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Prolonged corrected QT interval in hospitalized patients with coronavirus disease 2019 in Dubai, United Arab Emirates: a single-center, retrospective study

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Abstract

Objective: To evaluate the association of a prolonged corrected QT (QTc) interval in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its association with in-patient mortality.

Methods: A cohort of 745 patients were recruited from a single center between 1 March 2020 and 31 May 2020. We analyzed the factors associated with a prolonged QTc and mortality.

Results: A prolonged QTc interval >450 ms was found in 27% of patients admitted with SARS-CoV-2 infection. These patients were predominantly older, on a ventilator, and had hypertension, diabetes mellitus, or ischemic heart disease. They also had high troponin and

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D-dimer concentrations. A prolonged QTc interval had a significant association with the requirement of ventilator support and was associated with an increased odds of mortality. Patients who died were older than 55 years, and had high troponin, D-dimer, creatinine, procalcitonin, and ferritin concentrations, a high white blood cell count, and abnormal potassium concentrations (hypo- or hyperkalemia).

Conclusions: A prolonged QTc interval is common in patients with SARS-CoV-2 infection and it is associated with worse outcomes. Older individuals and those with comorbidities should have an electrocardiogram performed, which is noninvasive and easily available, on admission to hospital to identify high-risk patients.

Keywords

Prolonged corrected QT interval, severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, arrhythmia, myocarditis, troponin, D-dimer

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Introduction

The novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) leading to the coronavirus disease 2019 (COVID-19) pandemic has resulted in significant morbidity and mortality.[1] There have been >205 million cases of COVID-19 worldwide and >4.5 million deaths. This disease has affected more than 210 countries and territories worldwide and is still spreading at a high rate, causing lockdowns, travel restrictions, and health and economic crises.[2] In the United Arab Emirates, there have been approximately 700,000 confirmed cases with 2000 deaths.[2]

The clinical presentation of COVID-19 includes typical symptoms of pneumonia, such as fever, cough, and dyspnea, while some patients present with atypical features, such as fatigue, dry cough, and diarrhea.[3] People with COVID-19 can also not have any symptoms, leading to this disease's rapid spread from these silent carriers.[4] An older age, male sex, the presence of comorbidities, and increased inflammatory markers are associated with a poor prognosis.[5] Hypoxia, myocarditis, myocardial ischemia, arrhythmia, and electrolyte abnormalities are contributing factors of death due to COVID-19. While supportive care and nonspecific management continue, the mechanism of death has remained unclear.[6]

A prolonged heart rate-corrected QT (QTc) interval representing prolonged ventricular repolarization on a surface electrocardiogram (ECG) can predispose to torsade de pointes, malignant arrhythmias, and cardiac arrest.[7] The QTc, which is a quantitative tool and is easily measured on a resting 12-lead surface ECG, can potentially stratify the risk of adverse outcomes.

Several off-label medications, including chloroquine/hydroxychloroquine, azithromycin, and remdesivir, were introduced to manage this infection worldwide.[8] The primary concern and limitation of using these drugs are their association with a prolonged QTc, leading to life-threatening arrhythmias, cardiac arrest, and death.[9] An ECG to measure the QTc interval is routinely performed in patients before initiation of

management of COVID-19. Medications are discontinued if QTc prolongation is considerable during the treatment course.[10] The mechanism of death in these patients is unclear, and it is unknown whether modifying the risk factors contributing to a prolonged QTc interval will affect the outcome. Significant gaps remain in our understanding of how such involvement may alter the outcomes.

This study aimed to evaluate the incidence, predictors, and outcome of a prolonged QTc interval in patients who are hospitalized with COVID-19. We also aimed to evaluate the baseline characteristics, clinical and laboratory findings, and their associations with outcomes. Furthermore, we evaluated the association between a prolonged QTc interval and inpatient mortality.

Methods

Study design, setting, and participants

We performed an observational, retrospective cohort study of patients with COVID-19 who were admitted to Rashid Hospital, which is a tertiary multidisciplinary government hospital in Dubai, United Arab Emirates. The reporting of this study conforms to the STROBE guidelines. Patients who were admitted with a diagnosis of SARS-CoV-2 infection as shown by reverse transcription-polymerase chain reaction between 1 March 2020 and 31 May 2020 were included. Additionally, the patients were at least 18 years old, had a troponin measurement, and had at least two ECGs performed. We excluded COVID-19-positive individuals who were not hospitalized, those who did not have a troponin test or other baseline laboratory tests, and those who did not have at least two ECGs. A positive result on real-time reverse transcription-polymerase chain reaction, which was consistent with symptoms, and laboratory and radiological findings was defined as a confirmed case of COVID-19.

The national guideline protocol requires a baseline ECG for all patients with COVID-19 before initiating anti-COVID-19 therapy. An ECG was repeated every 24 to 48 hours for patients at high risk of QT prolongation, such as elderly patients and patients with a history of cardiac illness or arrhythmias.[11] Asymptomatic or presymptomatic infection was determined when individuals tested positive for SARS-CoV-2 using a virological test (i.e., a nucleic acid amplification test or an antigen test), but had no symptoms that were consistent with COVID-19. Mild illness was defined as having any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, and muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness was defined as having evidence of lower respiratory disease by clinical assessment or imaging, and an oxygen saturation $\geq$94% on room air at sea level. Severe illness was defined as having a respiratory frequency >30 breaths/minute, an oxygen saturation of <93%, and a ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen of <300%. Critical illness was defined as having respiratory failure, septic shock, and/or multiple organ dysfunction.[11]

Azithromycin, hydroxychloroquine, remdesivir, and ritonavir, which are associated with a prolonged QTc interval, were administered as a part of the anti-COVID-19 therapy in the initial months. Patients on these medications had a daily ECG performed if the baseline QTc was >450 ms or the ECG was repeated 24 to 48 hours after the initiation of management. If a patient was taking more than one medication affecting the QTc interval and QTc prolongation occurred, one of the medications was discontinued. If the

QTc interval persisted longer than 500 ms, the other medication was also discontinued.

The QTc was calculated from the QTc interval and the R-R interval using Bazett's formula. QTc prolongation was defined as a QTc interval >450 ms or 60 ms from a baseline ECG.

Data collection

The data were obtained from an electronic medical record system. We recorded various variables, including demographics, diagnosis, comorbidities, clinical characteristics, laboratory parameters, ECG, and outcome (ventilatory support, arrhythmia, and death) on a standardized data template. The investigators followed the clinical outcomes up until 31 July 2020.

Statistical analysis

Data were analyzed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables, such as age and body mass index, were categorized and analyzed. The outcome variable of QTc interval was categorized as >450 ms and ≤450 ms, and mortality was another outcome. The incidence of a QTc interval and mortality is presented with the 95% confidence interval (CI). Univariable analysis was performed to obtain outcomes. The associations between study variables and the outcomes were analyzed using the chi-square test. Because the event rates for mortality and a high QTc interval were >10%, logistic regression analysis with log links were performed separately. Adjusted and unadjusted logistic regression was performed to evaluate predictors of QTc prolongation and mortality. The potential variables for multivariable logistic regression analysis for the outcome of a high QTc interval were selected using p values from the univariable analysis. The variables with $p < 0.20$ were selected for this analysis. However, for the outcome of mortality, the selection of potential risk variables was based on $p < 0.05$. Evaluation of the model was performed using Hosmer–Lemeshow goodness fit statistics.

Ethical approval

The study was approved by the Dubai Scientific Research Ethics Committee (approval number: DSREC-05/2020_12). The need for informed consent was waived by the ethics committee because it was a retrospective study. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects, as well as with the Declaration of Helsinki.

Results

Patient cohort

Approximately 1700 patients were hospitalized during the study period and included moderate to severe cases. Our cohort finally included 745 patients because only the patients who had two sets of ECGs performed 24 to 48 hours apart and had troponin measurements were included. Of these patients, 708 had completed outcomes and 37 (5%) were still hospitalized at the end of the study. The patients' median age was 47 years, and 89% (662/745) were men. The median length of the hospital stay was 15 days, and the median time to viral clearance was 13 days. A total of 23% of the patients had a body mass index >30 kg/m^2 and 27% of patients required ventilatory support. A total of 39% had a history of type 2 diabetes mellitus and had a mean glycated hemoglobin value of 8.1%, 32% of the patients had hypertension, and 9% had a preexisting cardiac illness. Troponin concentrations >52 ng/L were found in 10% of patients and N-terminal prohormone of brain natriuretic peptide

(NT-proBNP) concentrations >125 pg/mL were found in 36% of patients.

A Baseline QTc interval >450 ms at admission, before starting medications, was present in 27.3% of the patients. The median QTc was 436 ms, and the median of the maximum QTc interval was 466 ms. A total of 80% of patients were on two or more medications prolonging the QTc interval, 88% were on chloroquine/hydroxychloroquine, 49% were on azithromycin, 78% were on Kaletra, and 43.6% were on favipiravir.

The mean delta QTc interval in patients on three or more medications was 39 ms, while that in those on two, one, and no medications was 27, 17, and 10 ms, respectively. The mean maximum QTc interval was also higher in patients taking two medications or more (Figure 1). However, there was no association between the number of QTc-prolonging medications and the outcome.

Incidence of a prolonged QTc interval (QTc >450 ms)

Table 1 shows the incidence of a prolonged QTc interval. The incidence rate of a QTc interval >450 ms was 27.3% (95% CI: 24.0, 35.0), and it was 26.8% (95% CI: 23.4, 38.2) and 31.6% (95% CI: 31.7, 42.0) in men and women, respectively. The incidence rate of a QTc interval >450 ms was approximately 30% in patients aged >40 years. The association between baseline characteristics and a prolonged QTc interval is shown in Table 2. There were significant associations between a prolonged QTc interval in patients aged >55 years (risk ratio, 1.78; 95% CI: 1.22, 2.60, $p = 0.003$) and ventilated patients (risk ratio, 1.7; 95% CI: 1.35, 2.16, $p < 0.001$). Patients with diabetes, hypertension, or heart disease had a 1.50, 1.31, and 1.67 times significantly higher risk of a prolonged QTc interval, respectively, than other patients who did not have these morbidities (all $p < 0.05$).

Univariable analysis of biochemical parameters and a prolonged QTc interval

Concentrations of troponin ≥52 ng/L (risk ratio, 2.30; 95% CI: 1.79, 2.94) NT-proBNP ≥125 pg/mL (risk ratio, 2.06; 95% CI 1.39, 3.04), D-dimer ≥0.5 µg/mL FEU (risk ratio, 3.23; 95% CI: 1.82, 5.74), creatinine ≥1.2 mg/dL (risk ratio, 1.80;

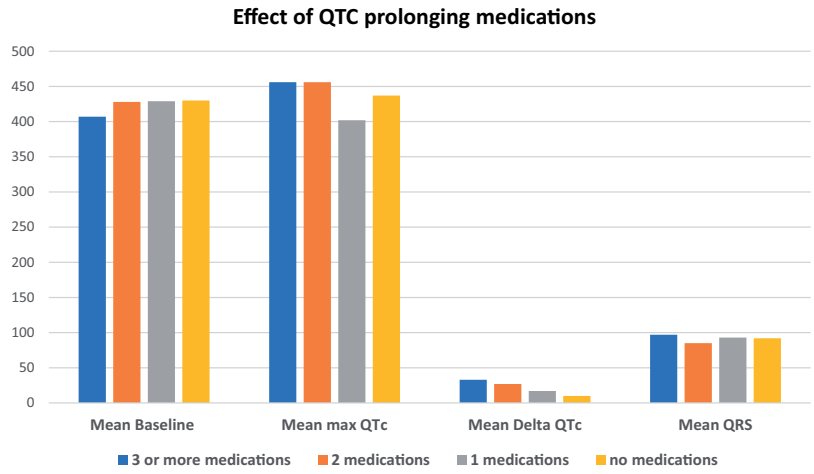

Figure 1. Effect of QTc-prolonging medications

Table 1. QTc interval according to age and sex.

	>450 ms		≤450 ms		
Variables	n	%	n	%	95% CI
Overall	195	27.3	518	72.7	24.0, 35.0
Age (years)					
<40	33	16.9	162	83.1	11.7, 22.1
40–55	106	31.9	226	68.1	26.9, 36.9
>55	56	30.1	130	69.9	23.5, 36.7
Sex					
Male	171	26.8	466	73.2	23.4, 38.2
Female	24	31.6	52	68.4	31.7, 42.0

QTc, corrected QT; CI, confidence interval.

Table 2. Univariable analysis of the associations between baseline characteristics and the QTc interval.

	QTc interval				Univariable analysis		
	>450 ms (n = 195)		≤450 ms (n = 518)				
Variables	n	%	n	%	Risk ratio	95% CI	p value
Age (years)							
<40	33	16.9	162	83.1	1.00		
40–55	106	31.9	226	68.1	1.89	1.33, 2.67	<0.001
>55	56	30.1	130	69.9	1.78	1.22, 2.60	0.003
Sex							
Male	171	26.8	466	73.2	0.85	0.60, 1.21	0.370
Female	24	31.6	52	68.4	1.00		
BMI (kg/m^2)*							
<25	62	28.7	154	71.3	1.00		
25–29	73	25.5	213	74.5	0.89	0.67, 1.19	0.426
30–35	40	33.9	78	66.1	1.18	0.85, 1.64	0.320
>35	15	31.9	32	68.1	1.11	0.70, 1.77	0.657
Ventilated patients							
Yes	78	39.0	122	61.0	1.71	1.35, 2.16	<0.001
No	117	22.8	396	77.2	1.00		
Diabetes							
Yes	97	34.3	186	65.7	1.50	1.19, 1.91	0.001
No	98	22.8	332	77.2	1.00		
Hypertension							
Yes	76	32.5	158	67.5	1.31	1.03, 1.66	0.030
No	119	24.8	360	75.2	1.00		
Heart disease							
Yes	28	43.1	37	56.9	1.67	1.23, 2.28	0.001
No	167	25.8	481	74.2	1.00		

QTc, corrected QT; CI, confidence interval; BMI, body mass index.
*Data of BMI are missing in 50 patients.

95% CI: 1.42, 2.27) white blood cell count $\geq 12 \times 10^3/\mu L$ (risk ratio, 1.38; 95% CI: 1.06, 1.8), and LDH ≥ 280 U/L (risk ratio, 1.69; 95% CI: 1.24, 2.32) were significantly associated with a prolonged QTc interval (all $p < 0.05$, Table 3).

Multivariable analysis of the factors associated with a high QTc interval

The results of a multivariable analysis of the factors associated with a high QTc interval are shown in Table 4. After adjusting for other risk variables, patients who had diabetes had a 1.3 times significantly higher risk of a prolonged QTc interval than those who did not have diabetes (95% CI: 1.01, 1.67, $p = 0.04$). Laboratory parameters with a significantly increased risk of a prolonged QTc interval were troponin concentrations ≥ 52 ng/L (risk ratio, 1.57; 95% CI: 1.17, 2.10) and D-dimer concentrations ≥ 0.5 μg/mL FEU (risk ratio, 2.83; 95% CI: 1.49, 5.38, both $p = 0.002$).

Predictors of mortality

The incidence of mortality according to age and sex is shown in Table 5. The incidence of mortality was 17.4% overall (95% CI: 14.7, 20.1), and that in men and women was 18.4% (95% CI: 15.4, 21.3) and 9.6% (95% CI: 3.2, 16.0), respectively. The incidence of mortality increased as age increased.

Univariable analysis of sociodemographic characteristics and mortality

The associations between sociodemographic characteristics and mortality are shown in Table 6. Patients aged 40 to 55 years had a 2.48 (95% CI: 1.41, 4.34) times significantly higher risk of mortality compared with those aged <40 years ($p = 0.002$). Similarly, patients aged >55 years had a 3.87 (95% CI: 2.16, 6.93) significantly higher risk compared with those aged <40 years ($p < 0.001$). Ventilated patients had a 135.0 (95% CI: 59.25, 307.96) times significantly higher risk of mortality compared with unventilated patients ($p < 0.001$). Patients with diabetes mellitus had a 1.49 (95% CI: 1.02, 2.18) times significantly higher risk of mortality than those who did not have diabetes ($p = 0.04$).

Univariable analysis of biochemical parameters, QTc, and mortality

Concentrations of troponin ≥ 52 ng/L (OR, 4.82; 95% CI: 2.93, 7.94), NT ProBNP ≥ 125 pg/mL (OR, 4.20; 95% CI: 2.34, 7.56), D-dimer ≥ 0.5 μg/mL FEU (OR, 65.19; 95% CI: 4.02, 1056.23), creatinine ≥ 1.2 mg/dL (OR, 11.57; 95% CI: 7.31, 18.3), ferritin ≥ 400 ng/mL (OR, 4.86; 95% CI: 2.45, 9.65), LDH ≥ 280 U/L (OR, 7.16; 95% CI: 3.62, 14.15), C-reactive protein ≥ 10 mg/L (OR, 4.56; 95% CI: 2.13, 9.76]), and procalcitonin ≥ 0.05 ng/mL (OR, 3.19; 95% CI: 1.06, 9.61) were associated with an increased probability of mortality (all $p < 0.05$) A white blood cell count $\geq 12 \times 10^3/\mu L$ (OR, 4.54; 95% CI: 3.00, 6.88) and abnormal potassium concentrations (> 3 or >5 mmol/L) (OR, 1.79; 95% CI: 1.2, 2.7) were also associated with an increased probability of mortality (both $p < 0.01$). A QTc interval >450 ms (OR, 2.08; 95% CI: 1.40, 3.10) was strongly associated with an increased odds of mortality ($p < 0.001$) (Table 7).

Multivariable analysis of mortality

In adjusted logistic regression, an age >55 years (OR, 2.18; 95% CI: 1.01, 4.7) was associated with an increased odds of mortality ($p = 0.047$). Additionally, concentrations of troponin ≥ 52 ng/L (OR, 1.77; 95% CI: 0.93, 3.37), D-dimer ≥ 0.5 μg/mL FEU (OR, 24.08; 95% CI: 1.38, 419.82), creatinine ≥ 1.2 mg/dL (OR, 8.16; 95%

Table 3. Univariable analysis of the association between biochemical parameters and the QTc interval.

	QTc interval				Univariable analysis		
	>450 ms (n = 195)		≤450 ms (n = 518)				
Variables	n	%	n	%	Risk ratio	95% CI	p value
Troponin - baseline (ng/L)							
≥52	40	55.6	32	44.4	2.30	1.79, 2.94	<0.001
<52	155	24.2	486	75.8	1.00		
NT-proBNP (pg/mL)*							
≥125	113	42.6	152	57.4	2.06	1.39, 3.04	<0.001
<125	23	20.7	88	79.3	1.00		
D-dimer (μg/mL)*							
≥0.5	172	32.0	365	68.0	3.23	1.82, 5.74	<0.001
<0.5	11	9.9	100	90.1	1.00		
Creatinine (mg/dL)							
≥1.2	95	38.6	151	61.4	1.80	1.42, 2.27	<0.001
<1.2	100	21.5	365	78.5	1.00		
WBC count ($\times 10^3/\mu L$)							
≥12	49	35.3	90	64.7	1.38	1.06, 1.8	0.016
<12	146	25.5	427	74.5	1.00		
Lymphocytes ($\times 10^3/\mu L$)							
≤1.0	13	23.6	42	76.4	0.85	0.52, 1.39	0.522
>1.0	182	27.7	474	72.3	1.00		
Ferritin (ng/mL)*							
≥400	150	29.1	366	70.9	1.22	0.9, 1.65	0.195
<400	40	23.8	128	76.2	1.00		
LDH (U/L)*							
≥280	151	31.5	329	68.5	1.69	1.24, 2.32	0.001
<280	39	18.6	171	81.4	1.00		
CRP (mg/L)							
≥10	160	27.6	420	72.4	1.02	0.74, 1.39	0.917
<10	35	27.1	94	72.9	1.00		
Procalcitonin (ng/mL)							
≥0.05	185	28.3	468	71.7	1.54	0.84, 2.82	0.159
<0.05	9	18.4	40	81.6	1.00		
Calcium (mg/dL)							
≤8.5	100	27.2	268	72.8	0.97	0.76, 1.23	0.785
>8.5	93	28.1	238	71.9	1.00		
Magnesium (mg/dL)							
≤1.5	8	40.0	12	60.0	1.48	0.85, 2.56	0.164
>1.5	187	27.1	504	72.9	1.00		
Potassium (mmol/L)							
<3 or >5	36	26.3	101	73.7	0.94	0.69, 1.28	0.681
3–5	159	28.0	408	72.0	1.00		

*NT-ProBNP, D-dimer, LDH, and ferritin data are missing for 355, 79, 32, and 38 patients, respectively.

*NT-ProBNP, D-dimer, LDH, and ferritin data are missing for 355, 79, 32, and 38 patients, respectively.

QTc, corrected QT; CI, confidence interval; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Table 4. Multivariable logistic regression analysis of the factors associated with a high corrected QT interval.

Variables	Risk ratio	95% CI	p value
Age (years)			
<40	1.00		
40–55	1.42	0.98, 2.07	0.063
>55	1.14	0.74, 1.75	0.561
Ventilated patients			
Yes	1.05	0.81, 1.37	0.707
No	1.00		
Diabetes			
Yes	1.30	1.01, 1.67	0.044
No	1.00		
Hypertension			
Yes	1.01	0.78, 1.30	0.928
No	1.00		
Heart disease			
Yes	1.15	0.85, 1.57	0.360
No	1.00		
Troponin - baseline (ng/L)			
≥52	1.57	1.17, 2.10	0.002
<52	1.00		
D-dimer (μg/mL FEU)			
≥0.5	2.83	1.49, 5.38	0.002
<0.5	1.00		
Creatinine (mg/dL)			
≥1.2	1.26	0.94, 1.69	0.120
<1.2	1.00		
WBC count ($\times 10^3/\mu L$)			
≥12	1.09	0.85, 1.41	0.497
<12	1.00		
LDH (U/L)			
≥280	1.02	0.71, 1.46	0.918
<280	1.00		
Procalcitonin (ng/mL)			
≥0.05	0.87	0.43, 1.78	0.706
<0.05	1.00		

Note: Variables that were significant at the 20% level in univariable analysis were included in the multivariable analysis. The variables NT-proBNP, ferritin, and magnesium were excluded because almost 50% of NT-proBNP data were missing, and regression analysis was not able to estimate the risk ratios for ferritin and magnesium.
CI: confidence interval; WBC, white blood cell; LDH, lactate dehydrogenase.

CI: 4.5, 14.8), ferritin ≥400 ng/mL (OR, 2.33; 95% CI: 0.91, 5.99), LDH ≥280 U/L (OR, 3.16; 95% CI: 1.27, 7.87), and procalcitonin ≥0.05 ng/mL (OR, 0.10; 95% CI: 0.02, 0.51), a white blood cell count ≥12 $\times 10^3/\mu L$ (OR, 2.33; 95% CI: 1.36, 3.97), and abnormal potassium concentrations (<3 or >5 mmol/L) (OR, 2.2; 95% CI: 1.21, 4.08) were associated with an increased odds of mortality. A prolonged QTc interval was not significantly associated with mortality (Table 8).

Table 5. Incidence of mortality by age and sex.

	Mortality				
	Dead		Alive		
Variables	n	%	n	%	95% CI
Overall	130	17.4	615	82.6	14.7, 20.1
Age (years)					
<40	17	8.1	192	91.9	4.6, 12.4
40–55	62	18.3	277	81.7	14.2, 22.4
>55	51	25.9	146	74.1	19.7, 32.0
Sex					
Male	122	18.4	540	81.6	15.4, 21.3
Female	8	9.6	75	90.4	3.2, 16.0

CI, confidence interval.

Ventricular arrhythmia

Eleven patients had high-grade ventricular arrhythmias among whom nine died between 2 and 4 days after the arrhythmia event (Table 9).

Discussion

In this study, we found that a prolonged QTc interval was present in 27% of patients. A prolonged QTc interval was associated with older age, comorbidities, specifically hypertension, diabetes mellitus, and ischemic heart disease, and elevated troponin and D-dimer concentrations.

QTc prolongation became a hot topic during the COVID-19 outbreak owing to a widespread and empirical administration of combinations of medications known to cause prolongation of the QTc

Table 6. Univariable penalized logistic regression analysis of the associations between baseline characteristics and mortality.

	Dead		Alive		Univariable analysis		
Variables	n	%	n	%	OR	95% CI	p value
Age (years)							
<40 years	17	8.1	192	91.9	1.00		
40–55 years	62	18.3	277	81.7	2.48	1.41, 4.34	0.002
>55 years	51	25.9	146	74.1	3.87	2.16, 6.93	<0.001
Sex							
Male	122	18.4	540	81.6	2.01	0.96, 4.20	0.062
Female	8	9.6	75	90.4	1.00		
BMI (kg/m^2)							
<25	28	12.6	194	87.4	1.00		
25–29	57	18.9	245	81.1	1.60	0.98, 2.6	0.059
30–35	29	23.8	93	76.2	2.15	1.22, 3.81	0.008
>35	13	26.5	36	73.5	2.52	1.21, 5.28	0.014
Ventilated patients							
Yes	124	62.0	76	38.0	135.08	59.25, 307.96	<0.001
No	6	1.1	539	98.9	1.00		
Diabetes							
Yes	61	21.0	229	79.0	1.49	1.02, 2.18	0.040
No	69	15.2	386	84.8	1.00		
Hypertension							
Yes	41	16.9	201	83.1	0.95	0.64, 1.43	0.819
No	89	17.7	414	82.3	1.00		
Heart disease							
Yes	16	24.2	50	75.8	1.61	0.89, 2.91	0.112
No	114	16.8	565	83.2	1.00		

OR, odds ratio; CI, confidence interval; BMI, body mass index.

interval, including azithromycin, hydroxychloroquine, and lopinavir/ritonavir.[12] Hydroxychloroquine and azithromycin prolong the QTc interval by blocking the delayed rectifier potassium current involved in the final rapid repolarization phase of the action potential. They specifically inhibit the human ether-a-go-go related gene (hERG, alpha subunit) potassium channel, which is a subunit of the delayed rectifier potassium current. This blockade of the hERG channel lengthens ventricular repolarization, which is shown on a surface ECG as a prolonged QTc interval.[13] Lopinavir/ritonavir is an antiretroviral agent inhibiting human immunodeficiency virus protease, and it also blocks the hERG channel.[14] Patients with COVID-19 have severe infection, inflammation and hypoxia. Therefore, the medication effect of a prolonged QTc interval is more pronounced in this group of patients than when administered for other conditions.[15] The treatment of COVID-19 has become challenging because most patients with COVID-19 develop a prolonged QTc interval. Patients on anti-covid medications need to be frequently monitored for the QTc interval by ECG or a cardiac monitor, which becomes difficult when hospitals are overwhelmed during peak times.[16]

Table 7. Univariable penalized logistic regression analysis of the associations between biochemical parameters and mortality.

	Dead		Alive		Univariable analysis		
Variables	n	%	n	%	OR	95% CI	p value
Troponin - baseline (ng/L)							
≥52	34	44.7	42	55.3	4.82	2.93, 7.94	<0.001
<52	96	14.3	573	85.7	1.00		
NT-proBNP (pg/mL)							
≥125	107	39.1	167	60.9	4.20	2.34, 7.56	<0.001
<125	15	12.9	101	87.1	1.00		
D-dimer (μg/mL FEU)							
≥0.5	121	22.0	430	78.0	65.19	4.02, 1056.23	0.003
<0.5	0	0.0	115	100.0			
Creatinine (mg/dL)							
≥1.2	103	40.7	150	59.3	11.57	7.31, 18.3	<0.001
<1.2	27	5.5	462	94.5	1.00		
WBC count ($\times 10^3/\mu L$)							
≥12	55	39.3	85	60.7	4.54	3.00, 6.88	<0.001
<12	75	12.4	528	87.6	1.00		
Lymphocytes ($\times 10^3/\mu L$)							
≤1.0	14	25.5	41	74.5	1.71	0.91, 3.22	0.094
>1.0	116	16.9	571	83.1	1.00		
Ferritin (ng/mL)							
≥400	113	21.4	416	78.6	4.86	2.45, 9.65	<0.001
<400	9	5.1	169	94.9	1.00		
LDH (U/L)							
≥280	119	24.2	373	75.8	7.16	3.62, 14.15	<0.001
<280	9	4.1	212	95.9	1.00		
CRP (mg/L)							
≥10	122	20.3	478	79.7	4.56	2.13, 9.76	<0.001
<10	7	5.0	133	95.0	1.00		
Procalcitonin (ng/mL)							
≥0.05	127	18.7	553	81.3	3.19	1.06, 9.61	0.039
<0.05	3	5.9	48	94.1	1.00		
Calcium (mg/dL)							
≤8.5	65	17.0	317	83.0	0.91	0.62, 1.33	0.639
>8.5	64	18.3	285	81.7	1.00		
Magnesium (mg/dL)							
≤1.5	3	14.3	18	85.7	0.89	0.28, 2.84	0.847
>1.5	126	17.5	596	82.5	1.00		
Potassium (mmol/L)							
<3 or >5	36	25.2	107	74.8	1.79	1.16, 2.77	0.008
3–5	94	15.9	499	84.1	1.00		
QTc interval							
≤450 ms	77	14.9	441	85.1	1.00		
>450 ms	52	26.7	143	73.3	2.08	1.40, 3.10	<0.001

OR, odds ratio; CI, confidence interval; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein; QTc, corrected QT.

Table 8. Multivariable penalized logistic regression analysis of mortality.

Variables	OR	95% CI	p value
Age (years)			
<40 years			
40–55 years	1.79	0.88, 3.66	0.110
>55 years	2.18	1.01, 4.7	0.047
BMI (kg/m^2)			
<25			
25–29	1.12	0.6, 2.08	0.730
30–35	1.30	0.64, 2.68	0.468
>35	2.10	0.76, 5.83	0.152
Diabetes			
Yes	0.99	0.59, 1.66	0.958
No	1.00		
Troponin - baseline (ng/L)			
≥52	1.77	0.93, 3.37	0.080
<52	1.00		
D-dimer (μg/mL FEU)			
≥0.5	24.08	1.38, 419.82	0.029
<0.5	1.00		
Creatinine (mg/dL)			
≥1.2	8.16	4.5, 14.8	0.000
<1.2	1.00		
WBC count (×10^3/μL)			
≥12	2.33	1.36, 3.97	0.002
<12	1.00		
Ferritin (ng/mL)			
≥400	2.33	0.91, 5.99	0.079
<400	1.00		
LDH (U/L)			
≥280	3.16	1.27, 7.87	0.013
<280	1.00		
CRP (mg/L)			
≥10	1.93	0.53, 7.07	0.319
<10	1.00		
Procalcitonin (ng/mL)			
≥0.05	0.10	0.02, 0.51	0.006
<0.05	1.00		
Potassium (mmol/L)			
<3 or >5	2.22	1.21, 4.08	0.010
3–5	1.00		
QTc			
>450 ms	1.06	0.62, 1.79	0.843
≤450 ms	1.00		

Note: Variables that were significant at the 5% level in the univariable analysis were included in the multivariable analysis. Ventilated patients were excluded because of the wider confidence interval.
OR, odds ratio; CI, confidence interval; WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein; QTc: corrected QT.

Apart from medications, the viral infection itself leads to the development of hypokalemia and other electrolyte abnormalities, such as hypomagnesemia and hypocalcemia, due to an interaction of SARS-CoV-2 with the renin–aldosterone system. This contributes to a prolonged QTc interval and arrhythmias.[17–19] Genetics and other medical comorbidities also predispose patients to a prolonged QTc interval.[20] Moderate to severe COVID-19 infection causes hypoxemia, myocardial injury, and severe systemic inflammation, contributing to a prolonged QTc interval.[21]

Several studies have reported that a prolonged QTc interval in patients with COVID-19 on hydroxychloroquine, azithromycin, or lopinavir/ritonavir does not significantly affect mortality.[22,23] However, Farré et al. reported that a prolonged QTc interval significantly affected mortality, even after adjustment for age, comorbidities, and treatment with hydroxychloroquine and azithromycin.[24] Our study showed that a prolonged QTc interval was associated with in-hospital mortality and ventilator support. Patients who died were older, had elevated troponin, D-dimer, creatinine, procalcitonin, ferritin, and LDH concentrations, had an elevated white blood cell count, and had abnormal potassium concentrations (hypo- or hyperkalemia).

Many studies have identified several risk factors associated with a poor prognosis and increased mortality rate in patients with COVID-19.[25,26] An older age was associated with worse outcomes in most studies, and similarly, those with diabetes, hypertension, or cardiovascular disease tended to have a poorer outcome than those with no comorbidities.[27] Several studies have reported the association of elevated troponin concentrations with poor outcomes and a higher mortality rate.[28] Moderate to severe COVID-19 cases

Table 9. Relationship between prolonged QTC and arrhythmia.

Case no.	QTc at baseline (ms)	Maximum QTc (ms)	Delta QTc (ms)	QRS	Type of arrhythmia	Management of arrhythmia	Died	Arrhythmia observed just before death
1	415	427	12	99	VT	Spontaneously reverted	No	Null
2	409	423	14	84	VT	Spontaneously reverted	No	Null
3	378	474	96	92	VT, VF	Electric cardioversion	Yes	Asystole
4	447	447	0	90	VT	Amiodarone	Yes	PEA
5	462	494	32	100	VT	Electric cardioversion	Yes	PEA
6	459	497	38	110	VT	Amiodarone	Yes	PEA
7	443	495	52	102	VT	Electric cardioversion	Yes	PEA
8	456	484	28	96	VT	Electric cardioversion	Yes	PEA
9	466	506	40	84	VT	Amiodarone	Yes	Asystole
10	347	477	130	104	VT	Electric cardioversion, amiodarone	Yes	PEA
11	450	518	68	82	VT	Electric cardioversion	Yes	VF

QTc, corrected QT; VT, ventricular tachycardia; VF, ventricular fibrillation, PEA, pulseless electrical activity.

develop a multi-system inflammatory response responsible for the high incidence of myocarditis observed in these patients, causing elevated troponin concentrations.[29] A prolonged QTc interval has a linear correlation with elevated troponin concentrations.[30] Our study showed that elevated troponin concentrations were associated with a significant increase in mortality. D-dimer concentrations are high in patients with COVID-19 and they are associated with an increase in the mortality rate. Our study also showed that elevated D-dimer concentrations were associated with a higher risk of mortality. Although increased rates of deep vein thrombosis and pulmonary embolism have been reported in patients with COVID-19, elevated D-dimer concentrations are common in these patients, even in the absence of thromboembolism detected in radiological studies.[31,32] Elevated D-dimer and creatinine concentrations in COVID-19 are attributed to extensive multiorgan micro-thrombosis, which is supported by post-mortem studies.[33]

Abnormal immune-inflammatory responses and a cytokine storm observed in severe COVID infection are associated with a high mortality.[34] The present study showed that the white blood cell count, and concentrations of procalcitonin, ferritin, and LDH were significantly higher in patients with an adverse outcome. Similar findings were found in several other studies.[35,36]

Limitations

The primary limitation of this study is its retrospective design and data were collected from medical records, some of which were missing. We attempted to overcome this limitation by cross-checking information about the medical history and comorbidities from the notes of the physicians and nurses. Some of the laboratory parameters, such as NT-proBNP, were not measured in many patients, and these were excluded from multiple logistic regression analysis. Patients with elevated troponin concentrations did not have echocardiographic or coronary assessment because of limited resources during the pandemic. Therefore, the causative mechanism of elevated

troponin concentrations could not be determined, and there were no follow-up data available. The rate of arrhythmia due to a prolonged QTC just before an episode of cardiac arrest was also unclear because only patients on QTc-prolonging medications had a regular ECG performed.

Because the severity of COVID-19 remains unpredictable, and there are currently no proven specific medications for this disease, there is an urgent requirement for multicenter, randomized trials to assess the usefulness and safety of the current therapies proven to prolong the QTc interval. Identifying the risk factors of a prolonged QTc interval will help physicians decide on therapy and decide on closer monitoring strategies. Because the causative factors of a prolonged QTc interval are not just medications, biochemical and metabolic parameters must be monitored even in moderate cases. The evidence on associations between a prolonged QTc interval and mortality is conflicting. Therefore, extensive multicenter studies need to be performed to provide more accurate results.

Conclusion

A prolonged QTc interval is common in patients with COVID-19 and is associated with worse outcomes. An older age, those with underlying cardiac disease, hypertension, or diabetes mellitus, and elevated troponin and D-dimer concentrations have an increased risk of a prolonged QTc interval. A prolonged QTC is significantly associated with a requirement for a ventilator, but is not associated with mortality in multivariable analysis. However, older patients, those with elevated troponin, D-dimer, creatinine, procalcitonin, ferritin, or LDH concentrations, abnormal potassium concentrations (hypo- or hyperkalemia), and an elevated white blood cell count have an increased risk of mortality. ECG is a non-invasive, minimally expensive tool and is widely available for use in risk stratification in patients with COVID-19. High-risk patients should have closer monitoring and a high dependency level of care.

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Author contributions

All of the authors made substantial contributions to the conception and design, acquisition, analysis, and interpretation of data, drafting the manuscript, revising it critically for important intellectual content, and final approval of the version to be published.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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