hopes for these medications may have lead to the underestimation of serious cardiac side effects such as torsade de pointes (TdP) type arrhythmias.[5-8] However, this combination should be interpreted with caution because of the potentially life threatening side effects associated with these molecules. Both HCQ and AZM are associated with corrected QT (QTc) prolongation, and the combined use may potentiate this adverse effect.[9] On the other hand, there is no consensus on the way to follow-up the QT interval prolongation related to HCQ and AZM treatment for COVID-19. Some authors suggested daily electrocardiogram (ECG) monitoring after obtaining a baseline ECG [10-12]; others suggested daily monitoring for high risk patients only in order to avoid contagion to the healthcare personnel.[13]

COVID-19 patients with pre-existing cardiovascular diseases are especially at risk to experience cardiac arrhythmias and sudden cardiac death.[14] However, few studies have investigated cardiac safety of HCQ and AZM treatment in patients with COVID-19. Therefore, we aimed to assess the implications of HCQ and HCQ + AZM treatment regimens on QTc interval and malignant ventricular arrhythmias in hospitalized patients with COVID-19.

What's known

- HCQ and AZM are widely used in off-label treatment of COVID-19.
- This combination is associated with QTc prolongation in other clinical conditions.
- Cardiac safety of these drugs is still controversial in COVID-19.

What's new

- COVID-19 patients who were treated with HCQ or HCQ + AZM had a significantly increased QTc interval after treatment administration.
- QTc prolongation was more likely to occur in those received HCQ + AZM combination.
- Baseline QTc interval and HCQ + AZM treatment were independently associated with QTc prolongation.
- No patient experienced malignant ventricular arrhythmias during treatment.
- All of patients completed the 5-days treatment without interruption.

2 | METHODS

2.1 | Study participants

This is a single-center, retrospective, observational study evaluating consecutive hospitalized adults with COVID-19 at Manisa Merkezefendi State Hospital (Pandemic hospital), Turkey. All data were extracted from the electronic medical records. The present study comprised 101 hospitalized patients diagnosed with COVID-19 by polymerase chain reaction (PCR) test (SARS-CoV-2, qPCR Detection Kit by Bio-Speedy). Patients who were prescribed only HCQ (loading dose 2x400 mg, maintenance dose 2x200 mg), and HCQ in addition to AZM (loading dose 1x500 mg, maintenance dose 1x250 mg) between March 20, 2020 and April 20, 2020 were included. Five-days only HCQ or HCQ + AZM combination treatment was prescribed to the patients according to the recommendation of The Ministry of Health of Turkish Republic treatment protocol. All patients underwent thorax computed tomography, and patients with associated pneumonia received HCQ combined with AZM.[15] The protocol was administered by caring physicians in accordance with clinical and laboratory findings of patients.

Exclusion criteria were; patients with QRS width ≥120 ms before treatment, left bundle branch block, right bundle branch block, pre-excitation syndromes, patients with implantable-cardioverter defibrillator or cardiac resynchronization therapy, patients with cardiac pacemaker, pregnants, and patients who have to use other drugs (antipsychotics, antidepressants, antiarrhythmics, other antimicrobials etc) that may cause QTc prolongation. Also, patients requiring intensive care unit were excluded as they recieved oseltamivir treatment known to prolong further the QT interval.[16]

This study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data. The study was approved by the Clinical Research Ethics Committee of Manisa Celal Bayar University (15/06/2020, Decision No: 82). Approval was also obtained from The Ministry of Health of Turkish Republic.

2.2 | Assessment of laboratory findings, ECG and QTc interval

The ECG recording device was MAC 2000, GE Medical Systems Information Technologies, Inc, Milwaukee, USA. The treatments were initiated after obtaining a first standard 12 derivation ECG on admission which was repeated after 5-days of treatment (25 mm/s paper speed, 10 mm/mV amplitude, and 250 Hz sampling rate). QT values were extracted from all ECGs as noncorrected, with QT intervals being determined using the tangent method. The QT interval was calculated as the time from the start of the QRS complex to the end of the T wave. The measurements were performed on lead II and lead V5 for all patients, and the longest QT intervals were used for the analyses. ECG measurements of QT and QRS intervals were performed by two cardiologists blind to the patient data. Calipers and magnifying glasses were used to reduce measurement errors. QT corrections were performed using the Bazett

method on the patients' initial ECG and post-treatment ECG. The current clinical standard is the most widely used Bazett's formula which provides a known overcorrection at high heart rates and undercorrection at lower rates.[17] Therefore, QTc was evaluated with the Framingham method in six patients who had an initial heart rate over 100 beats per minutes. The limits of QTc prolongation were considered over 470 ms for women and 450 ms for men.[18] A QTc interval >500 ms or an increase of more than 60 ms was defined as severely prolonged. Tisdale risk score was used to predict prognosis of QT prolongation in participants.[19-21] We monitored daily electrolyte levels of patients with high risk for arrhythmia according to Tisdale risk score. Malignant ventricular arrhythmias were defined as sustained or non-sustained ventricular tachycardia, ventricular fibrillation or TdP. Ventricular arrhythmia records were examined. Also, comorbid conditions and laboratory parameters were analysed.

The participants were divided into two groups: patients with treated only HCQ and patients with treated HCQ + AZM combination therapy. The initial and post-treatment mean QTc intervals were calculated and compared. Incidence of malignant ventricular arrhythmia during treatment, associated factors with QTc prolongation and in-hospital deaths secondary to ventricular arrhythmias were evaluated.

2.3 | Statistical analysis

Categorical variables are shown as frequencies and percentages, and continuous variables as means with SDs or median with interquartile range. The Chi-square test was used to determine the correlation between the categorical variables. The Kolmogorov-Smirnov test was used to check whether the continuous variables were distributed normally. Non-parametric tests were used to analyse the data as the variables did not exhibit a normal distribution. A 1-sample *t* test (if samples were normally distributed) or a 1-sample Wilcoxon signed-rank test (if samples were not normally distributed) was performed to compare mean QTc interval before and after treatment in HCQ and HCQ + AZM combination groups. Mann-Whitney-U test was used to compare parameters if samples did not have normal distributions. Univariate and multiple regression analyses were used to calculate hazard ratio (HR) and 95% confidence interval (CI). Multivariable analysis was performed to find associated factors with QTc prolongation. All analyses were performed with IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). A 2-sided *P* value of <.05 was considered statistically significant.

3 | RESULTS

A total of 101 hospitalized COVID-19 patients (mean age of 49.60 ± 18 years, 54.4% men) were included. Patients were treated with HCQ alone or HCQ + AZM combination during 5 days. The maximum follow-up time was 7 days and ECG follow-up time was 5 days for all participants. Clinical characteristics of all population are presented in Table 1. Twenty-nine patients (28.7%) were smokers and the mean body mass index was 27.3 kg/m^2. 19.8% of patients had morbid obesity. Patients prescribed HCQ + AZM combination therapy were older and were more frequent smokers. The mean heart rate was similar in two groups and all of participants were in sinus rhythm at admission. Hypertension (38.6%) was the most common comorbidity in all population. HCQ + AZM combination therapy group was more likely to have hypertension ($P = .002$), coronary artery disease ($P = .034$), chronic heart failure ($P = .020$) and chronic obstructive pulmonary disease ($P = .034$). There were no significant differences in diabetes mellitus and hyperlipidemia between the two groups. Serum creatinine, sodium, potassium, calcium, magnesium, aspartate aminotransferase, alanine aminotransferase levels were also similar in between HCQ and HCQ + AZM groups. During follow-up, because of electrolyte deficiencies, potassium replacement was performed in two patients and magnesium replacement in three patients. Thereby, one of the well-known risk factors for arrhythmias were eliminated. COVID-19 patients who received HCQ + AZM combination had comparatively higher Tisdale risk score (6.64 ± 0.7 vs 4.26 ± 1.4, $P < .001$). The use of β-blockers and nondihydropyridine calcium channel blockers were similar in two groups. Arrhythmic events during follow-up are also given in Table 1. Sinus bradycardia was observed during follow-up in five (11.1%) patients in the HCQ treatment group, and seven (12.5%) patients in the HCQ + AZM group. However, no malignant ventricular arrhythmia or death because of ventricular arrhythmia was detected during the treatment in both groups. Of note, new-onset atrial fibrillation was not detected.

Individual QTc intervals before and after treatment are given in Figure 1. The mean initial QTc interval was 416 ± 29.8 ms for all patients. As expected, women had longer initial mean QTc interval compared to men (423.9 ± 32.4 vs 409.3 ± 25.9 ms, $P = 0{,}020$). However, there was no significant difference after therapy in women and in men (436.9 ± 35.6vs 427.6 ± 27.1 ms, $P = .213$). Also, ΔQTc level was similar in women and in men (12.9 ± 18.9 vs 18.2 ± 18.1 ms, $P = .153$) (Table 2). Before treatment, QTc interval was longer than 450 ms in three (2.9%) men, and was longer than 470 ms in four (3.9%) women patients. After treatment, QTc interval was longer than 450 ms in nine (8.9%) men, and was longer than 470 ms in 10 (9.9%) women patients. Three of these patients (2.9%) had severe QTc prolongation. One (1.7%) patient in HCQ + AZM treatment group had an increase of more than 60 ms and two (3.5%) patients' QTc interval exceeded 500 ms on the fifth day of treatment, but no complaints such as syncope, palpitation and chest pain were noted. Further significant increase in the QTc was observed after treatment in all seven patients with prolonged QTc before treatment ($P < .05$).

In whole cohort, 19 patients (18.8%) had QTc prolongation after treatment, and 12 of 19 patients (63.1%) were in HCQ + AZM combination treatment group. All of 101 patients completed the 5-days treatment without interruption. No patient experienced malignant ventricular arrhythmias and all patients remained free of arrhythmia symptoms throughout hospital stay.

TABLE 1 Clinical characteristics of study population

	Total (n = 101)	HCQ alone (n = 45)	HCQ + AZM combination (n = 56)	*P* value
Gender, male, n (%)	55 (54.4)	29 (64.4)	26 (46.4)	.070
Age, y	49.60 ± 18	46.0 ± 16	53.5 ± 19	<.001
Body mass index, kg/m^2	27.32 ± 3.15	28.12 ± 3.65	27.02 ± 2.95	.090
Smoking, n (%)	29 (28.7)	8 (17.7)	21 (37.5)	.030
Initial heart rate, bpm	75.1 ± 20	74.5 ± 18	77.2 ± 23	.198
Comorbidities, n (%)				
Diabetes mellitus	18 (17.8)	7 (15.5)	11 (19.6)	.593
Hypertension	39 (38.6)	10 (22.2)	29 (51.7)	.002
Hyperlipidemia	7 (6.9)	3 (6.6)	4 (7.1)	.925
Coronary artery disease	9 (8.9)	1 (2.2)	8 (14.2)	.034
Chronic heart failure	10 (9.9)	1 (2.2)	9 (16)	.020
Chronic obstructive pulmonary disease	9 (8.9)	1 (2.2)	8 (14.2)	.034
Laboratory data				
Creatinine, mg/dL	0.8 (0.6-2.4)	0.8 (0.6-1.5)	0.9 (0.5-2.4)	.882
Aspartate aminotransferase, μ/L	25 (18-76)	27 (20-80)	24 (19--42)	.461
Alanine aminotransferase, μ/L	23 (16-124)	22 (18-98)	24 (21-124)	.501
Sodium, mEq/L	139 (136-140)	139 (135-139)	140 (136-141)	.339
Potassium, mEq/L	3.9 (3.7-4.2)	4.0 (3.8-4.3)	3.9 (3.6-4.2)	.212
Calcium, mEq/L	8.8 (8.4-9.4)	8.7 (8.3-9.2)	8.9 (8.4-9.5)	.109
Magnesium, mEq/L	1.9 (1.7-2.3)	1.9 (1.6-2.3)	2.0 (1.7-2.3)	.289
Tisdale risk score	5.9 ± 1.2	4.26 ± 1.4	6.64 ± 0.77	<.001
Medications, n (%)				
β-blockers	10 (9.9)	4 (8.8)	6 (10.7)	.760
Nondihydropyridine calcium blockers	4 (3.9)	2 (4.4)	2 (3.5)	.823
Antiarrhythmic drugs	0 (0)	0 (0)	0 (0)	—
Arrhythmic events, n (%)				
New-onset atrial fibrillation	0 (0)	0 (0)	0 (0)	—
Sinus bradycardia	12 (11.8)	5 (11.1)	7 (12.5)	.830
Non-sustained ventricular tachycardia	0 (0)	0 (0)	0 (0)	—
Sustained ventricular tachycardia	0 (0)	0 (0)	0 (0)	—
Torsade de pointes/ ventricular fibrillation	0 (0)	0 (0)	0 (0)	—
In-hospital mortality secondary to ventricular arrhythmia, n (%)	0 (0)	0 (0)	0 (0)	—

Abbreviations: AZM, azithromycin; HCQ, hydroxychloroquine.

Comparison of the mean QTc interval at admission and after 5-days treatment in two groups are shown in Figure 2. The mean QTc interval before treatment was longer in HCQ group than in HCQ + AZM group (424.9 ± 34.6 vs 408.8 ± 29.4 ms, $P < .001$). Of note, significant increase in the QTc interval was observed in both two groups ($P < .001$) after treatment. However, in terms of the mean QTc interval, there was no significant difference after 5-days of treatment between HCQ and HCQ + AZM groups (432.4 ± 34.1 vs 431.3 ± 23.4 ms, $P = .733$). HCQ + AZM combination group had significantly higher ΔQTc compared to HCQ group (22.5 ± 18.4 vs 7.5 ± 15.3 ms, $P < .001$). In other words, more pronounced increase in the QTc interval was observed in patients with HCQ + AZM therapy compared to only HCQ treatment (Figure 3).

Predictors of QTc prolongation for whole cohort are given in Table 3. Univariate analyses showed that chronic heart failure, baseline QTc interval, only HCQ treatment, and HCQ + AZM combination

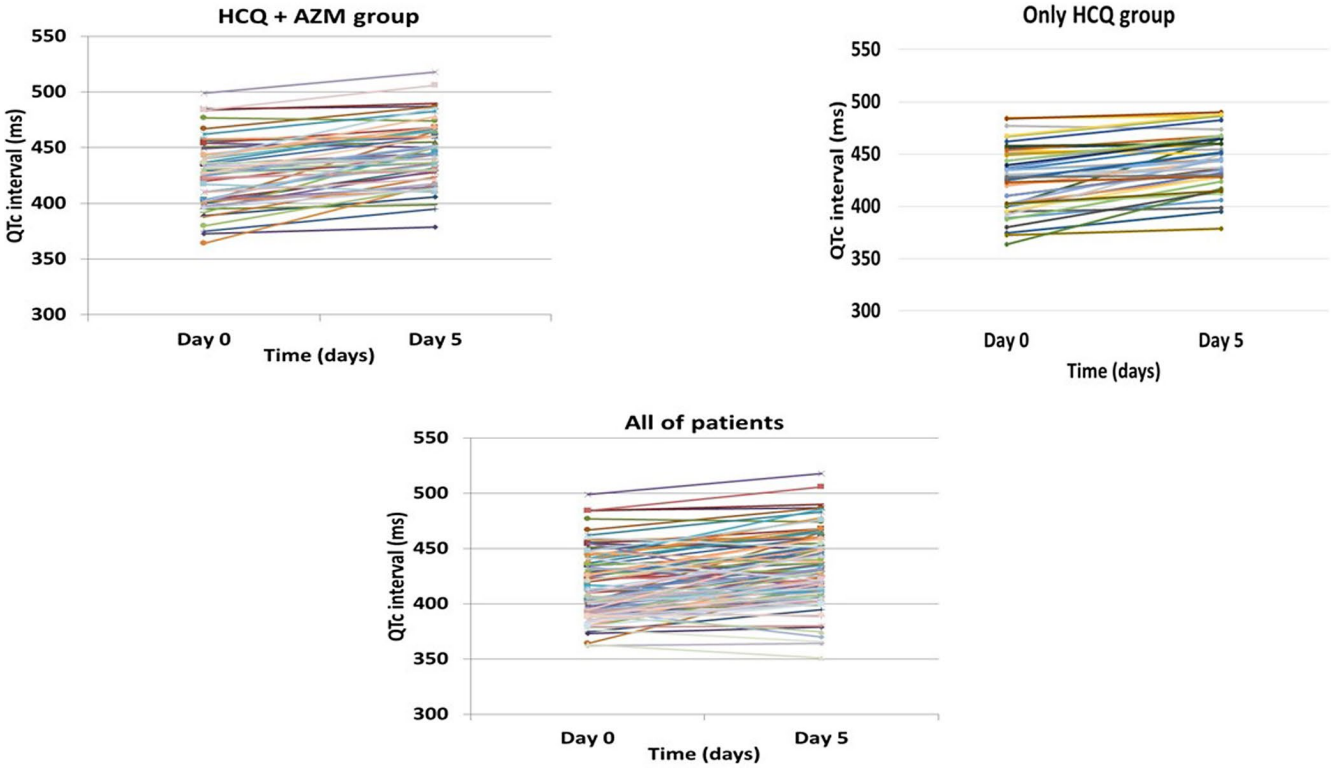

FIGURE 1 Individual QTc intervals before and after treatment in HCQ + AZM group, only HCQ group, and all population. AZM, azithromycin; HCQ, hydroxychloroquine

TABLE 2 Gender disparities in mean QTc interval before and after COVID-19 treatment

	Women (n = 46)	Men (n = 55)	*P* value
QTc interval before treatment, ms	423.9 ± 32.4	409.3 ± 25.9	.020
QTc interval after treatment, ms	436.9 ± 35.6	427.6 ± 27.1	.213
ΔQTc, ms	12.9 ± 18.9	18.2 ± 18.1	.153

therapy were associated with QTc prolongation. However, after adjusting for other potential confounding factors, multivariable analyses showed that only baseline QTc interval (HR: 1.37, 95% CI 1.21-1.78, *P* = .001) and HCQ + AZM combination therapy (HR: 1.25, 95% CI 1.17-1.49, *P* = .002) were independently associated with QTc prolongation.

4 | DISCUSSION

This study investigated the effects of 5-days uninterrupted HCQ or HCQ + AZM treatment on QTc interval and malignant ventricular arrhythmias in hospitalized COVID-19 patients at single center. Our results revealed that (a) significant increase in the QTc interval was detected after HCQ and HCQ + AZM treatments. (b) QTc prolongation was more likely to occur in patients received HCQ + AZM combination therapy. Also, (c) baseline QTc interval and HCQ + AZM treatment were independently associated with QTc prolongation. However, (d) no patient experienced malignant ventricular arrhythmias during treatment, and (e) all of patients completed the 5-days treatment without interruption.

After some preliminary reports from small scale clinical trials HCQ and AZM started to be widely used worldwide for the treatment of COVID-19.[3,4] At the cellular level, HCQ prolongs cardiac action potential duration, enhances automaticity, and reduces the maximum diastolic potential. As a consequence, HCQ causes prolongation of the QT and QRS intervals on the surface ECG.[22] There have been several findings showing pronounced QT interval prolongation and TdP following the AZM administration.[23] Previous studies showed that HCQ and AZM combination have been independently associated with increase the risk in other populations for QT-interval prolongation, drug-induced malignant ventricular arrhytmia and drug-induced sudden cardiac death.[6,8,24] On the other hand, it has not been demonstrated that HCQ and AZM treatments have clear benefit in outcomes of COVID-19.[25] Therefore, the use of these drugs in COVID-19 treatment is still controversial. As a result of widespread use all over the world, it is important to characterize the cardiac adverse effect profile of these medications in COVID-19 patients.

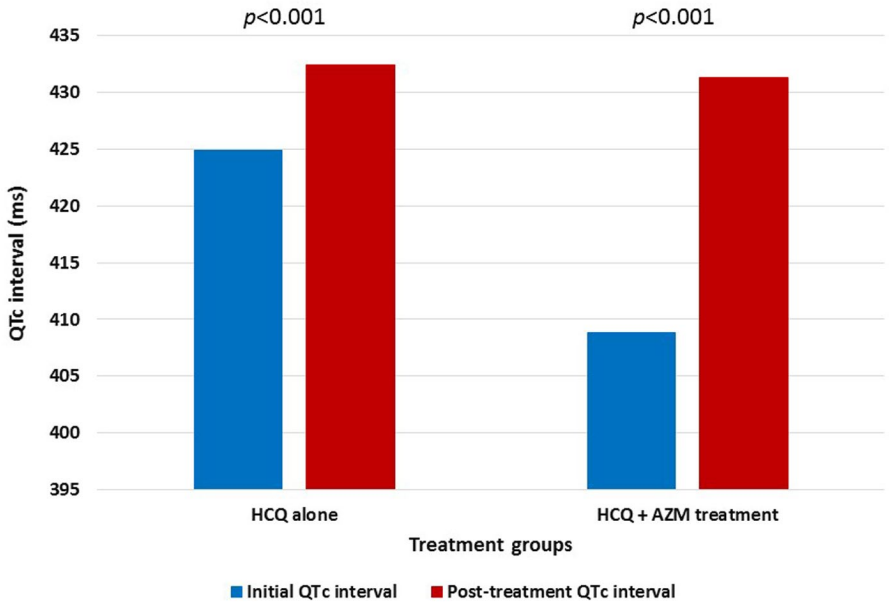

FIGURE 2 The mean QTc intervals at admission and after 5-days treatment in two treatment groups

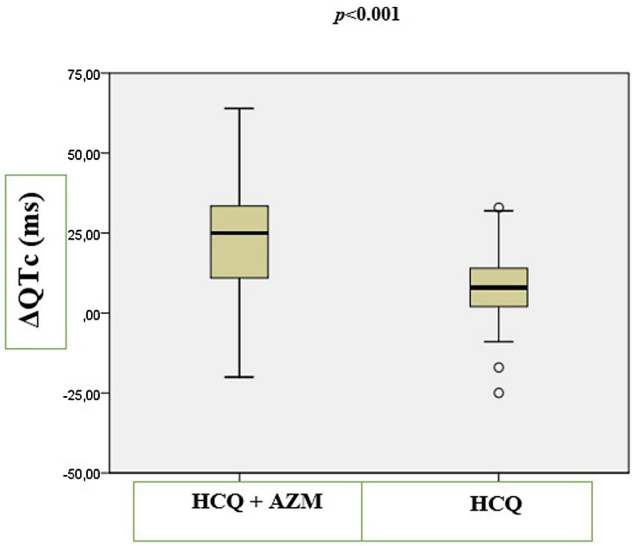

FIGURE 3 Comparison of the mean QTc increase (ΔQTc) after treatment between HCQ + AZM and HCQ groups. AZM, azithromycin; HCQ, hydroxychloroquine

The largest report of adverse effects and safety of HCQ and AZM among patients with COVID-19 has recently been published by Rosenberg et al.[26] In this large scale, multicenter study revealed that among 1438 hospitalized patients with a diagnosis of COVID-19, treatment with HCQ, AZM or both, compared with neither treatment, was not significantly associated with differences in-hospital mortality. Additionally, there were no significant differences in the relative likelihood of abnormal ECG findings.[26]

Some studies have recently reported that although HCQ + AZM combination therapy may induce increase in the QTc interval, this treatment is not associated with mortality because of ventricular arrhythmias.[27,28] Saleh et al prospectively analysed 201 hospitalized COVID-19 patients who received HCQ monotherapy or HCQ and AZM combination.[28] They found that the maximum QTc interval during treatment was significantly longer in the combination group vs the monotherapy group. Although participants experienced QTc interval prolongation, especially when combination therapy was used, the risk of arrhythmic death and TdP were not increased in this study. Therefore, authors suggested that though the beneficial effects of HCQ and AZM in patients with COVID-19 is unproven, the malignant arrhythmic risk appears to be low and may not warrant monitoring in most hospitalized patients.[28] Ramireddy et al studied 98 hospitalized COVID-19 patients.[29] Sixty-one of these patients received HCQ + AZM treatment, and they concluded that a total of 12% of patients manifested critical QTc prolongation, and the combination caused greater prolongation than either drug alone. Also, no patients manifested TdP in this study.[29] In French prospective study,[30] 73 patients with COVID-19 who were prescribed HCQ + AZM treatment were assessed for QT prolongation and arrhythmia. At the end of study no patient presented syncope, TdP or cardiac arrest under HCQ + AZM treatment.[30] Similar to the previous data, our results showed that although HCQ + AZM combination was associated with QTc prolongation, malignant ventricular arrhythmia or related death was not observed in any patient.

Another study[31] enrolled 90 participants to retrospectively evaluate the risk and degree of QT prolongation in patients with COVID-19 in association with their use of HCQ or/and AZM. Patients who received HCQ + AZM combination had a greater median change in QT interval compared with those received HCQ alone.[31] In line with these findings, ΔQTc was significantly higher in HCQ + AZM group in our cohort. In this study, of patients who received combination, 11 of 53 (21%) had prolonged QTc of 500 ms or more and 7 of 53 (13%) had a change in QTc of 60 ms or more and 1 case had TdP.[31] QTc interval over 500 ms and the increase of QTc over 60 ms are considered important risk factors for TdP.[32] In our entire cohort, one (1.7%) patient in combination group experienced increase of more than 60 ms and two (3.5%) patients had prolonged QTc interval of 500 ms or more. However, no ventricular arrhythmia was observed in any of

TABLE 3 Univariate and multivariable analysis for associated factors with QTc prolongation (n = 19 of 101 [18.8%])

Univariate analysis	Hazard ratio (95% CI)	*P* value	Multivariable analysis	Hazard ratio (95% CI)	*P* value
Age	1.02 (0.97-1.03)	.582	—	—	—
Gender, female	1.32 (0.87-2.32)	.189	—	—	—
Hypertension	1.41 (0.79-2.78)	.201	—	—	—
Diabetes mellitus	1.01 (0.89-1.11)	.781	—	—	—
Coronary artery disease	1.32 (0.85-1.98)	.106	—	—	—
Chronic heart failure	1.98 (1.34-4.87)	**.020**	**Chronic heart failure**	1.02 (0.98-1.10)	.073
Creatinine	1.01 (0.98-1.02)	.320	—	—	—
Potassium	1.24 (0.82-1.37)	.109	—	—	—
Baseline QTc	1.83 (1.38-2.49)	**<.001**	**Baseline QTc**	1.37 (1.21-1.78)	**.001**
HCQ alone	1.43 (1.15-3.19)	**.010**	**HCQ alone**	1.26 (0.96-2.08)	.098
HCQ + AZM	1.69 (1.26-2.01)	**<.001**	**HCQ + AZM**	1.25 (1.17-1.49)	**.002**

Note: Univariate and multivariable logistic regression analysis is used to obtain the hazard ratios.
Abbreviations: AZM, azithromycin; HCQ, hydroxychloroquine.
Statistically significant values are set in bold.

the patients. This may be related that, our participants were younger and comorbid conditions such as coronary artery disease, hypertension, chronic heart failure and diabetes mellitus were relatively less in our study population. Also, patients who needed intensive care unit and had to use other drugs that could cause QT prolongation were excluded from our study.

The daily ECG monitoring may be hard to perform during a pandemic with a highly contagious virus, as hospitals have also to protect the healthcare workers from infection as much as possible. In our cohort, before treatment, all of patients had QTc interval shorter than 500 ms We did not observe any malignant ventricular arrhythmia or death in our COVID-19 population after 5-days HCQ + AZM treatment. Therefore, as suggested before,[26] daily ECG monitoring for only patients with QTc interval longer than 500 ms seems to be an easy-to-feasible and plausible approach.

4.1 | Study limitations

This study has several limitations. The retrospective design of the study and a relatively small sample size were major limitations. As patients needed intensive care unit were excluded from the study because of received oseltamivir, we could not evaluate the effects of HCQ/AZM therapy on QTc interval and arrhythmias in severe COVID-19 patients. Another possible reason that more QTc prolongation was not seen was because of the fact that other drugs that prolong QTc were avoided. Higher risk groups may not have been represented, because our study population was relatively younger. However, no comments on cardiac safety of HCQ and AZM therapy in outpatient can be extrapolated from this analysis, as daily inpatient care may have influenced cardiac safety in ways not measured by this study. Other major limitation is the absence of a control cohort of patients with a diagnosis of COVID-19 that were not treated with any of these medications. Because of single center design, our findings may not be representative for every COVID-19 patients.

5 | CONCLUSIONS

In this retrospective study, we observed a significant increase in the mean QTc interval of patients with COVID-19 during treatment that was more pronounced in patients treated with HCQ + AZM combination therapy. However, this increase did not require interruption of treatment in any patient. Moreover, there were no patients of malignant ventricular arrhythmias or arrhythmic death in the entire cohort. Large scale, prospective studies are needed to determine the exact effects of HCQ/AZM treatment regimens on arrhythmias in patients with COVID-19.

DISCLOSURE

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author [B.Ö], or principal author [İ.H.Ö., dribrahimhalilozdemir@gmail.com] upon reasonable request.

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