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QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin

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BACKGROUND There is no known effective therapy for patients with coronavirus disease 2019 (COVID-19). Initial reports suggesting the potential benefit of hydroxychloroquine/azithromycin (HY/AZ) have resulted in massive adoption of this combination worldwide. However, while the true efficacy of this regimen is unknown, initial reports have raised concerns about the potential risk of QT interval prolongation and induction of torsade de pointes (TdP).

OBJECTIVE The purpose of this study was to assess the change in corrected QT (QTc) interval and arrhythmic events in patients with COVID-19 treated with HY/AZ.

METHODS This is a retrospective study of 251 patients from 2 centers who were diagnosed with COVID-19 and treated with HY/AZ. We reviewed electrocardiographic tracings from baseline and until 3 days after the completion of therapy to determine the progression of QTc interval and the incidence of arrhythmia and mortality.

RESULTS The QTc interval prolonged in parallel with increasing drug exposure and incompletely shortened after its completion. Extreme new QTc interval prolongation to >500 ms, a known marker of high risk of TdP, had developed in 23% of patients. One patient developed polymorphic ventricular tachycardia suspected as TdP, requiring emergent cardioversion. Seven patients required premature termination of therapy. The baseline QTc interval of patients exhibiting extreme QTc interval prolongation was normal.

CONCLUSION The combination of HY/AZ significantly prolongs the QTc interval in patients with COVID-19. This prolongation may be responsible for life-threatening arrhythmia in the form of TdP. This risk mandates careful consideration of HY/AZ therapy in light of its unproven efficacy. Strict QTc interval monitoring should be performed if the regimen is given.

KEYWORDS COVID-19; QT interval; Torsade de pointes; Hydroxychloroquine; Azithromycin

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Introduction

The evidence supporting effective drug therapy for coronavirus disease 2019 (COVID-19) is limited. In vitro studies have suggested that hydroxychloroquine (HY) alone and in combination with azithromycin (AZ) could be a viable therapy.[1,2] A small controversial study enrolling 26 treated patients and 16 nonrandomized controls showed that HY/AZ shortened the viral shedding of severe acute respiratory syndrome coronavirus 2.[3] On the basis of this, clinicians in many countries have begun using these medications, and multiple randomized trials are ongoing.[4] However, HY and AZ have each been independently shown to increase the risk of QT interval prolongation, drug-induced torsade de pointes (TdP), and sudden cardiac death.[5–8] We recently reported QT interval prolongation in a preliminary series of 84 patients with COVID-19 treated with HY/AZ.[9] Here we report a study from 2 centers evaluating the effects of HY/AZ on the QT interval and the arrhythmic risk in patients with COVID-19.

Methods

This is a retrospective study including 251 consecutive adult patients hospitalized at NYU Langone Health (211 patients)

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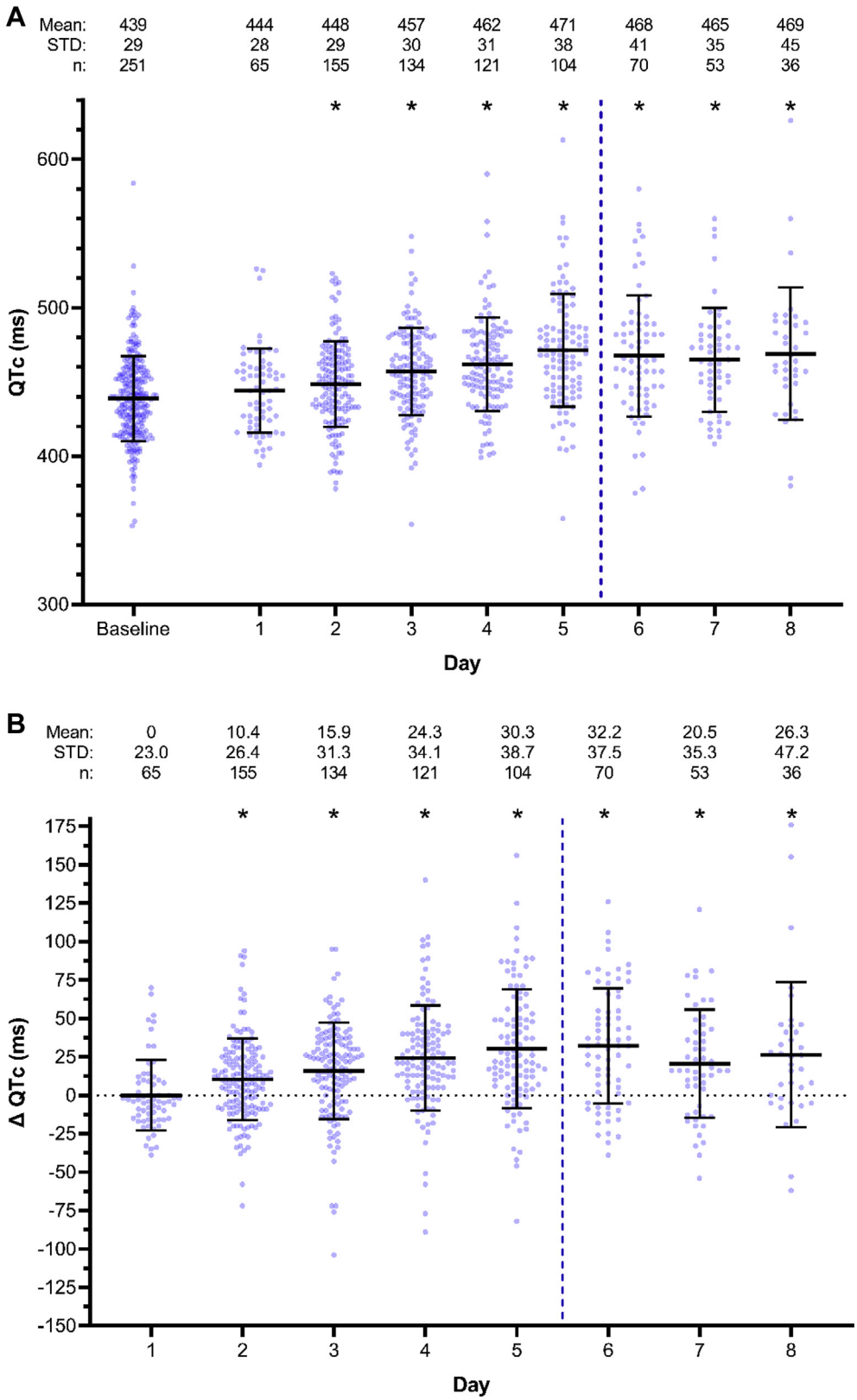

Figure 1 **A:** Daily absolute QTc interval in patients treated with HY/AZ. **B:** Change in QTc interval by day. Number of patients and mean QTc interval ± SD are presented at each day. *$P < .01$ for the comparison with baseline QTc interval. The *blue lines* indicate end of HY/AZ therapy.

and at San Paolo University Hospital (40 patients) with COVID-19, treated with the combination of HY/AZ. Patients with a baseline electrocardiogram (ECG) and at least 1 ECG performed after medication administration were included. Of the 325 patients screened, we excluded 40 patients without baseline ECG (12.3%) and 34 patients without follow-up ECG (10.4%).

Of the 211 patients from the NYU site, 84 were reported in our recent publication.[9] HY was given orally at 400 mg twice daily for 1 day (loading dose) followed by 200 mg twice daily for 4 days. AZ was given orally at a dose of 500 mg daily for 5 days. For corrected QT (QTc) interval measurements, 5 cardiologists trained and experienced in QT interval measurements performed all ECG measurements. The QT interval was measured using the "tangent" method.[10] Briefly, a tangent is drawn to the steepest last limb of the presumed T wave to define the end of the T wave as the intersection of this tangent with the baseline. The QTc interval was calculated from the QT and R-R intervals using the Bazett formula. The QRS interval was measured from the onset of the Q wave, or the R wave if no Q wave was visible, to the J point. The JTc interval was calculated by subtracting the QRS duration from the QTc interval (QTc interval – QRS duration).

For quality assurance, QT interval measurements were validated by a senior electrophysiologist experienced in QT interval measurements who repeated measurements at arbitrary times, corroborating ~10% of all QT interval measurements (100 of 978). This validation showed high agreement between measurements, with a correlation coefficient of $R = 0.95$ ($P < .01$). The closing date of follow-up was April 15, 2020. The primary end point was extreme QTc interval prolongation. This included absolute QTc interval > 500 ms (or JTc interval > 410 ms to adjust for patients with QRS duration > 120 ms), a known marker of high risk of malignant arrhythmia and sudden cardiac death,[11–13] or QTc interval prolongation of >60 ms, another high-risk marker regardless of the baseline QRS duration.[14,15]

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 26 (IBM, Armonk, NY), and figures were constructed using GraphPad Prism 8 (GraphPad Software, Inc., San Diego, CA). Continuous variables are expressed as mean ± SD, and categorical variables are expressed as percentages (95% confidence interval). Normality of data samples was assessed using the Shapiro-Wilk test. Two-sample hypothesis testing for continuous variables was performed using the Student *t* test if samples had normal distributions, Mann-Whitney *U* test if samples did not have normal distributions, or paired samples *t* test for paired samples. Two-sample hypothesis testing for categorical variables was performed using the Fisher exact test. For Figure 1A, a mixed-effects analysis with Geisser-Greenhouse correction was performed, followed by Dunnett's multiple comparison test, to compare each day's QTc interval with the baseline QTc interval. For Figure 1B, 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 each sample against a ΔQTc interval of 0 ms (ie, no change from baseline), and *P* values were adjusted using the Holm-Bonferroni method to $\alpha < .05$. Univariate and multivariate logistic regressions were performed to identify predictors of prolonged JTc, ΔQTc, and QTc intervals. The univariate predictors with $P < .05$ and greatest clinical utility were selected for subsequent multivariate analysis, as allowed by our sample size.

The study was performed according to the NYU's Institutional Review Board and Quality Improvement initiative and the University Hospital of Milan Institutional Review Board guidance in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Table 1 Baseline characteristics (N = 251)

Characteristic	Value
Age (y)	64 ± 13
Sex: male	75 (70–81)
Weight (kg)	86.0 ± 17.9
Coronary artery disease	12 (8–16)
Hypertension	54 (48–60)
Chronic kidney disease	11 (7–15)
Diabetes mellitus	27 (21–32)
Chronic obstructive pulmonary disease	7 (4–10)
Congestive heart failure	3 (1–5)
Creatinine level at initiation (mg/dL)	1.2 ± 0.9
Creatinine level at the maximum QTc interval (mg/dL)	1.6 ± 1.5
CrCl level at initiation (mL/min)	84 ± 43
CrCl level at the maximum QTc interval (mL/min)	80 ± 52
Abnormal LFTs at initiation	21 (16–27)
Abnormal LFTs at the maximum QTc interval	38 (27–48)
Potassium level at baseline (mEq/L)	4.1 ± 0.6
Potassium level at the maximum QTc interval (mEq/L)	4.2 ± 0.5
QTc-prolonging medications	
Psychiatric medications	12 (8–16)
Antimicrobials	10 (7–14)
Amiodarone	9 (6–13)
No. of QTc-prolonging medications	0.3 ± 0.5
0 medications	71 (65–77)
1 medication	27 (22–33)
2 medications	2 (0–4)
Baseline QTc interval (ms)	439 ± 29
Maximum QTc interval (ms)	473 ± 36
Maximum ΔQTc interval (ms)	34 ± 35
Day of the maximum QTc interval	4.1 ± 2.0
Baseline JTc interval (ms)	342 ± 25
Maximum JTc interval (ms)	375 ± 35
Maximum ΔJTc interval (ms)	33 ± 36
Day of the maximum JTc interval	4.1 ± 1.9
Mortality	20 (14–25)

Values are presented as mean ± SD or percentage (95% confidence interval).

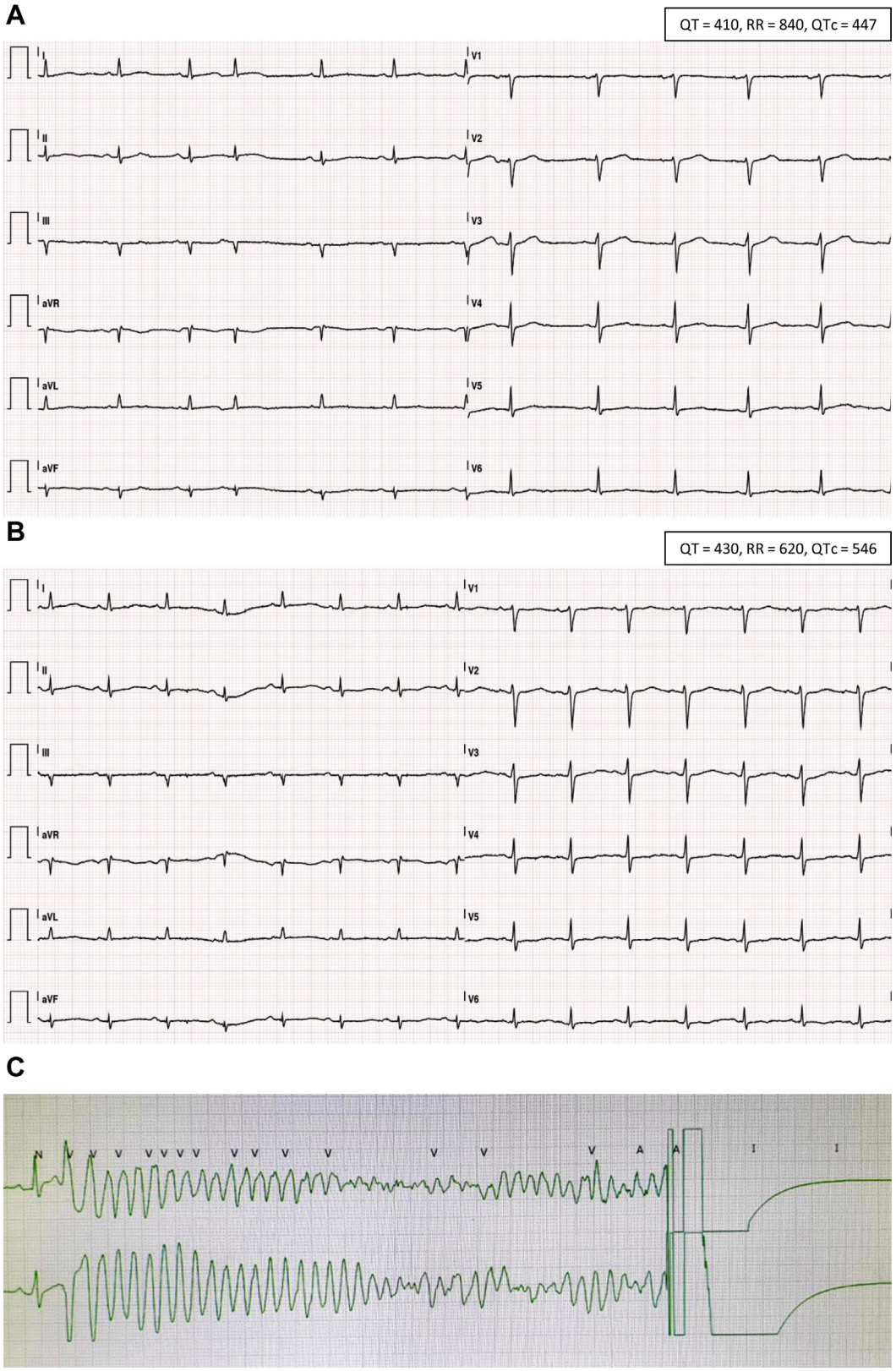

Figure 2 QTc interval prolongation and torsdaes de pointes. This 68-year-old male patient without any medical history was found to be positive for SARS-COV-2, and HY/AZ was initiated. The patient did not receive any other QT-prolonging medications. **A:** Baseline ECG. ECG before the initiation of HY/AZ. QTc interval = 447 ms. QTc interval prolonged gradually to 477 ms on day 1, to 480 ms on day 2, and to 505 ms on day 3. **B:** ECG at day 4 of HY/AZ revealed QTc interval prolongation to 546 ms. **C:** On the same night, multiple short runs of TdP were noted on telemetry. HY/AZ was discontinued, and the patient developed TdP requiring cardioversion, which was given in <10 seconds because of the incidental presence of a physician by the patient. The laboratory test results from day 4 revealed a creatinine level of 1.1 mg/dL, a potassium level of 3.5 mEq/L, and mildly elevated liver function test results.

Results

We included 251 patients in our cohort with a maximum follow-up of 8 days and the mean ECG follow-up time of 5.2 ± 2 days (Table 1). The median age was 64 ± 13 years, and 75% were men. Forty-four patients (17.5%) died of respiratory or multiorgan failure. One patient with extreme QTc interval prolongation developed TdP and required emergent cardioversion (Figure 2), representing an arrhythmic risk of 0.4%. The QTc interval prolonged from a baseline of 439 ± 29 ms to a maximum value of 473 ± 36 ms ($P < .001$), which occurred on day 4.1 ± 2 of therapy in the general cohort (Figure 1). The JTc interval prolonged from a baseline of 342 ± 25 ms to a maximum value of 375 ± 35 ms, which occurred on day 4.1 ± 1.9. For patients with QRS duration < 120 ms, the QTc interval prolonged from a baseline of 434 ± 25 ms to a maximum of 469 ± 34 ms, which occurred on day 4 ± 1.9. The individual change between baseline and maximum QTc intervals is presented in Figure 3. Figure 4 presents the distribution of QTc interval ranges at each day. Of note, in 58 of 251 patients (23%), at least 1 measure of extreme QTc interval prolongation was observed. Specifically, QTc interval > 500 ms was seen in 28 of 222 patients with QRS duration < 120 ms (13%). JTc interval > 410 ms was seen in 4 of 29 patients with QRS duration > 120 ms (14%), and ΔQTc interval > 60 ms was seen in 51 of 251 patients with any QRS duration (20%). These numbers include 25 patients who had >1 of these end points. Thirty-five of 58 patients (60%) who met the composite end point were not on any other QTc-prolonging medication. In this high-risk group, the QTc interval increased from a baseline of 431 ± 32 to 513 ± 38 ms and the JTc interval increased from 335 ± 28 to 417 ± ms ($P < .01$ for both). In 8 patients, extreme QTc interval prolongation triggered discontinuation of therapy prematurely, including the patient who developed TdP where therapy was halted on day 4. In 29 patients (11.5%), the baseline QRS duration was >120 ms. The baseline JTc and maximum ΔJTc intervals were similar between patients with and without QRS duration ≥ 120 ms (Table 2). In multivariate analysis, baseline QTc interval and coadministration of amiodarone were significant predictors of QTc interval > 500 ms while baseline creatinine and coadministration of amiodarone were predictors of ΔQTc interval > 60 ms (Tables 3 and 4). The predictors of extreme JTc interval prolongation > 410 ms included baseline JTc interval and creatinine level (Online Supplemental Table 1). Patients with extreme QTc interval prolongation had lower body weight, higher frequency of kidney disease, and greater amiodarone exposure (Online Supplemental Table 2).

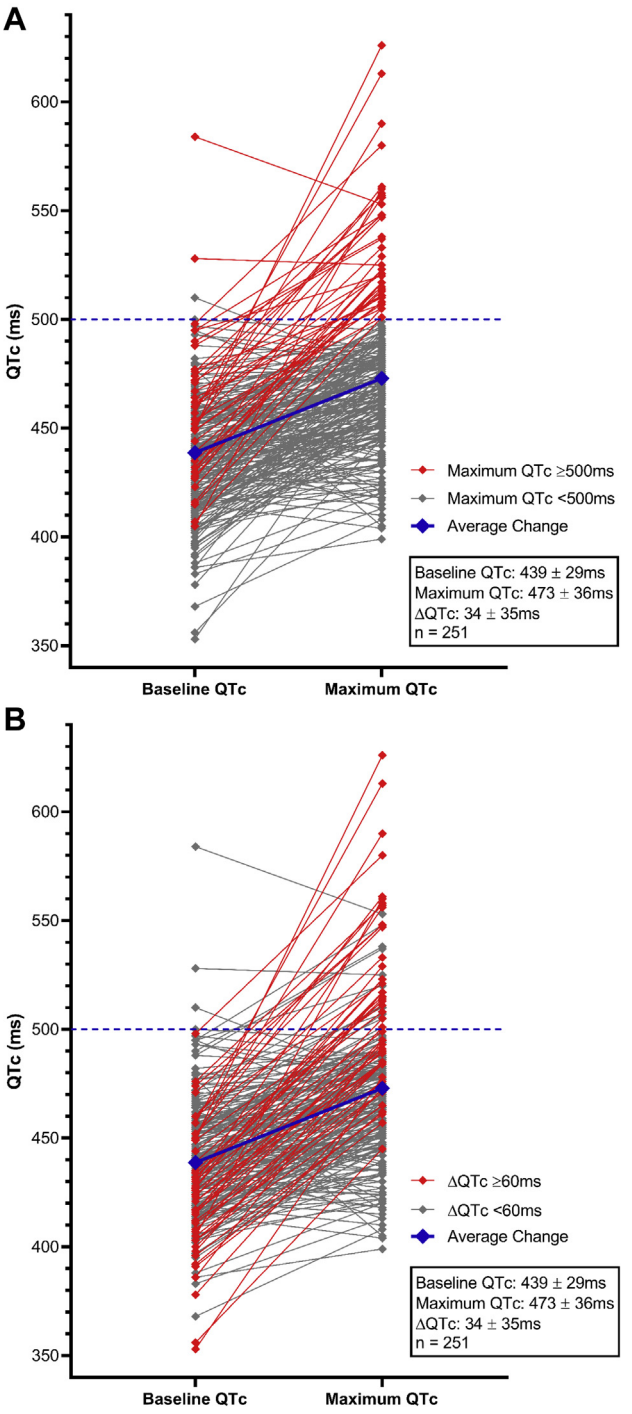

Figure 3 Individual QTc interval changes from baseline to the individual maximum QTc interval. **A:** Patients with maximum QTc interval > 500 ms are marked in *red*. **B:** Patients with ΔQTc interval > 60 ms are marked in *red*.

Discussion

Drug-induced QT interval prolongation is an important substrate for TdP, a potentially lethal polymorphic ventricular tachycardia (VT). In our study of 251 patients with COVID-19, we found a high incidence of QTc interval prolongation, with at least 1 documented polymorphic VT (suspected TdP) for a rate of 0.4%. To put the incidence of TdP in perspective, the risk of TdP induction by sotalol is estimated at 0.1%.[16] Because of this risk, sotalol is introduced under ECG monitoring in the hospital for at least 3 days. In our study, we observed QTc interval prolongation in parallel with increasing HY/AZ exposure, which partially shortened

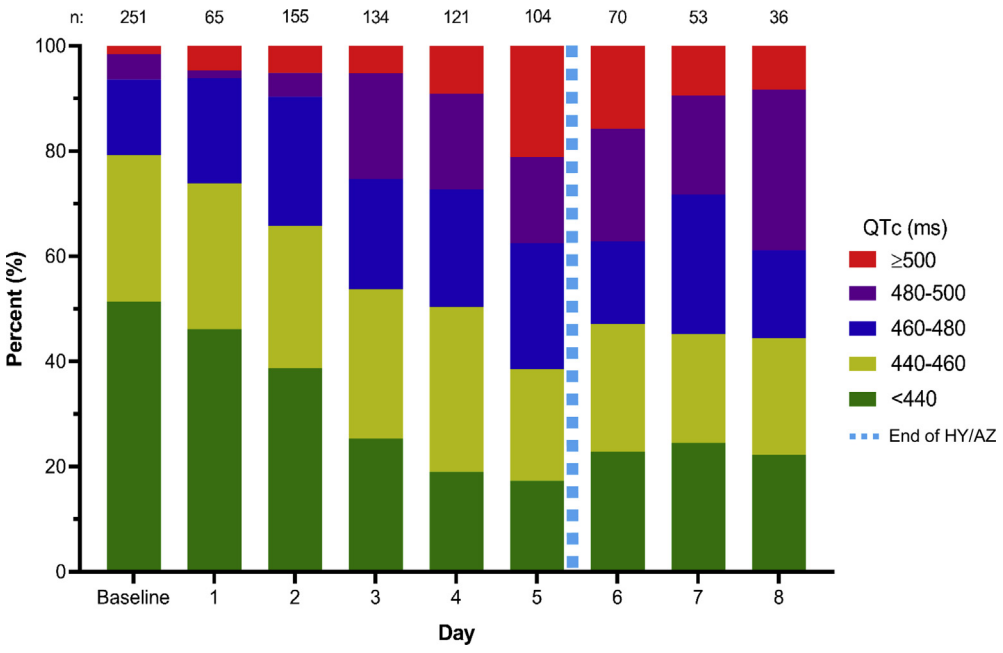

Figure 4 Distribution of QTc interval ranges by day of therapy. Note that therapy was given on days 1–5 (*dashed line*).

after medication cessation. For example, the proportion of patients with QTc interval > 500 ms was 20% at day 4 after the completion of HY/AZ therapy and declined to 10% 1 day later. Baseline QTc/JTc interval, creatinine level, and coadministration of amiodarone were significant predictors of extreme QTc/JTc interval prolongation and ΔQTc interval > 60 ms. We show that the effect on the QTc interval was driven entirely by prolonging repolarization and regardless of QRS duration, as evident by the corresponding JTc interval prolongation. In this regard, it is worth mentioning that there are limited data on high arrhythmic risk markers in patients with QRS duration > 120 ms and QTc interval prolongation. We used QTc interval change by >60 ms as a marker, a cutoff that was initially proposed in an algorithm designed to automatically detect QTc interval prolongation taking into account the normal variation in QTc interval.[17] In addition, we used a cutoff of JTc interval > 410 ms as the correlate of QTc interval > 500 ms for patients with wide QRS duration on the basis of the deduction of the mean QRS value we found in our patients with the normal QRS value, which was 90 ms. Previous information on the potential proarrhythmic effect of the combination chloroquine/HY and AZ is limited. In a randomized, placebo-controlled, parallel trial in 116 young healthy controls receiving chloroquine alone or in combination with AZ, coadministration increased the QTc interval (Fridericia) by up to 14 ms.[18,19] However, the risk of drug-induced TdP is substantially higher in hospitalized patients. This is due to the higher prevalence of other risk factors for TdP, including older age, presence of underlying heart disease, genetic factors,[20] electrolyte disturbances, and cotreatment with other QT-prolonging medications.[21–24] Indeed, in a recent study assessing chloroquine therapy in patients with COVID-19, extreme QT interval prolongation, and excess cardiac mortality in the higher-dose arm led to premature interruption of the regimen.[25] Concordantly, recently published studies confirmed a QT-prolonging effect of HY/AZ ranging between 23 and 41 ms (Online Supplemental Table 3). In the present study, we found a significant proportion of patients with extreme QTc interval prolongation, 23%, with at least 1 polymorphic VT requiring cardioversion. Another 7 patients who developed extreme QTc interval prolongation by day 3 had the treatment discontinued, possibly preventing additional arrhythmic events. Interestingly, the coupling interval of the arrhythmia-initiating beat observed in our study was ∼380 ms, which is shorter than expected for TdP.[26] In this regard, AZ has been shown to induce short-coupled polymorphic VT regardless of QT interval prolongation.[27] It is thus impossible to be certain about the nature of the arrhythmia. Since this polymorphic VT occurred at the time of significant QT interval prolongation, it is reasonable to assume that HY/AZ played an important proarrhythmic role. However, in view of its relatively short coupling interval, it is not clear whether this is true TdP or a polymorphic VT triggered by AZ via increased sodium current. The alarming proportion of patients with COVID-19 developing extreme QT interval prolongation with HY/AZ therapy in our study can be explained by the specific characteristics of this population, which includes older age, higher prevalence of underlying and acute renal failure, and coadministration of additional QT-prolonging medications, particularly amiodarone.

Recently published guidance statements addressing QTc surveillance and arrhythmic risk in patients with COVID-19 are based on long QT syndrome risk stratification

Table 2 Characteristics by baseline QRS duration (N = 251)

Characteristic	Baseline QRS duration < 120 ms (n = 222)	Baseline QRS duration ≥ 120 ms (n = 29)	*P*
Age (y)	63 ± 13	73 ± 9	<.01
Sex: male	75 (70 to 81)	76 (59 to 92)	>.99
Weight (kg)	85.8 ± 17.5	87.7 ± 21.1	.54
Coronary artery disease	10 (6 to 14)	21 (5 to 36)	.12
Hypertension	53 (47 to 60)	59 (40 to 78)	.69
Chronic kidney disease	9 (6 to 13)	21 (5 to 36)	.10
Diabetes mellitus	24 (18 to 30)	48 (29 to 68)	.01
Chronic obstructive pulmonary disease	8 (4 to 11)	3 (−4 to 11)	.70
Congestive heart failure	1 (0 to 3)	14 (0 to 27)	<.01
Creatinine level at initiation (mg/dL)	1.2 ± 0.9	1.6 ± 1.4	.01
Creatinine level at the maximum QTc interval (mg/dL)	1.6 ± 1.5	1.7 ± 0.9	.02
CrCl level at initiation (mL/min)	87 ± 43	65 ± 35	.01
CrCl level at the maximum QTc interval (mL/min)	82 ± 53	59 ± 36	.03
Abnormal LFTs at initiation	22 (17 to 28)	15 (0 to 29)	.46
Abnormal LFTs at the maximum QTc interval	40 (28 to 52)	19 (3 to 34)	.23
Potassium level at baseline (mEq/L)	4.1 ± 0.6	4.2 ± 0.4	.65
Potassium level at the maximum QTc interval (mEq/L)	4.2 ± 0.5	4.0 ± 0.4	.16
QTc-prolonging medications			
Psychiatric medications	11 (7 to 15)	17 (3 to 32)	.35
Antimicrobials	11 (7 to 15)	7 (−3 to 17)	.75
Amiodarone	8 (4 to 11)	21 (5 to 36)	.04
No. of QTc-prolonging medications	0.3 ± 0.5	0.4 ± 0.6	.12
0 medications	73 (67 to 78)	59 (40 to 78)	.13
1 medication	26 (20 to 31)	38 (19 to 57)	.18
2 medications	2 (0 to 4)	3 (−4 to 11)	.46
Baseline QTc interval (ms)	434 ± 25	475 ± 33	<.01
Maximum QTc interval (ms)	469 ± 34	503 ± 39	<.01
Maximum ΔQTc interval (ms)	35 ± 35	29 ± 40	.43
Day of the maximum QTc interval	4.0 ± 1.9	4.8 ± 2.2	.05
Baseline JTc interval (ms)	344 ± 24	333 ± 26	.06
Maximum JTc interval (ms)	377 ± 35	363 ± 33	.01
Maximum ΔJTc interval (ms)	33 ± 36	30 ± 39	.52
Day of the maximum JTc interval	4.0 ± 1.9	4.7 ± 2.3	.13
No. of follow-up ECGs	2.9 ± 1.3	3.2 ± 1.5	.33
Follow-up time (d)	5.2 ± 2.0	5.8 ± 1.9	.09

Values are presented as mean ± SD or percentage (95% confidence interval).

principles and include pretreatment assessment of the QTc interval, considering discontinuing other QTc-prolonging medications, and providing special attention to those with highest-risk features.[15,28,29] Yet, our findings suggest that risk stratification of patients with COVID-19 may be more complex. For example, we found that the baseline QTc interval in patients with extreme QTc interval prolongation was only 431 ± 32 ms, within the "normal" QTc interval range. Moreover, 42 of 58 patients (72%) in the high-risk group had baseline QTc interval < 450 and JTc interval < 350 ms. In addition, it is important to consider that even careful monitoring of the QT interval may only partially mitigate the risk of TdP. This is because arrhythmia often occurs in the setting of sudden intermittent changes in the R-R interval, such as when PVCs, APCs, or pauses occur. In these cases, TdP can present even if the QTc interval in only mildly prolonged at baseline.[30] We therefore suggest that individual risk/benefit assessment should be applied before treating with HY/AZ. We recommend daily ECG monitoring, with reassessment of therapy if high-risk markers appear (QTc interval > 500 ms or ΔQTc interval > 60 ms). For this, triggered alerting systems may be applied.[31] Finally, we observed only partial resolution of the QTc interval at 3 days after the completion of therapy. This may be attributed to the prolonged half-life of HY, which is ∼20 days. This finding requires special attention when considering discharging patients receiving HY/AZ or if outpatient treatment with HY/AZ is planned.

Limitations

Our study has several limitations. This is an observational retrospective study. We did not include patients treated

Table 3 Predictors of the maximum QTc interval ≥500 ms (n = 40 of 251 [16%])

Variable	*P*	OR	95% CI
Univariate logistic regression			
Age	0.62	1.01	0.98–1.03
Sex: male	0.25	1.66	0.7–3.97
Weight	0.25	0.99	0.97–1.01
Coronary artery disease	0.21	1.82	0.72–4.61
Hypertension	0.87	1.06	0.54–2.09
Chronic kidney disease	0.05	2.53	1.02–6.26
Diabetes mellitus	0.20	1.61	0.78–3.3
Chronic obstructive pulmonary disease	0.93	1.06	0.29–3.84
Congestive heart failure	0.01	7.70	1.66–35.87
Creatinine level at initiation	0.01	1.79	1.2–2.69
Creatinine level at the maximum QTc interval	<0.01	1.35	1.12–1.63
CrCl level at initiation	0.04	0.91	0.84–1.0
CrCl level at the maximum QTc interval	<0.01	0.88	0.8–0.95
Abnormal LFTs at initiation	0.72	1.16	0.51–2.64
Abnormal LFTs at the maximum QTc interval	0.42	0.74	0.35–1.55
Potassium level at baseline	0.61	0.84	0.42–1.65
Potassium level at the maximum QTc interval	0.86	0.94	0.44–1.99
Psychiatric medications	0.21	1.82	0.72–4.61
Antimicrobials	0.94	0.96	0.31–2.94
Amiodarone	<0.01	5.08	2.05–12.61
No. of QTc-prolonging medications	0.01	2.40	1.31–4.38
Baseline QTc interval	<0.01	1.32	1.16–1.51
No. of follow-up ECGs	<0.01	2.05	1.54–2.73
Follow-up time	0.01	1.28	1.06–1.55
Multivariate logistic regression			
Congestive heart failure	0.53	1.79	0.3–10.65
Creatinine level at initiation	0.06	1.54	0.99–2.4
Amiodarone	0.02	3.27	1.18–9.11
Baseline QTc interval	<0.01	1.26	1.09–1.45

Table 4 Predictors of the maximum ΔQTc interval ≥60 ms (n = 51 of 251 [20%])

Variable	*P*	OR	95% CI
Univariate logistic regression			
Age	0.18	1.02	0.99–1.04
Sex: male	0.56	1.25	0.59–2.61
Weight	0.03	0.98	0.96–1.0
Coronary artery disease	0.05	2.32	1.01–5.37
Hypertension	0.15	1.59	0.84–2.98
Chronic kidney disease	0.08	2.17	0.91–5.16
Diabetes mellitus	0.23	1.50	0.77–2.92
Chronic obstructive pulmonary disease	0.69	0.77	0.21–2.77
Congestive heart failure	0.59	1.59	0.3–8.45
Creatinine level at initiation	0.04	1.38	1.02–1.87
Creatinine level at the maximum QTc interval	0.01	1.27	1.05–1.52
CrCl level at initiation	0.07	0.93	0.86–1.01
CrCl level at the maximum QTc interval	<0.01	0.90	0.83–0.96
Abnormal LFTs at initiation	0.26	0.62	0.27–1.42
Abnormal LFTs at the maximum QTc interval	0.39	0.76	0.4–1.43
Potassium level at baseline	0.22	1.49	0.79–2.82
Potassium level at the maximum QTc interval	0.24	1.52	0.76–3.04
Psychiatric medications	0.59	1.29	0.52–3.21
Antimicrobials	0.71	1.20	0.46–3.16
Amiodarone	0.01	3.51	1.44–8.55
No. of QTc-prolonging medications	0.03	1.88	1.07–3.31
Baseline QTc interval	<0.01	0.78	0.69–0.89
No. of follow-up ECGs	<0.01	1.82	1.41–2.34
Follow-up time	<0.01	1.44	1.2–1.74
Multivariate logistic regression			
Weight	0.11	0.98	0.96–1.0
Creatinine level at initiation	0.02	1.73	1.1–2.7
Amiodarone	<0.01	5.47	1.87–16.02

with each medication separately and each patient served as a self-control. Patients without a baseline or follow-up ECG were excluded from the analysis, which can represent a bias. This is partially mitigated by the consecutive inclusion of patients meeting study criteria. The population in our study was primarily Caucasian, thus applicability to other populations warrants further study. Relatively short follow-up time after HY/AZ regimen completion was available. We did not assess serum drug concentrations.

Conclusion

Treatment of COVID-19 with HY/AZ prolongs the QTc interval to an extreme degree in a significant proportion of patients, increasing the risk of TdP. Risk/benefit considerations should be carefully and individually evaluated, and preventive measures should be applied when using this regimen.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2020.05.014.

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