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...
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

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. 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. In the United Arab Emirates, there have been approximately 700,000 confirmed cases with 2000 deaths.

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. People with COVID-19 can also not have any symptoms, leading to this disease’s rapid spread from these silent carriers. An older age, male sex, the presence of comorbidities, and increased inflammatory markers are associated with a poor prognosis. 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.

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. 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. 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. 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.\textsuperscript{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.

\section*{Methods}

\textbf{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.\textsuperscript{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 $\geq94\%$ 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.\textsuperscript{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 $>450\text{ms}$ 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/m² 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;
Table 1. QTc interval according to age and sex.

| Variables | >450 ms | ≤450 ms | 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.

| Variables | QTc interval | Univariable analysis | | |
|-----------|--------------|----------------------| | |
| QTc interval | >450 ms (n = 195) | ≤450 ms (n = 518) | 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/m²)* | | | | | |
| <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 \( \geq 280 \) 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 \( \geq 52 \) ng/L (risk ratio, 1.57; 95% CI: 1.17, 2.10) and D-dimer concentrations \( \geq 0.5 \mu g/mL \) 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 (\( p = 0.04 \)).

**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 \( \geq 52 \) ng/L (OR, 1.77; 95% CI: 0.93, 3.37), D-dimer \( \geq 0.5 \mu g/mL \) FEU (OR, 24.08; 95% CI: 1.38, 419.82), creatinine \( \geq 1.2 \) mg/dL (OR, 8.16; 95%
Table 3. Univariable analysis of the association between biochemical parameters and the QTc interval.

| Variables                  | QTc interval |       |       | Univariable analysis |
|----------------------------|--------------|-------|-------|-----------------------|
|                            | >450 ms (n = 195) | ≤450 ms (n = 518) | 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 (×10^3/µL)       | ≥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 (×10^3/µL)     | ≤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.
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 ×10^9/μL (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 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                        | 1.15       | 0.85, 1.57 | 0.360   |
| 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 (×10^9/μL)       |            |            |         |
| ≥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.

**Table 5.** Incidence of mortality by age and sex.

| Variables | Dead | Alive | 95% CI |
|-----------|------|-------|--------|
| Age (years) |      |       |        |
| <40        | 17   | 81    | 4.6, 12.4 |
| 40–55      | 62   | 18.3  | 14.2, 22.4 |
| >55        | 51   | 25.9  | 19.7, 32.0 |
| Sex        |      |       |        |
| Male       | 122  | 18.4  | 15.4, 21.3 |
| Female     | 8    | 9.6   | 3.2, 16.0 |

CI, confidence interval.

procalcitonin ≥0.05 ng/mL (OR, 0.10; 95% CI: 0.02, 0.51), a white blood cell count ≥12 ×10^9/μL (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).

**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 interval.
interval, including azithromycin, hydroxychloroquine, and lopinavir/ritonavir.\textsuperscript{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.\textsuperscript{13} Lopinavir/ritonavir is an antiretroviral agent inhibiting human immunodeficiency virus protease, and it also blocks the hERG channel.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16}

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

| Variables                  | Dead | Alive | Univariable analysis |
|----------------------------|------|-------|----------------------|
|                            | 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.
Table 7. Univariable penalized logistic regression analysis of the associations between biochemical parameters and mortality.

| Variables                        | Dead | Alive | 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      | 1.00    |          |         |
| 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 (×10³/µL)              |      |       |             |            |         |
| ≥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 (×10³/µL)            |      |       |             |            |         |
| ≤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.
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.\textsuperscript{17-19} Genetics and other medical comorbidities also predispose patients to a prolonged QTc interval.\textsuperscript{20} Moderate to severe COVID-19 infection causes hypoxemia, myocardial injury, and severe systemic inflammation, contributing to a prolonged QTc interval.\textsuperscript{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.\textsuperscript{22,23} However, Farr\textsuperscript{e}/C19 et al. reported that a prolonged QTc interval significantly affected mortality, even after adjustment for age, comorbidities, and treatment with hydroxychloroquine and azithromycin.\textsuperscript{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.\textsuperscript{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.\textsuperscript{27} Several studies have reported the association of elevated troponin concentrations with poor outcomes and a higher mortality rate.\textsuperscript{28}

### Table 8. Multivariable penalized logistic regression analysis of mortality.

| Variables             | OR    | 95% CI       | p value |
|-----------------------|-------|--------------|---------|
| Age (years)           |       |              |         |
| <40 years             | 1.79  | 0.88, 3.66   | 0.110   |
| 40–55 years           | 1.90  | 0.73, 4.94   | 0.270   |
| >55 years             | 2.18  | 1.01, 4.70   | 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) |   |          |         |
| \(\geq 52\)          | 1.77  | 0.93, 3.37   | 0.080   |
| <52                   | 1.00  |              |         |
| D-dimer (\(\mu g/mL\) FEU) |      |            |         |
| \(\geq 0.5\)         | 24.08 | 1.38, 419.82 | 0.029   |
| <0.5                  | 1.00  |              |         |
| Creatinine (mg/dL)    |       |              |         |
| \(\geq 1.2\)         | 8.16  | 4.5, 14.8    | 0.000   |
| <1.2                  | 1.00  |              |         |
| WBC count (\(\times 10^3/\mu L\)) |     |            |         |
| \(\geq 12\)          | 2.33  | 1.36, 3.97   | 0.002   |
| <12                   | 1.00  |              |         |
| Ferritin (ng/mL)      |       |              |         |
| \(\geq 400\)         | 2.33  | 0.91, 5.99   | 0.079   |
| <400                  | 1.00  |              |         |
| LDH (U/L)             |       |              |         |
| \(\geq 280\)         | 3.16  | 1.27, 7.87   | 0.013   |
| <280                  | 1.00  |              |         |
| CRP (mg/L)            |       |              |         |
| \(\geq 10\)          | 1.93  | 0.53, 7.07   | 0.319   |
| <10                   | 1.00  |              |         |
| Procalcitonin (ng/mL) |       |              |         |
| \(\geq 0.05\)        | 0.10  | 0.02, 0.51   | 0.006   |
| <0.05                 | 1.00  |              |         |
| Potassium (mmol/L)    |       |              |         |
| \(< 3 \text{ or } > 5\) | 2.22  | 1.21, 4.08   | 0.010   |
| 3–5                   | 1.00  |              |         |
| QTc                   |       |              |         |
| \(\geq 450\) 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.
develop a multi-system inflammatory response responsible for the high incidence of myocarditis observed in these patients, causing elevated troponin concentrations. A prolonged QTc interval has a linear correlation with elevated troponin concentrations. 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. Elevated D-dimer and creatinine concentrations in COVID-19 are attributed to extensive multiorgan micro-thrombosis, which is supported by post-mortem studies.

Abnormal immune-inflammatory responses and a cytokine storm observed in severe COVID infection are associated with a high mortality. 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.

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

Table 9. Relationship between prolonged QTC and arrhythmia.

| Case no. | QTc at baseline (ms) | Maximum QTc (ms) | Delta QTc (ms) | Delta 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  | PEÀ                                  |
| 11      | 450                 | 518             | 68            | 82        | VT                | Electric cardioversion  | Yes  |VF                                   |

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