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Prognostic significance of Tp-e interval and Tp-e/QTc ratio in patients with COVID-19

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Abstract. – OBJECTIVE: Ventricular arrhythmias were the most frequent manifestations in patients with COVID-19. Both the natural course of the disease and the treatment drugs used have effects on ventricular repolarization. The objective of this study was to evaluate the effects of repolarization parameters obtained from surface electrocardiography (ECG) on prognosis.

PATIENTS AND METHODS: Participants were 205 consecutive patients hospitalized with COVID-19 diagnosis. The 12-lead surface ECG was obtained from each patient on admission. The ECG results were evaluated against the patients' clinical characteristics and outcomes by experienced cardiology specialists.

RESULTS: The mean age was higher in the non-survivor group compared to the survivor group (57.4 ± 15.7 *vs.* 65.6 ± 16.6; $p = 0.001$). The demographical characteristics were similar between the survivor and non-survivor groups. Multivariate analyses demonstrated that age (OR: 1.041; $p = 0.009$), D-dimer (OR: 1.002; $p = 0.031$), high-sensitivity troponin I (hs-TnI) (OR: 1.010; $p = 0.041$), pneumonia on computed tomography (CT) (OR: 4.985; $p < 0.001$), the peak-to-end interval of the T wave (Tp-e) (OR: 3.421; $p < 0.001$), and Tp-e/QTc ratio (OR: 1.978; $p = 0.013$) were statistically significant independent predictors in terms of determining mortality.

CONCLUSIONS: Prolonged Tp-e interval and increased Tp-e/QTc ratio on admission are decent predictors and linked with mortality. ECG is a practical study to evaluate prognosis and potential arrhythmias, as well as initiating suitable treatment.

Key Words:
COVID-19, QTc interval, Tp-e interval, Tp-e/QTc.

Introduction

The SARS-CoV-2 virus, which was identified as a respiratory illness that started in China at the end of 2019, has spread to more than 213 countries[1]. The World Health Organization (WHO) called this disease the COVID-19 pandemic due to its highly contagious characteristic and transmission beyond different countries. COVID-19 has been demonstrated to affect the cardiovascular system by causing thromboembolism, myocardial injury, and arrhythmias[2-4]. As expected, mortality is significantly higher in COVID-19 patients with myocardial injury as myocarditis and arrhythmias are frequently encountered during the progress of the disease, especially in patients with severe clinical conditions[4,5]. Two recent studies[6,7] have shown the relationship between COVID-19 and electrocardiography (ECG).

In addition, it is well established that commonly used drugs, such as chloroquine and azithromycin, affect the depolarization phase and refractory period of Purkinje fibers, and prolong QT interval; they may also increase the risk of ventricular arrhythmias, torsade de pointes, and sudden cardiac death (SCD)[8,9]. The 12-lead surface ECG recorded

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for each patient during their first evaluation may yield information related to cardiac involvement and arrhythmia risk. Repolarization abnormalities may be evaluated from the 12-lead ECG results; they are associated with malignant ventricular arrhythmias[10,11]. QT interval (QT), corrected QT interval (QTc), and the newer ECG parameters, such as T wave peak-to-end (Tp-e) interval, Tp-e/QT ratio, and Tp-e/QTc ratio, have been shown[12-14] to be correlated with repolarization abnormalities and ventricular arrhythmia risk. A recent small study[15] reported that these parameters were abnormal compared to the control group.

In this study, we aimed to investigate the clinical use and prognostic importance of these parameters in COVID-19 patients.

Patients and Methods

Patients

In this retrospective study, we gathered the medical data from 205 consecutive patients hospitalized with COVID-19 diagnosis, established with positive Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) tests between 10 June 2020 and 25 August 2020. Patients' demographical characteristics, co-morbid conditions, and in-hospital events, such as requirement of intensive care unit (ICU) or mechanical ventilation (MV), were collected from medical records. Venous blood samples analyzed on admission were used to collate hemoglobin (Hgb), white blood cell (WBC), urea, creatinine (Cre), sodium, potassium, glucose, high-sensitivity troponin I (hs-TnI), D-dimer, creatinine kinase (CK)-MB, and c-reactive protein (CRP) data for the study. Patients with a history of coronary artery disease, heart failure, atrial fibrillation, conduction abnormalities, cardiomyopathy, severe valve disease, malignancy, inflammatory disease or pregnancy and patients under 18 years old were excluded from this study. This study complies with the principles of the Declaration of Helsinki and was approved by the Local Ethics Committee of the Health Ministry.

The diagnosis of COVID-19 disease was defined in the Public Health Microbiology Reference Laboratory of the Health Ministry *via* real-time RT-PCR method in compliance with the WHO guideline. The severe group was defined as patients with any of the following: (1) respiratory distress (respiratory rate ≥30 breaths per min); (2) oxygen saturation at rest ≤93%; (3) ratio of the partial pressure of arterial oxygen (PaO_2) to the fractional concentration of oxygen inspired air (FiO_2) (PaO_2: FiO_2, ≤300 mmHg); or (4) critical complication (respiratory failure and MV required, septic shock, and/or multiple organ dysfunction/failure and ICU admission required)[16].

Electrocardiography

All 12-lead ECGs were recorded during patient evaluation in the emergency department. ECGs were performed with the digital caliper software Cardio Calipers version 3.3 (Iconico Inc., NY, USA) and were standardized to filter range 0.5-150Hz, AC filter 60Hz, and recorded with 25 mm/s speed and 10 mm/mV amplitude. The ECG recordings were evaluated by two independent cardiologists blinded to the clinical condition and medications of the study participants. The QT, PR interval, and QRS duration were measured from DII or V5-6 derivation manually. The QT distance was accepted from the beginning of the Q wave till the point of the T wave intersected with the isoelectric line. Bazzet formula was performed for QTc: QTc (ms) = QT interval/$\sqrt{}$RR interval[17]. The distance between the peak of the T wave and the end point was defined as the Tp-Te interval and measured from the precordial leads. Tp-e interval (ms) was measured according to the tangent method[18]. The Tp-Te/QTc ratio was calculated in compliance with these indexes.

Statistical Analysis

All statistical tests were conducted using the Statistical Package for the Social Sciences 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to analyze normality of the data. Continuous data were expressed as mean ± SD, and categorical data were expressed as percentages. Chi-square test was used to assess differences in categorical variables between groups. Student's *t*-test or Mann-Whitney U test was used to compare unpaired samples as needed. Receiver operating characteristic (ROC) curves were obtained and the optimal values with the greatest total sensitivity and specificity in the prediction of mortality were selected. Univariate and multivariate logistic regression analyses were used to identify independent variables of mortality. After performing the univariate analysis, significantly obtained variables were selected for the multivariate logistic regression analysis with the stepwise method. The results

Table I. Demographic and clinical characteristics of patients survivor and non-survivor.

Characteristic	Survivor (n = 142)	Non-survivor (n = 63)	p
Age (years)	57.4 ± 15.7	65.6 ± 16.6	0.001
Male, n (%)	83 (58%)	34 (54%)	0.550
BMI (kg/m^2)	25.6 ± 5.3	26.7 ± 6.4	0.712
Chronic medical illness			
HT, n (%)	67 (47%)	39 (61%)	0.052
DM, n (%)	44 (31%)	16 (25%)	0.417
HLD, n (%)	17 (12%)	11 (17%)	0.291
Laboratory findings on admission hospital			
Haemoglobin (g/dl)	13.0 ± 2.9	11.1 ± 2.5	< 0.001
WBC (10^3/µl)	6.4 (4.7-7.8)	8.4 (5.8-11.4)	< 0.001
Creatinine (mg/dl)	0.7 (0.6-0.9)	0.9 (0.7-1.2)	0.019
Sodium (mmol/L)	137.6 ± 3.4	138.7 ± 5.6	0.139
Potassium (mmol/L)	4.1 ± 0.4	3.9 ± 0.7	0.109
Glucose (mg/dL)	117.4 ± 42.8	144.1 ± 53.9	0.001
CRP (mg/dL)	31 (10-91)	72 (20-163)	0.002
Procalcitonin (ng/mL)	0.12 (0.12-0.18)	0.21 (0.12-0.94)	< 0.001
hs-TnI(pg/ml) (NR < 14 pg/ml)	4.6 (2.8-7.8)	23.0 (14.0-93.0)	< 0.001
D-dimer (ng/mL) (NR < 500 ng/mL)	661 (437-899)	1170 (618-2790)	< 0.001
CK-MB (ng/mL)	1.0 (0.5-1.4)	2.0 (1.0-3.8)	< 0.001
Clinical outcome			
Clinical severity of COVID-19	107 (75%)	58 (92%)	0.005
Pneumonia on CT, n (%)	114 (80%)	60 (95%)	0.006
ICU, n (%)	6 (4%)	42 (66%)	< 0.001
MV, n (%)	9 (6%)	46 (73%)	< 0.001

Abbreviations: BMI, Body mass index; HT, hypertension; DM, diabetes mellitus; HLD, hyperlipidemia; WBC, white blood cell, CRP, C-reactive protein; hs-TnI, high sensitive Troponin I; CK, creatinine kinase; CT, computed tomography; ICU, intensive care unit; MV, mechanical ventilation.

of univariate and multivariate logistic regression analyses were presented as odds ratio with 95% confidence interval (CI). Significance was assumed at a two-sided $p < 0.05$.

Results

205 hospitalized patients due to COVID-19 infection were included in the study. The patients' demographical and clinical properties are shown in Table I. Sixty-three patients died (30.7%) and 142 patients were discharged. The survivor cases were significantly younger compared to the deceased patients (57.4 ± 15.7 *vs.* 65.6 ± 16.6; $p < 0.01$). There were no statistically significant differences between the survivor and non-survivor groups in terms of gender, frequency co-morbid diseases, and body mass index.

Regarding the laboratory parameters, WBC, Cre, glucose, CRP, procalcitonin, hs-TnI, D-dimer, and CK-MB levels were found to be significantly higher in the non-survivor group; while Hgb levels in the non-survivor group were significantly lower than the survivor group. The levels of sodium and potassium in the blood samples were similar between the groups (Table I). The comparison of ICU stay (4% *vs.* 66%; $p = 0.001$) and MV requirement (6% *vs.* 73%; $p = 0.001$) frequencies presented statistically significant increases in the non-survivor group. When patients were evaluated according to disease severity, severe COVID-19 was observed in 75% of patients in the survivor group and 92% of patients in the non-survivor group. The presence of pneumonia in the lungs on CT scans during patient admission was observed in 80% of the survivor group and in 95% of the non-survivor group.

When the ECG characteristics (Table II) were compared, there were no statistical differences between the survivor and non-survivor groups in terms of heart rate (88.7 ± 15.1 *vs.* 90.4 ± 20.4; $p = 0.525$) and QTc (429.4 ± 23.9 *vs.* 430.8 ± 63.6; $p = 0.819$). Conversely, the Tp-e interval (80.5 ± 11.1 *vs.* 86.8 ± 15.0; $p = 0.001$), P end to Q wave (64.8 ± 18.4 *vs.* 73.1 ± 29.9; $p = 0.017$), and Tp-e/QTc ratio (0.18 ± 0.02 *vs.* 0.19 ± 0.03; $p = 0.044$) were significantly higher in the non-survivor group than in the survivor group.

To evaluate the variables predicting mortality *via* logistic regression analysis, parameters were

Table II. Electrocardiographic characteristics of COVID-19 patients.

	Surviver (n = 142)	Non-surviver (n = 63)	p
Heart rate, per minute	88.7 ± 15.1	90.4 ± 20.4	0.525
Tp-e interval, (ms)	80.5 ± 11.1	86.8 ± 15.0	0.001
P end to Q wave	64.8 ± 18.3	73.1 ± 29.9	0.017
QTc interval, (ms)	429.4 ± 23.9	430.8 ± 63.6	0.819
Tp-e/QTc ratio	0.18 ± 0.02	0.19 ± 0.03	0.044

Abbreviations: Tp-e, the peak-to-end interval of the T wave; QTc, corrected QT.

primarily analyzed by univariate and multivariate tests. Age, gender, D-dimer, CRP, hs-TnI, Tp-e interval, P end to Q wave, and Tp-e/QTc ratio parameters were first evaluated in univariate analysis, and then, all these variables were re-evaluated by multivariate analysis. Consequently, age, D-dimer, hs-TnI, Tp-e interval, and Tp-e/QTc ratio were found to be statistically significant independent predictors in terms of predicting mortality: age (OR: 1.041; $p = 0.009$), D-dimer (OR: 1.002; $p = 0.031$), hs-TnI (OR: 1.010; $p = 0.041$), pneumonia on CT (OR: 4.985; $p < 0.001$), Tp-e interval (OR: 3.421; $p < 0.001$), and Tp-e/QTc ratio (OR: 1.978; $p = 0.013$). Univariate and multivariate logistic regression analyses on the mortality risk factors associated with ECG and patients characteristics are presented in Table III.

The ROC curves of the Tp-e interval for the prediction of mortality are shown in Figure 1. A Tp-e interval of 84.5 ms was defined as the optimal cutoff point for discriminating mortality. The best performing value of Tp-e interval (84.5 ms) to predict mortality was associated with 71% sensitivity, 69% specificity. The area under curve (AUC) of the Tp-e interval for the prediction of mortality was 0.813 (95% CI: 0.751-0.875; $p < 0.001$) (Figure 1).

Discussion

The results of this study demonstrated that the mean Tp-e interval, P end to Q wave, and Tp-e/QTc ratio were related to poor prognosis in patients suffering from COVID-19. The P end to Q wave and Tp-e interval were significantly longer in the non-survivor group.

We know the COVID-19 pandemic, which infected more than 15 million people, causes cardiac involvement by inducing cardiomyopathy, acute coronary syndromes, myocarditis, acute heart failure, or SCD[19]. Cardiac involvement can be measured by cardiac biomarkers, such as CK-MB, troponin, which are sensitive to myocardial injury; any conduction system defects may be reflected in ECGs as abnormal repolarization parameters. A recent study published by Ozturk et al[15] showed that repolarization markers, such as QTc, QTd, and Tp-e/QTc ratio were significantly

Table III. Univariate and multivariate logistics regression analysis on the risk factors associated mortality in patients with COVID-19.

Variable	Univariate			Multivariate		
	OR	95% C	p	OR	95% CI	p
Age	1.048	1.019-1.087	< 0.001	1.041	1.020-1.076	0.009
Gender	0.854	0.492-1.387	0.484	0.913	0.712-1.201	0.511
D-dimer	1.002	1.001-1.003	< 0.001	1.002	1.001-1.003	0.031
CRP	1.010	1.003-1.021	0.007	0.891	0.631-1.621	0.417
hs-TnI	1.002	1.001-1.003	0.019	1.010	1.001-1.061	0.041
Pneumonia on CT	5.852	2.018-11.705	< 0.001	4.985	1.972-10.112	< 0.001
Tp-e interval	4.147	2.221-7.821	< 0.001	3.421	1.899-7.831	< 0.001
P end to Q wave	1.018	1.005-1.037	0.022	1.105	0.909-1.351	0.429
Tp-e/QTc	3.254	1.526-6.298	< 0.001	1.978	1.102-3.253	0.013

Abbreviations: CRP, C-reactive protein; hs-TnI, high-sensitive troponin I; CT, computed tomography; Tp-e, the peak-to-end interval of the T wave; QTc, corrected QT.

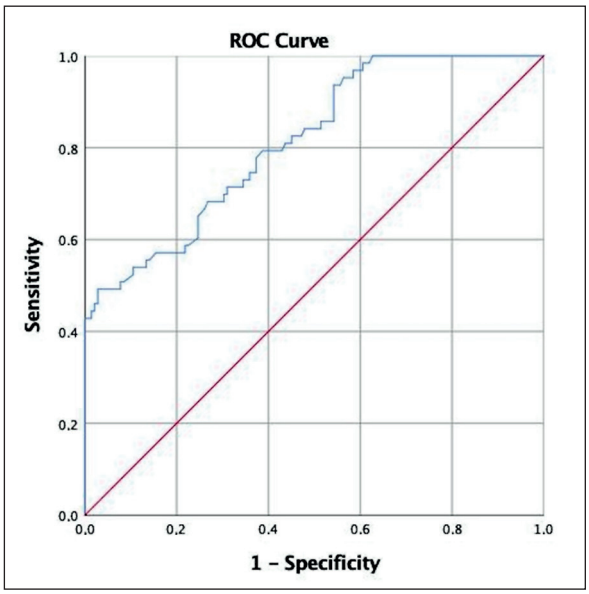

Figure 1. Predictive ability of Tp-e, the peak-to-end interval of the T wave (Tp-e) interval for mortality.

increased in COVID-19 patients. In a study[5] published from Wuhan, China, the arrhythmia rates in COVID-19 patients were 16.7% and were more frequently seen in patients hospitalized in ICU (44.4% *vs.* 6.9%; $p < 0.001$). Another report[20] from Wuhan studied 187 COVID-19 patients; the rate of malignant ventricular arrhythmia was 5.9% and the rate of myocardial injury was significantly higher (1.5% *vs.* 17.3%; $p < 0.001$). Du et al[21] reported that 62.9% of the 81 fatal cases had arrhythmia and two of the cases had malignant ventricular arrhythmia.

Myocardial repolarization is evaluated by QT dispersion, Tp-e interval, and the ratio of Tp-e interval to QTc; these measurements have prognostic contribution to predict ventricular arrhythmias and consequently SCD[11,22]. QT, QTc, and QT dispersion are the known parameters, and novel indexes, such as Tp-e interval and Tp-e/QTc ratio were conceded as subjects for assessment of myocardial repolarization[23]. The distribution difference of ion channels and ion kinetics between myocardial regions causes positional heterogeneity also known as repolarization dispersion. It has been established that increased dispersion of ventricular repolarization is also a serious substrate for ventricular arrhythmias. The Tp-e is a transmural dispersion marker. The peak of the T wave presented the end of repolarization of epicardium, and the end of the T wave coincided with the end of the mid-myocardial label. Middle myocardial M cells have longer action potential time than other cells in myocardium; therefore, the prolongation of Tp-e interval ultimately represents interrupted dispersion of repolarization[24-26]. COVID-19 infection precipitates extreme cytokine release and this cytokine storm was charged with the cause of fulminant myocarditis. Moreover, the functional receptor of coronavirus is ACE2, which also exists in myocardium, as well as the lungs. Increased inflammation secondary to COVID-19 infection with cardiac involvement may cause deterioration in myocyte by impairing ion channel regulation, which may ruin the heterogeneity of repolarization[27]. Other chronic diseases, such as psoriasis and rheumatoid arthritis, induce intense inflammation and cytokine discharge, which may prolong Tp-e interval and increase Tp-e/QT ratio; however, there is not enough research on whether the repolarization parameters are linked with prognosis or severity of these diseases[28]. Apart from inflammatory diseases, prolongation of Tp-e interval and increase in Tp-e/QTc ratio are associated with increased mortality in myocardial infarction, cardiomyopathy, Brugada syndrome, and long QT syndrome[10]. The drugs used in COVID-19 treatment are another issue predisposing factor for arrhythmias, particularly lopinavir/ritonavir, chloroquine, and azithromycin. Lopinavir and ritonavir may alter cardiac conduction by prolonging PR and QT duration[29]. Saleh et al[30] published the first article about 201 COVID-19 patients treated with hydroxychloroquine/azithromycin; 30% of the patients had QT prolongation more than 40 ms; and 11% of the treated patients' QT duration exceeded 500 ms, however none of the patients suffered from torsade de pointes. Genetic polymorphism, hepatic failure, electrolyte imbalance, female gender, bradycardia, and structural cardiac history are the factors influencing excess repolarization of ion currents associated with increased risk of torsades de points. Chloroquine and hydroxychloroquine have limited effects of causing prolonged QT interval and consequently torsade de pointes. There are case reports[30,31] in literature where this occurred at high dose administrations. Another widely used drug in the treating COVID-19 is azithromycin. Azithromycin is a macrolide derivative antibiotics, which may prolong QT by enhancing intracellular sodium quantity. Azithromycin has been discussed in literature to have slight effects in prolonging QT distance without significantly increasing the risk of torsade de

pointes[32]. In our study, mortality was more frequently seen in older patients and in patients with increased inflammatory markers on admission. In addition, receiving MV was linked with mortality. Severe systemic inflammatory responses and the treatment drugs likely affected repolarization parameters, such as Tp-e interval, P end to Q wave, and Tp-e/QTc ratio, which increased the torsade de pointes and other malignant ventricular arrhythmia risks. Our study results showed that altered repolarization parameters were linked with reduced survival rates.

Conclusions

Ventricular arrhythmias and abnormal repolarization are a common manifestation in COVID-19 patients. Consequently, in this study, we established that prolonged Tp-e interval and increased Tp-e/QT and Tp-e/QTc ratios were associated with poor prognosis in COVID-19 patients. The changes in repolarization parameters may occur as a consequence of viruses causing the infection or adverse effects of the antiviral drugs used for treatment. Recent studies clarified the prolongation of Tp-e interval and increases in Tp-e/QT ratio and Tp-e/QTc ratio in COVID-19 patients compared to healthy subjects. Furthermore, we demonstrated that alteration of repolarization indexes may impair the prognosis and increase the requirement for MV and ICU stays and, ultimately, the risk of imminent mortality. A standard surface ECG may predict the prognosis independently of pro-arrhythmogenic drug administration.

Study Limitations

Our study had some limitations. One major restriction was that the study could not determine whether the cause of death in the non-survivor group was due to malignant ventricular arrhythmias or if the survivor group suffered from arrhythmias. In addition, ventricular repolarization parameters may present variability according to different times of day, nutrition, and physical activity; therefore, long-term rhythm recordings were required. Another limitation was the relatively short follow-up period. However, a longer follow-up period after discharge may lead to poorer outcomes for the non-survivor group. Finally, the fact that none of the participants had healthy ECG records could be considered another limitation of this study.

Conflict of Interest

This study received no grant from any funding agency in the public, commercial or not-for-profit sectors. The authors report no conflicts of interest.

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