RESEARCH LETTER

Electrocardiography Holter monitoring in critically ill patients with coronavirus disease 2019 (COVID-19)

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Introduction In December 2019, an outbreak (later called pandemic) of pneumonia occurred in Wuhan, Hubei province of China, due to novel coronavirus (2019-nCoV) (also known as severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) and the first reports were published in China in late February and early March 2020.[1] Iran was no exception in this pandemic and the first documented reports of patients with coronavirus disease 2019 (COVID-19) were announced by the Ministry of Health in late February. In addition to common respiratory symptoms and pulmonary involvement (which may be severe), there are recent reports of other organ involvements in the course of the disease, eg, the nervous system,[2] and cardiac involvement.[3,4]

There is increasing awareness of the cardiovascular presentations of COVID-19 and the adverse impact of cardiovascular involvement on the prognosis. Cardiac involvement in the context of COVID-19 is mainly related with myocardial injury and manifests with elevated myocardial injury biomarkers including troponin.[3] In a study of 138 hospitalized patients with COVID-19, arrhythmia (not further specified) was reported in 16.7% of all patients and in 16 of 36 patients admitted to the intensive care unit (ICU).[5] The aim of this study was to evaluate the prevalence of arrhythmia in critically ill patients with COVID-19 using a 24-hour electrocardiography (ECG) Holter monitoring.

Patients and methods This observational cross-sectional study was conducted in patients with laboratory-confirmed critical COVID-19, who were admitted to the ICU of 2 university hospitals in Iran during the outbreak of COVID-19 in March 2020. The Imam Khomeini Hospital Complex is the largest university-based hospital in Iran and is the referral center for COVID-19 with up to 340 patients with COVID-19 (on average, 35 new admissions daily). A confirmed case of COVID-19 was defined as a positive result of a reverse transcriptase–polymerase chain reaction (RT-PCR) assay of a specimen collected with a nasopharyngeal swab. Patients' heart rate and rhythm were monitored for 24 hours using the Mortara H3 Plus Holter device (Mortara, Milwaukee, Wisconsin, United States) 3 to 5 days after the initiation of medications. Since the novel coronavirus is highly contagious, all precautions required for the hospital staff and devices were practiced for handling the patients. Data were collected using a checklist including demographic characteristics, comorbidities, antiviral and antibacterial regimens, and ECG Holter findings. Two reviewers analyzed ECG Holter findings. QTc was calculated using the Bazett formula. In case of atrial fibrillation (AF), mean QT interval for each patient was corrected using the mean RR interval. Since the QT interval is one of the variables affected by electrolyte imbalance and some medications, potassium and magnesium levels were corrected and unnecessary drugs that could prolong the QT interval were discontinued prior to Holter monitoring. This study complied with the Declaration of Helsinki and was approved by the institutional ethics committee of Tehran University of Medical Sciences (no. 1399.112). Patients provided written informed consent to participate in the study.

Statistical analysis Data are expressed as mean (SD), median (interquartile range), or number (percentage) as appropriate. Data analysis was performed using the Microsoft Excel 2017 and

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TABLE 1 Electrocardiographic Holter findings of 32 patients with coronavirus disease 2019

Holter parameter	Value
Minimum HR, bpm, mean (SD)	61.72 (19.19)
Mean HR, bpm, mean (SD)	89.71 (17.08)
Maximum HR, bpm, mean (SD)	121.63 (24.09)
SDNN, median (IQR)	83.5 (65–143.25)
SDANN, median (IQR)	72 (50.25–113.25)
Mean QT, ms, mean (SD)	383 (65)
Mean QTc, ms, mean (SD)	448 (60)
AF, n (%)	5 (15.6)
Nonsustained VT, n (%)	2 (6.25)
Sustained VT, n (%)	0
Pause >3 seconds, n (%)	2 (6.25)
Atrioventricular block, n (%)	1 (3.12)

Abbreviations: AF, atrial fibrillation; HR, heart rate; IQR, interquartile range; SDANN, standard deviation of the averages of normal sinus beats; SDNN, standard deviation of normal sinus beats; SVT, supra ventricular tachycardia; VT, ventricular tachycardia

SPSS version 20 (IBM Corp., Armonk, New York, United States) for descriptive variables.

Results A total of 32 patients were enrolled in this study. The mean (SD) age of the patients was 65.5 (14.03) years (range, 37–94 years; median, 67 years). The majority of patients were male (59.3%) and just 25% of patients did not have any known risk factors (diabetes mellitus, hypertension, chronic kidney disease, older age [>65 years]). In accordance with the national guideline, all patients received hydroxychloroquine. All patients were treated with at least 1 antiviral agent.

Twenty-four-hour ECG Holter findings are shown in TABLE 1. The mean (SD) heart rate was 89.7 (17.08) bpm and the mean (SD) QTc interval was 448 (60) milliseconds. Nine patients had QTc greater than 470 milliseconds, of whom 5 had a maximal QTc (>500 milliseconds), 1 patient had a mean QTc of 638 milliseconds (Supplementary material, *Table S1*). Despite a prolonged mean QTc interval, there were no cases of polymorphic ventricular tachycardia or torsades de pointes during the hospitalization, even in the patient with the longest QT interval. Patients who received hydroxychloroquine, atazanavir, and fluoroquinolone together had the longest QT interval.

Five patients had AF (15.6%), and 4 patients had permanent AF since many years ago. Just one of the patients had new onset paroxysmal AF during the ICU stay. Two patients had bradycardia. Sudden onset complete heart block occurred in one patient (3.1%), which was transient and disappeared after atropine injection and cardiopulmonary resuscitation. The other patient had permanent AF with episodes of slow ventricular conduction. Nine patients (28.1%) died while still in the ICU without evidence of arrhythmias.

Discussion This case series describes the 24-hour Holter monitoring findings of 32 critically ill patients with proven COVID-19 admitted to the ICU due to acute respiratory failure. The patients admitted with critical COVID-19 had a higher risk of arrhythmia due to hypoxemia, metabolic abnormalities, polypharmacy, autonomic dysfunction, acute myocardial injury, and concomitant other organ failure. The imbalance between metabolic demand due to infection and reduced cardiac reserve in the setting of accentuated inflammatory response and myocardial damage may increase the risk of heart failure and arrhythmias. Acute myocarditis and ventricular arrhythmias might be the first clinical presentation of COVID-19.[6]

Proarrhythmia is one of the potential etiologies of cardiac arrhythmias in this group of patients due to sinus bradycardia, atrioventricular block, and QT prolongation. Daily ECG and cardiac telemetry in the ICU may underestimate the true prevalence of arrhythmias, particularly specific arrhythmias in critically ill patients with COVID-19. Wang et al[5] found that the prevalence of arrhythmia in hospitalized patients was 16.7%. Guo et al[4] showed ventricular tachyarrhythmia in 5.9% of 187 hospitalized patients. In another study, the overall arrhythmia rate was higher in ICU patients (44% as compared with 6.9% in non-ICU patients). Despite the relevance of these data, the authors did not report the arrhythmia type.[5] In the present study, 5 patients had AF (15.6%) and 1 patient had a reversible complete heart block (3.1%). Four patients had permanent AF since many years. Only one of the patients had a new onset paroxysmal AF during the ICU stay. Serum electrolytes, troponin level, and echocardiography findings were unremarkable. The mechanism of AF in this patient might be catecholamine release and hypoxemia.

Sudden-onset complete heart block occurred in 1 patient (3.1%), which was transient and disappeared after atropine injection and cardiopulmonary resuscitation. This is the first report of atrioventricular block in a patient with COVID-19.[7] It could have been due to atrioventricular involvement in the context of myocarditis by coronavirus, a drug (lopinavir / ritonavir), hypoxia or central autonomic dysfunction and parasympathetic activation in the medulla.[2]

One of the challenging issues in COVID-19 treatment is the excessive QT prolongation and risk of drug-induced malignant arrhythmias, especially in the ICU patients with multiple comorbidities.[8,9] Combining hydroxychloroquine with additional antiviral drugs such as lopinavir / ritonavir (which are both potent CYP3A4 inhibitors) and azithromycin might result in higher plasma levels and a significant QT prolongation. Giudicessi et al[8] proposed a simple QTc surveillance strategy to mitigate the risk of malignant ventricular arrhythmia in COVID-19 patients treated with a hypothetical treatment algorithm with "off-label" hydroxychloroquine alone or in combination with azithromycin. They provided urgent

guidance on how to use a 12-lead ECG, telemetry or smartphone-enabled mobile ECG to determine the patient's QTc as a marker to identify patients at an increased risk of malignant ventricular arrhythmia.

In the present study, the QTc interval was more than 470 milliseconds in 9 patients (28%), and more than 500 milliseconds in 4 patients (12%). Eight out of nine patients with a QTc greater than 470 milliseconds were treated with hydroxychloroquine and atazanavir. The patient who had a QTc of 638 milliseconds received a combination of hydroxychloroquine, atazanavir, sofosbuvir, and levofloxacin. Fortunately, torsades de pointes was not seen during Holter monitoring. Serum potassium and magnesium levels were above 4.5 mmol/l and 1.2 mmol/l, respectively, in all above patients. The QT interval prolongation was common in the present study, which could be due to administration of multiple antiviral medications combined with hydroxychloroquine and sometimes fluoroquinolones. We suggest daily QT measurement in patients with COVID-19 admitted to the ICU and correction of treatable causes of QT interval prolongation as well as avoidance—or at least limitation—of QT-prolonging drugs. Routine Holter monitoring is not recommended in critically ill patients with COVID-19 for several reasons: 1) The risk of infection of hospital staff and contamination of Holter devices should be assessed in the context of benefits of the monitoring. 2) Despite prolonged QTc detected with Holter, no malignant arrhythmic events occurred during prolonged monitoring. 3) Data could also be achieved by a simple limb-lead ECG and novel smartphone ECG applications for real-time QTc monitoring.[10]

A larger sample size is needed to conclude about prevalence of malignant arrhythmia in critically ill patients with COVID-19.

Conclusion The results of this study highlighted the importance of QTc surveillance in critically ill patients with COVID-19 that are most susceptible to this potential adverse effect. It is justifiable to be cautious in prescribing drugs with QT prolonging properties and avoiding electrolyte abnormality.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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