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Predictive factors for cardiac conduction abnormalities with hydroxychloroquine-containing combinations for COVID-19

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ABSTRACT

This longitudinal, prospective cohort study aimed to assess risk of QTc interval prolongation and its predicting factors in subjects treated with combinations containing hydroxychloroquine (HCQ) for COVID-19. Moderate-to-severe QTc prolongation during therapy was defined as a QTc interval >470 ms in men or >480 ms in women. Patients were treated under strict cardiac supervision. A total of 105 adults were included [56% male; median (IQR) age 69 (57–79) years]. All patients received therapy with HCQ in combination with azithromycin (AZM), and 95 (90%) also with lopinavir/ritonavir (LPV/r). Concomitant medications classified as having risk of developing torsades de pointes (TdP) were simultaneously used in 81 patients (77%). Moderate-to-severe QTc prolongation was observed in 14 patients (13%), mostly at Days 3–5 from baseline, with 6 (6%) developing severe prolongation (>500 ms). There was no evidence of TdP arrhythmia or TdP-associated death. Adding LPV/r to HCQ+AZM did not significantly prolong the QTc interval. Multivariable Cox regression revealed that comedications with known risk of TdP (HR = 11.28, 95% CI 1.08–117.41), higher neutrophil-to-lymphocyte (NLR) ratio (HR = 1.10, 95% CI 1.03–1.18 per unit increase) and higher serum hs-cardiac troponin I (HR = 4.09, 95% CI 1.36–12.2 per unit increase) were major contributors to moderate-to-severe QTc prolongation. In this closely screened and monitored cohort, no complications derived from QTc prolongation were observed during pharmacological therapy containing HCQ for COVID-19. Evidence of myocardial injury with elevated troponin and strong inflammatory response, specifically higher NLR, are conditions requiring careful QTc interval monitoring.

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1. Introduction

Since its emergence in late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has claimed the lives of more than 250 000 individuals worldwide (as of the first week of May 2020) [1]. Although no proven effective therapies currently exist for coronavirus disease 2019 (COVID-19), the disease caused by SARS-CoV-2, there has been worrying mass consumption of off-label and/or compassionate-use drugs, with no demonstrated efficacy and with potential toxicity. Among the toxicities, cardiac

conduction abnormalities associated with certain commonly used drugs for COVID-19 [2–5], such as chloroquine/hydroxychloroquine (CQ/HCQ) and azithromycin (AZM), are especially concerning. The three drugs have been classified into the category of ‘known risk’ of potentially fatal torsades de pointes (TdP) ventricular arrhythmias or sudden cardiac death [6], and comprehensive evidence supports that concomitant administration of more than one corrected QT interval (QTc)-prolonging drug further increases the risk [7–10]. Moreover, although the most common clinical presentation of COVID-19 involves the respiratory tract, cardiovascular manifestations are also being increasingly recognised [11–14], which might additionally contribute to exacerbate drug toxicity. A randomised clinical trial conducted in Brazil in patients with COVID-19 that compared high versus low doses of CQ, given in combination with AZM, and in most cases with oseltamivir, has been prematurely stopped due to a potential increase in mortality in the high-dose

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group [15]. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have recently warned about serious potential adverse events with CQ/HCQ owing to heart rhythm problems, especially at high doses or when combined with AZM or other QTc-prolonging medicines [16,17].

In March 2020, the Spanish Agency of Medicines and Medical Devices granted an emergency-use authorisation for HCQ to treat patients with COVID-19 requiring hospital admission. Due to limited availability, health authorities recommended a HCQ dose of 200 mg twice daily for 5 days, which is lower than doses used in several clinical trials worldwide for this indication [15,18]. Based on data from an observational study suggesting a faster virological response [5], in our setting HCQ was often prescribed in combination with AZM.

Our centre developed specific guidelines for treating patients with COVID-19 with HCQ-containing regimens. The protocol included close screening and monitoring of patients receiving this drug combination and an investigation of the predictive factors for cardiac conduction abnormalities. Here we describe the risk of QTc interval prolongation and its predicting factors.

2. Methods

This prospective, observational study was carried out at the University Hospital of Elche, Spain. All patients who required admission due to COVID-19 from 10 March 2020 to 17 April 2020 and were treated with HCQ+AZM were included in the investigation. According to national recommendations and institutional guidelines, the dose of HCQ was 400 mg twice daily as a loading dose, followed by 200 mg twice daily for an additional 4 days; the dose of AZM was 500 mg on the first day followed by 250 mg for another 4 days. In mechanically ventilated patients, HCQ and AZM treatment was given through a feeding tube. HCQ and AZM could be used in combination with other drugs, including lopinavir/ritonavir (LPV/r) with or without interferon- β -1b, remdesivir and tocilizumab in patients with more severe disease. Candidates for treatment with HCQ and AZM had their QTc measured before starting therapy to identify subjects at risk of developing cardiac conduction abnormalities and underwent close electrocardiogram (ECG) monitoring during therapy. Moderate-to-severe QTc prolongation during therapy was defined as a QTc interval exceeding 470 ms in men or 480 ms in women. When the baseline QTc exceeded 500 ms, the guideline-recommended therapy with HCQ and/or AZM was subjected to clinical equipoise with in-depth assessment of the expected benefits and potential risks, and if finally started, the recommendation was using HCQ alone and discontinuing any other unnecessary QTc-prolonging comedications, assessing and correcting the contributing electrolyte abnormalities, along with close QTc monitoring 2–4 h after initiation and every 12–24 h thereafter; if no improvement of the QTc was observed, a strong recommendation to stop HCQ was given. When the baseline QTc was between 470–500 ms in men and 480–500 ms in women, the guidelines allowed therapy with HCQ and AZM after evaluating and correcting electrolytes and discontinuing other QTc-prolonging comedications; in this case, ECG monitoring every 24 h was scheduled with a strong recommendation to stop AZM and HCQ sequentially if the QTc rose above 500 ms or if it increased from baseline by more than 60 ms. The study was approved by the local institutional ethics board as part of the COVID-19@Spain study, and verbal consent was obtained from all patients to participate in the study.

Clinical information including demographics, medical history (time from illness onset), laboratory examinations, co-morbidities (previous diagnosis of cardiovascular, respiratory or kidney disease, hypertension or diabetes, and smoking status) and Charlson comorbidity index, pharmacological treatments for COVID-19 used

during the episode (HCQ, AZM, LPV/r, tocilizumab, remdesivir and interferon- β -1b) and outcomes was collected on admission and during hospitalisation by attending physicians. Serial 12-lead ECGs were performed before pharmacological treatments for COVID-19 were started and on Days 1, 3, 5 and 7 thereafter. Manual measurement of the heart rate-corrected QTc interval [Bazett formula and correction for cases of widening of the QRS as $QTc = (QRS - 100 \text{ ms})$] [19] was performed and was classified according to the recent recommendations of Giudicessi et al. [20] into three risk categories as follows: mild prolongation, if the QTc was below 470 ms in men or 480 ms in women; moderate prolongation, if the QTc was above 470 ms in men or 480 ms in women, but below 500 ms; and severe prolongation, if the QTc was above 500 ms or the QTc increased >60 ms from baseline. Bazett's formula was chosen because, unlike others (e.g. Fridericia's correction), this formula overcorrects at elevated heart rates, thus potentially preventing patients with prolonged QTc from being overlooked. The following outcomes were evaluated: number of cases and proportion of sudden cardiac death; observed TdP episodes; and reaching a moderate-to-severe QTc prolongation during follow-up.

Statistical analysis was performed using R Project software. Continuous variables are expressed as the median [interquartile range (IQR)] and categorical variables are expressed as number (percentage). Normality of data samples was assessed using the Shapiro-Wilk test. Comparison between baseline and maximum QTc achieved was done using paired-samples *t*-test. Univariate and multivariate Cox regression was used to identify predictors of reaching a QTc interval above 470 ms in men or 480 ms in women. For this analysis, the selection of variables was based on their clinical relevance and/or the presence of a *P*-value of <0.1 in the univariate analysis. Our study sample, in a two-sided matched *t*-test contrast and assuming an alpha error of 0.05, had a 92% statistical power to detect mean \pm standard deviation paired QTc changes above 5 ± 15 ms.

3. Results

Of 120 patients admitted to the hospital during the study period, 105 were treated with HCQ+AZM-containing combinations and were finally included in the study. Patients' demographic, clinical and laboratory findings on admission are shown in Table 1. The median (IQR) age was 69 years (57–79 years) and 56% were male. Co-morbidities were present in more than three-quarters of patients and the median (IQR) Charlson index score was 2 (0–5). In 95 patients (90%), HCQ+AZM was used in combination with LPV/r, and 60 (57%) patients received tocilizumab (Table 1). Reasons for not receiving HCQ and AZM in those 15 patients excluded from the analysis were renal failure in the case of 3 patients who did not receive HCQ, and disease onset before it was included in the institutional COVID-19 guidelines in 12 patients who did not receive AZM. Concomitant medications classified as with 'known' (16 patients; 15%), 'possible' (3 patients; 3%) or 'conditional' (62 patients; 59%) risk of TdP were simultaneously used with pharmacological treatments for COVID-19 in 81 patients (77%). Five patients were transferred to the intensive care unit and two patients died because of respiratory failure at the cohort censoring date (17 April 2020). There was no evidence of TdP arrhythmia in any of the cases. All but two study patients, who finished the treatment course 1 day and 2 days after hospital discharge, completed the HCQ+AZM treatment at the hospital.

The median (IQR) QTc at baseline was 405 ms (385–428 ms) and the median (IQR) change from baseline at Days 1, 3, 5 and 7 or beyond were $+2$ ms (-15 , $+30$ ms; $P = 0.314$), $+20$ ms (-10 , $+57$ ms; $P = 0.001$), $+0.2$ ms (-43 , $+30$ ms; $P = 0.562$) and -16 ms (-39 , $+28$ ms; $P = 0.154$), respectively (Fig. 1). The median (IQR) maximal QTc rise throughout follow-up was $+30$ ms (0, $+59$ ms)

Table 1
Demographic, clinical, laboratory and electrocardiographic findings on admission

Baseline variable	All patients		QTc above 470 ms in men or 480 ms in women after baseline		
			Yes	No	P-value
No. of patients	105		14 (13)	91 (87)	–
Male sex [n (%)]	59 (56)		10 (71)	49 (54)	0.345
Age at cohort entry >60 years [n (%)]	74 (71)		13 (93)	61 (67)	0.060
Current smoker [n (%)]	8 (8)		0 (0)	8 (9)	0.593
Charlson comorbidity index [median (IQR)]	2 (0, 5)		4.5 (3, 5)	2 (0, 4.5)	0.010
Co-morbidity [n (%)]	79 (75)		12 (86)	67 (74)	0.520
Hypertension	50 (63)		10 (83)	40 (60)	0.215
Diabetes	29 (37)		5 (42)	24 (36)	0.951
Cardiovascular disease	20 (25)		5 (42)	15 (22)	0.292
Chronic obstructive pulmonary disease	12 (55)		2 (67)	10 (53)	1.000
Chronic kidney disease	12 (11)		3 (21)	9 (13)	0.554
Time from illness onset to hospital admission (days) [median (IQR)]	7 (4, 11)		9 (7, 12)	7 (3, 11)	0.202
Laboratory findings [median (IQR)]					
Haemoglobin (g/dL)	13.6 (12.2, 14.7)		12.7 (12.1, 15.6)	13.6 (12.4, 14.6)	0.932
Lymphocyte count ($\times 10^3/\mu\text{L}$)	1.11 (0.80, 1.54)		0.93 (0.62, 1.38)	1.14 (0.82, 1.59)	0.172
Neutrophil-to-lymphocyte ratio	5.2 (2.7, 8.1)		8.2 (3.7, 11.4)	4.9 (2.7, 7.6)	0.089
Potassium (mmol/L)	4.2 (3.9, 4.5)		3.8 (3.8, 4.3)	4.2 (3.9, 4.6)	0.047
Magnesium (mg/dL)	2.1 (1.9, 2.2)		2.1 (2.0, 2.2)	2.1 (1.9, 2.2)	0.880
Lactate dehydrogenase (U/L)	268 (209, 351)		330 (235, 419)	260 (205, 346)	0.082
Creatine kinase (U/L)	61 (45, 94)		83 (54, 157)	59 (41, 90)	0.064
hs-Cardiac troponin I (ng/mL)	0.02 (0.02, 0.03)		0.03 (0.02, 0.04)	0.02 (0.02, 0.03)	0.062
D-dimer ($\mu\text{g/mL}$)	0.73 (0.39, 1.59)		0.67 (0.35, 0.98)	0.73 (0.41, 1.65)	0.426
Ferritin (ng/mL)	311 (172, 539)		359 (265, 607)	306 (172, 521)	0.377
IL-6 (pg/mL)	94 (30, 198)		152 (99, 420)	84 (29, 194)	0.127
Creatinine (mg/dL)	0.8 (0.7, 1.0)		1.0 (0.8, 1.3)	0.8 (0.7, 1.0)	0.015
eGFR (mL/min)	88 (67, 97)		74 (48, 89)	88 (69, 101)	0.049
COVID-19-directed therapy [n (%)]					
HCQ+AZM+LPV/r combination	95 (90)		13 (93)	82 (90)	0.847
HCQ+AZM combination	10 (9)		1 (7)	9 (10)	–
Tocilizumab	60 (57)		9 (64)	51 (56)	0.766
Remdesivir	1 (1)		0 (0)	1 (1)	1.000
Interferon- β -1b	10 (10)		4 (28)	6 (7)	0.026
Other QT-active drugs ^a [n (%)]					
Any category	81 (77)		10 (71)	71 (78)	0.837
Known risk of TdP	16 (15)		2 (14)	14 (15)	0.926
Possible risk of TdP	3 (3)		1 (7)	2 (2)	0.817
Conditional risk of TdP	62 (59)		7 (50)	55 (60)	0.902
Baseline QTc (ms) [median (IQR)]	405 (385, 428)		404 (391, 416)	405 (384, 429)	0.777
Max Δ QTc during follow-up ^b (ms) [median (IQR)]	+30 (0, +59)		+98 (+62, +140)	+17 (0, +42)	0.010
Fatal ventricular arrhythmia	0		0	0	–
ICU admission	5		3	2	0.014
Death	2		0	2	1.000

QTc, heart rate-corrected QT interval (Bazett formula [19]); IQR, interquartile range; hs, high-sensitivity; IL-6, interleukin 6; eGFR, estimated glomerular filtration rate [using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula]; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; AZM, azithromycin; LPV/r, lopinavir/ritonavir; TdP, torsades de pointes; ICU, intensive care unit.

^a Drugs classified as 'known, possible or conditional risk of torsades de pointes (TdP)' in CredibleMeds [6] administered simultaneously with COVID-19 therapy. If drugs from more than one category were administered to in a patient simultaneously, that patient was assigned to the higher risk category.

^b Median (IQR) maximal QTc rise throughout follow-up.

(Table 1). In six patients (6%), the QTc exceeded 500 ms during follow up at a median (IQR) of 4 days (3–8 days) from baseline, which led to the withdrawal of treatment with HCQ and AZM in three of them. The baseline QTc increased above 470 ms in men or 480 ms in women in 14 patients (13%), with a median (IQR) maximum increase of +98 ms (+62, +140 ms). Most of these patients were older than 60 years (93% vs. 67%; $P = 0.060$), had a higher Charlson comorbidity index [4.5 (3, 5) vs. 2 (0, 4.5); $P = 0.010$], and had at baseline lower median (IQR) serum potassium levels [3.8 (3.8, 4.3) vs. 4.2 (3.9, 4.6) mmol/L; $P = 0.047$], higher serum creatinine levels [1.0 (0.8, 1.3) vs. 0.8 (0.7, 1.0) mg/dL; $P = 0.015$] and lower Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)-estimated glomerular filtration rate [74 (48, 89) vs. 88 (69, 101) mL/min; $P = 0.049$] than patients who remained in the mild QTc prolongation category throughout the study. They also tended to have a stronger inflammatory response, specifically a higher neutrophil-to-lymphocyte ratio (NLR) [8.2 (3.7, 11.4) vs. 4.9 (2.7, 7.6); $P = 0.089$] and higher plasma concentration of interleukin-6 (IL-6) [152 (99, 420) vs. 84 (29, 194) pg/mL; $P = 0.127$] as well

as abnormal cardiac injury biomarkers, including higher creatine kinase [83 (54, 157) vs. 59 (41, 90) U/L; $P = 0.064$] and high-sensitivity (hs) cardiac troponin I plasma levels [0.03 (0.02, 0.04) vs. 0.02 (0.02, 0.03) U/L; $P = 0.062$ ng/mL] (Table 1). Nine (6%), two (14%) and seven (7%) patients had myocardial injury, defined as hs-cardiac troponin I plasma levels above our laboratory 99th percentile of the upper limit reference (i.e. 0.12 ng/mL), within all the patient's sample and in those whose baseline QTc did and did not increase above 470 ms in men or 480 ms in women, respectively. An exaggerated QTc response (increase >60 ms) was found in 25 patients (23%), who significantly also exhibited a stronger inflammatory response manifested as higher NLR [6.6 (4.3, 10.5) vs. 4.4 (2.6, 7.7); $P = 0.033$] and higher IL-6 levels [74 (24, 192) vs. 29 (12, 61) pg/mL; $P = 0.006$], and a trend towards higher levels of the cardiac injury biomarker hs-cardiac troponin I [0.03 (0.02, 0.04) vs. 0.02 (0.02, 0.03) U/L; $P = 0.069$ ng/mL].

Concomitant pharmacological therapy with LPV/r did not induce a different QTc response compared with HCQ+AZM without LPV/r in terms of proportion of patients reaching a severe QTc pro-

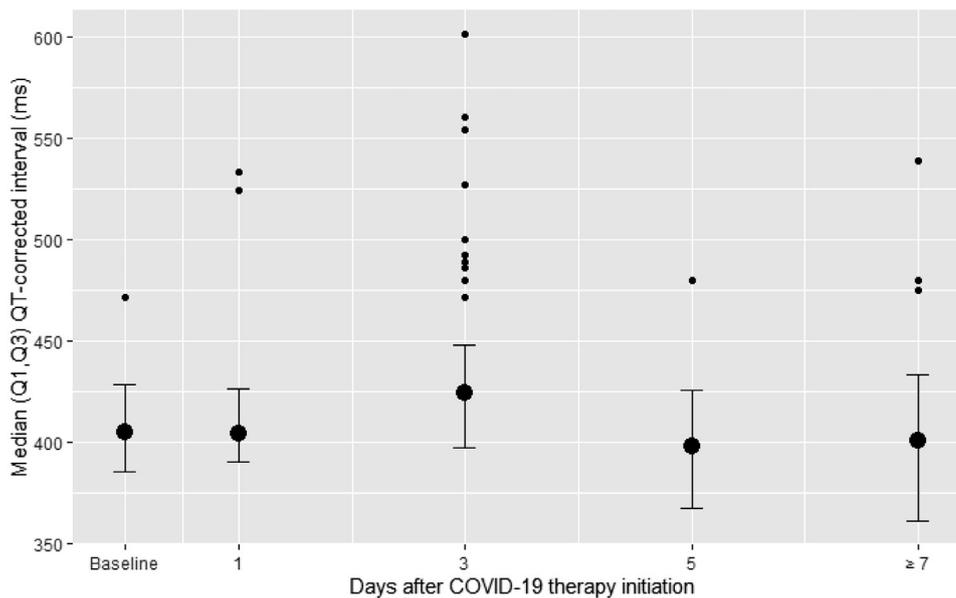


Fig. 1. QTc changes during coronavirus disease 2019 (COVID-19) therapy with hydroxychloroquine-containing regimens. Q1,Q3 = interquartile range (IQR).

Table 2

Factors associated with QTc changes (Δ QTc) from baseline

	QTc interval at baseline (ms) [median (IQR)]	Δ QTc ^a	P-value	
			From baseline	Between categories
All	405 (385, 428)	+30 (0, +59)	–	–
Sex				0.689
Male	412 (375, 426)	+25 (0, +61)	<0.001	
Female	402 (392, 436)	+27 (0, +57)	<0.001	
Age				0.066
≥60 years	412 (390, 431)	+28 (0, +30)	<0.001	
<60 years	399 (374, 419)	+18 (0, +43)	<0.001	
e-GFR				0.495
<60 mL/min	426 (387, 450)	+37 (+2, +64)	<0.001	
≥60 mL/min	402 (380, 425)	+24 (0, +57)	<0.001	
Potassium				0.272
<3.5 mmol/L	418 (400, 444)	+26 (+3, +54)	0.059	
≥3.5 mmol/L	406 (385, 426)	+23 (0, +46)	<0.001	
hs-Cardiac troponin I				0.030
≥0.2 ng/mL	402 (376, 417)	+32 (0, +63)	<0.001	
<0.2 ng/mL	417 (388, 436)	+24 (0, +57)	<0.001	
Neutrophil-to-lymphocyte ratio				<0.001
>4	405 (383, 428)	+30 (0, +59)	<0.001	
2–4	412 (391, 430)	+19 (0, +43)	<0.001	
<2	400 (400, 400)	+1 (+1, +1)	1.000	
COVID-19-directed therapy				0.789
HCQ+AZM+LPV/r combination	402 (384, 427)	+23 (0, +60)	<0.001	
HCQ+AZM combination	412 (398, 436)	+16 (0, +33)	0.022	
Other QT-active drugs ^b				0.011
Yes	402 (383, 427)	+28 (0, +62)	<0.001	
No	414 (387, 437)	+18 (0, +42)	<0.001	
Baseline QTc ^c				<0.001
Borderline prolonged	436 (433, 462)	0 (0, +30)	0.075	
Normal	402 (380, 420)	+32 (+8, +63)	<0.001	

QTc, heart rate-corrected QT interval (Bazett formula [19]); IQR, interquartile range; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate [using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula]; hs, high-sensitivity; HCQ, hydroxychloroquine; AZM, azithromycin; LPV/r, lopinavir/ritonavir.

^a Median (IQR) maximal QTc rise throughout follow-up.

^b Drugs classified as 'known, possible or conditional risk of torsades de pointes' in CredibleMeds [6] administered simultaneously with triple or dual COVID-19 therapy. If drugs from more than one category were administered to a patient simultaneously, that patient was assigned to the higher risk category.

^c Baseline QTc value categories: normal, <430 ms in males and <450 ms in females; borderline, 431–450 ms in males and 451–470 ms in females; and prolonged >450 ms in males and >470 ms in females [19].

longation (6% vs. 0%; $P = 0.918$), a moderate-to-severe QTc prolongation (14% vs. 10%; $P = 0.1$) or an exaggerated QTc response >60 ms (26% vs. 10%; $P = 0.451$).

Table 2 shows factors associated with maximal QTc changes from baseline during follow-up. Longer prolongations of the QTc

were associated with higher levels of hs-cardiac troponin I and higher NLR, with a graded increase with increasing ratio category, and with concomitant therapy with QTc-active drugs.

Multivariable Cox regression was performed to identify predictors of reaching a moderate-to-severe QTc prolongation (Table 3).

Table 3

Cox regression analysis for factors associated with a QTc prolongation above 470 ms in men or 480 ms in women after baseline

Variable	Cox regression analysis for QTc above 470 ms in men or 480 ms in women after baseline			
	Univariate		Multivariate ^a	
	HR (95% CI)	P-value	HR (95% CI)	P-value
e-GFR	0.98 (0.96–1.07)	0.202	1.02 (0.98–1.06)	0.227
Serum potassium (per mmol/L)	0.36 (0.12–1.09)	0.072	0.16 (0.02–1.21)	0.076
hs-Cardiac troponin I (per ng/mL)	2.91 (1.49–5.72)	0.002	4.09 (1.36–12.2)	0.011
Neutrophil-to-lymphocyte ratio (per unit)	1.07 (1.02–1.13)	0.004	1.10 (1.03–1.18)	0.003
COVID-19-directed therapy				
HCQ+AZM+LPV/r combination	1.01 (0.13–8.12)	0.959	0.86 (0.08–9.06)	0.904
HCQ+AZM combination	1		1	
Other QTc-active drugs ^b				
Yes	1.35 (0.29–6.20)	0.697	11.28 (1.08–117.41)	0.042
No	1		1	
Baseline QTc (per ms)	0.99 (0.98–1.01)	0.589	1.01 (0.98–1.03)	0.904

QTc, heart rate-corrected QT interval (Bazett formula [19]); HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate [using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula]; hs, high-sensitivity; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; AZM, azithromycin; LPV/r, lopinavir/ritonavir.

^a Multivariate analysis was also adjusted for sex, age and therapy with interferon- β -1b.

^b Drugs classified as 'known risk of torsades de pointes'; in CredibleMeds [6] administered simultaneously with COVID-19 therapy.

The Cox proportional hazard survival model revealed that concomitant use of drugs with known risk of TdP [hazard ratio (HR) = 11.28, 95% confidence interval (CI) 1.08–117.41; $P = 0.042$], and baseline serum lower potassium levels (HR = 0.16, 95% CI 0.02–1.21 per mmol/L decrease; $P = 0.076$), higher NLR (HR = 1.10, 95% CI 1.03–1.18 per unit increase; $P = 0.003$) and higher hs-cardiac troponin I (HR = 4.09, 95% CI 1.36–12.2 per unit increase; $P = 0.011$) were major contributors to the abnormal QTc response. These effects weakened when the combined event of moderate-to-severe QTc prolongation and/or an exaggerated QTc response >60 ms was considered: concomitant use of drugs with known risk of TdP (HR = 3.06, 95% CI 0.83–11.31; $P = 0.092$); baseline serum lower potassium levels (HR = 0.35, 95% CI 0.14–0.93 per mmol/L decrease; $P = 0.036$); higher NLR (HR = 1.05, 95% CI 1.01–1.10 per unit increase; $P = 0.045$); and higher hs-cardiac troponin I (HR = 1.66, 95% CI 0.78–3.50 per unit increase; $P = 0.182$).

4. Discussion

Our cohort includes patients treated with a drug combination against COVID-19 with inherent arrhythmogenic potential and therefore with a likely risk of developing complications. The QTc interval increased more than 60 ms in one-quarter of patients, and in 13% of them it reached a moderate-to-severe QTc prolongation during treatment; however, severe prolongation of >500 ms occurred in only 6% of patients and there were no episodes of TdP or death due to arrhythmia. We found that concomitant use of QTc-prolonging drugs, higher levels of hs-cardiac troponin I, higher NLR and, to a lesser degree, lower levels of serum potassium, were predictors of moderate-to-severe QTc prolongation. Compared with therapy with HCQ+AZM, there was a slight non-significant increase in the QTc length when LPV/r was part of the combination.

To date, data from clinical studies evaluating the influence on the QTc of drug combinations including HCQ in the scenario of COVID-19 are very limited. We found no complication from QTc prolongation when daily doses of 400 mg of HCQ are used. This is a lower dose than the 600 mg or 800 mg doses employed in some ongoing clinical trials. Chorin et al. reported a QTc increase of >500 ms in 11% of 84 patients treated with HCQ+AZM [21]. Although the dose of HCQ used in their study was the same, AZM was given at double dose (500 mg daily) compared with our study. Like HCQ, AZM is another drug with known risk of TdP, and this higher dose might have contributed to explain the higher fre-

quency of severe QTc prolongation compared with our study, although in contrast to other macrolide drugs such as erythromycin and clarithromycin, azithromycin has the lowest risk of QTc prolongation [22]. Interestingly, in our centre most patients received LPV/r in addition to HCQ and AZM. Although a marginally higher increase in the QTc was observed in these patients, there were not significant differences compared with therapy with HCQ and AZM. LPV/r is a mild inhibitor of cytochrome 2D6, which is involved in CQ/HCQ metabolism, and has been classified as a drug with 'possible risk' of TdP, in contrast to the 'known risk' of HCQ and AZM. Apart from the lower doses of HCQ and AZM, there could be additional reasons for the low rate of complications observed in our patients. As stated, we followed local institutional guidelines to manage all patients admitted with COVID-19, where clinical procedures and pharmacological therapy were pre-defined and programmed. The protocol included close monitoring of patients, with baseline and follow-up ECGs, and stop rules when abnormal QTc intervals were reached and/or more frequent ECGs if a prolonged interval was present at baseline. The protocol also considered a thorough review of concomitant medications with activity on the QTc, and their discontinuation when not considered as essential. Co-prescribing QTc-prolonging drugs has been associated with higher a mortality rate and longer duration of hospitalisation owing to pharmacodynamic drug–drug interactions [7]. We found that co-administering QTc-prolonging drugs was associated with a higher increase in the QTc, and it turned out to be an independent predictor of reaching a moderate-to-severe QTc prolongation. This reinforces the importance of reviewing the patient's medical history and of closer monitoring of such patients. Although it did not remain as a significant factor in the multivariate analysis, comorbidity measured by the Charlson comorbidity index is a variable linked with higher use of comedications, and patients with a higher index might also merit greater supervision. Our analyses also found that low levels of potassium were associated with QTc prolongation, as previously described [23].

Whether the QTc prolongation may simply be the result of pharmacological toxicity, or if the adverse drug event could be facilitated in a heart already damaged by the virus or the disease, remains unknown. Previous studies have found an increase in the concentrations of serum cardiac biomarkers in patients with COVID-19, such as hs-cardiac troponin I [24], whose increase has been associated with markedly higher mortality [25]. Interestingly, in our cohort higher levels of hs-cardiac troponin I in-

dependently predicted moderate-to-severe QTc prolongation, suggesting that myocardial harm might also have contributed to drug toxicity. In a recent case series of ST elevations in patients with COVID-19, some patients had non-obstructive disease on coronary angiography, which indicates non-coronary myocardial injury [26]. Angiotensin-converting enzyme 2 (ACE2), the host cellular receptor for SARS-CoV-2 spike protein, is highly expressed in the pericytes of adult human hearts. Binding of the virus might induce subsequent capillary endothelial cell dysfunction and microcirculation disorder [27]. An imbalance between infection-induced increase in metabolic demand and reduced cardiac reserve, coinciding with an accentuated inflammatory response, are some of the theories proposed to explain the cardiovascular involvement in COVID-19 [26,28]. Inflammation associated with the cytokine storm is a recognised characteristic feature of COVID-19. In support of inflammation as a potential pathogenic mechanism, we observed that moderate-to-severe prolongation of the QTc in our study was associated with a higher NLR, a marker of the inflammatory status and severity of disease [29]. Endomyocardial biopsy of patients with COVID-19 and cardiogenic shock has shown viral particles in interstitial cytopathic macrophages, where they might have activated an exaggerated inflammatory response leading to myocardial injury [30]. This damaged myocardium may, at the same time, heighten drug toxicity.

Limitations of the study include those inherent to its observational nature; the absence of a concurrent control group receiving higher doses of HCQ and AZM to assess whether different changes occurred in the QTc; some patients received tocilizumab and/or interferon- β -1b, which might also contribute to QTc prolongation; and the individual effect on the QTc of HCQ and AZM cannot be established. Strengths are the homogeneity of the procedures and treatment applied to all patients under strict supervision, and the novelty of providing data about QTc with a combination including also LPV/r.

In summary, combined therapy including HCQ, AZM and LPV/r for COVID-19, when given at low doses and under close screening and cardiac monitoring, was not associated with incident TdP or sudden cardiac death. In addition to drug toxicity, disease-related myocardial damage and inflammation might be implicated in the pathogenesis of cardiac conduction abnormalities in patients with COVID-19. Therefore, evidence of myocardial injury with elevated troponin and strong inflammatory response, specifically a higher NLR and increased IL-6, warrants careful QTc interval monitoring. Additional predictive factors for developing cardiac conduction abnormalities were comedications and low serum potassium levels, which should be taken into account to reduce the risk of serious complications, especially in patients with altered myocardial enzymes and enhanced inflammatory response.

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