The relationship between length of stay in intensive care unit and Tpeak-Tend and Tpeak-Tend/QTc ratio in COVID 19 patients with acute coronary syndrome

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1 INTRODUCTION

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been affecting the entire world since December 2019, causing the coronavirus 2019 (COVID-19) pandemic. The virus primarily affects the respiratory system. During the clinical course or even after recovery, the virus can affect other organs, especially the cardiovascular system. As a result of its effects on the cardiovascular system, patients can develop cardiac injury resulting in cardiac arrhythmias, myocarditis, and acute coronary syndrome (ACS). In this study, we aimed to investigate whether COVID-19 infection affects ventricular repolarization parameters such as Tpeak-Tend interval (Tp-e), QT interval, corrected QT (QTc), Tp-e/QT, and Tp-e/cQT in patients with ACS.

Methods: The study consisted of two groups. The first group included patients with ACS and COVID-19 (Group 1) (n = 50). Polymerase chain reaction test positive patients were enrolled. The second group included patients with only ACS (Group 2) (n = 100). The risk of ventricular arrhythmias was evaluated on the basis of the measured electrocardiographic Tp-e and QT interval, and QTc, Tp-e/QT, and Tp-e/QTc values.

Results: Tp-e interval, QTc, and Tp-e/QTc were significantly higher in the group1 than group 2 (p < .001, p < .018, and p < .001, respectively). Significant positive correlations were found between Tp-e, D-dimer level, and C-reactive protein (CRP) level in the group1 (p = .002, p = .03, and p = .021, respectively). Univariate and multivariate regression analyses revealed that Tp-e was one of the independent predictor of length of stay in the intensive care unit (ICU). (B = 1.662, p = .006 and B = 1.804, p = .021, respectively).

Conclusions: In the patients with ACS, COVID-19 infection caused increases in QTc, Tp-e, and Tp-e/QTc ratio. In addition, age and prolonged Tp-e were found to be independent predictors of prolonged ICU stay.

KEYWORDS
acute coronary syndrome, cardiac arrhythmias, COVID-19, electrocardiography, intensive care unit
system, acute coronary syndrome (ACS), pulmonary thromboembolism, malignant ventricular arrhythmias, acute myocarditis, and acute pericarditis may occur.\textsuperscript{1,2}

Life-threatening arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF) can occur owing to prolonged or impaired ventricular repolarization. The QRS complex and T wave on the ECG depict ventricular depolarization and repolarization. Obtained from these, QT interval, corrected QT interval (QTc), Tpeak-Tend interval (Tp-e), Tp-e/QT, and Tp-e/QTc ratios are associated with ventricular transmural electrical activity. Increased dispersion of repolarization is a possible predisposing factor to malignant ventricular arrhythmias. Long Tp-e interval indicates abnormal spread in ventricular repolarization and has been associated with increased risk of ventricular arrhythmias in patients with long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, and post-ACS status.\textsuperscript{3-5}

Electrocardiography (ECG) is an effective, easily accessible, and feasible tool for predicting ventricular arrhythmias and sudden cardiac death. Tp-e is an ECG interval associated with the dispersion of ventricular repolarization.\textsuperscript{6} Prolonged Tp-e and increased Tp-e/QT are associated with ventricular arrhythmias (e.g., VT and VF).\textsuperscript{7} The incidence of ventricular arrhythmias is higher in patients with inflammatory and infectious diseases than in the healthy population.\textsuperscript{8,9} Recent studies have shown that the Tp-e interval is longer in patients with COVID-19 than in control subjects.\textsuperscript{10-12} To the best of our knowledge, no previous studies have investigated the potential usefulness of Tp-e and Tp-e/QTc as markers of ventricular arrhythmogenesis in ACS patients with COVID-19 infection. In this study, we aimed to determine whether differences exist in QTc, Tp-e, and Tp-e/QTc between ACS patients with and those without COVID-19.

2 | METHODS

2.1 | Patient selection

The study was designed as a single-center retrospective. The study consisted of 50 patients with ACS who had COVID-19 infection (group 1) and 100 patients with ACS who had not COVID-19 infection (group 2). Controls were selected in consecutive cohorts. Diagnosis of ACS was made according to the diagnostic criteria of the European Society of Cardiology non-ST elevation myocardial infarction (NSTEMI) guideline published in 2020 and the ST-elevation myocardial infarction (STEMI) guideline published in 2017.\textsuperscript{13,14} COVID-19 diagnose were first made by clinical findings and computed thoracic tomography and then confirmed by COVID-19 swab test using real-time reverse transcriptase-polymerase chain reaction (RT-PCR). Patients who were not pregnant and aged >18 years were included in the study. The patients in group 1, who were clinically stable, were discharged to complete their quarantine period at home. Patients with severe heart failure (left ventricular ejection fraction ≤30%), severe chronic renal (GFR < 30 ml/min/1.73 m\textsuperscript{2}) and liver failure, abnormal serum electrolyte values such as hypokalemia and hypomagnesemia, atrial fibrillation, complete or incomplete branch block, pace rhythm, and patients using QT interval lengthening drugs such as hydroxychloroquine sulfate were not included in the study. The medical history of patients was obtained from hospital records. The study was reviewed and approved by the Institutional Review Board of our institution Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital on September 09, 2021 (no: 2021/187) by the Declaration of Helsinki and other regulations. Informed consent was obtained from the patients.

2.2 | Evaluation of blood sample tests

Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, and fasting blood glucose were studied from the blood samples taken after at least 8 h of fasting. Creatinine, C reactive protein (CRP), procalcitonin, fibrinogen, D-dimer, high sensitive troponin I (hs troponin I), and complete blood count were studied from the blood tests taken immediately after admission to the hospital.

2.3 | Echocardiographic evaluation

Transthoracic echocardiography was performed at hospital admission. Heart chamber diameters, valvular pathology, systolic pulmonary artery pressure, and ejection fraction (EF) (measured using the modified Simpson method) data were obtained from the apical and parasternal axes with a 2.5 MHz transducer and echocardiography machine (Vivid 5; GE Healthcare, Inc.)

2.4 | Electrocardiographic assessment

All patients had 12-lead ECG in the supine position (GE Marquette Mac 1200). Each ECG was taken at a paper rate of 25 mm/s, a gain of 10 mV. ECGs of the patients at the first admission to the hospital were compared. ECGs were interpreted by two different cardiologists independently. All patients were in sinus rhythm. No patient had fewer than nine measurable leads and all precordial derivations were included in the measurements. QT interval was measured from the onset of the QRS complex to the end of the T-wave. The end of T wave was defined with tangent method.\textsuperscript{15} The QTc interval was calculated by using Bazett’s formula.\textsuperscript{16}

The Tp-e interval is defined as the interval from the peak of the T wave to the end of the T wave. The measurements were performed on lead II and lead V5, and the longest QT and Tp-e intervals were used for the analyses.\textsuperscript{17,18} Then, Tp-e was divided by the QTc time to calculate the ratio of Tp-e / QTc.
2.5 | Statistical analysis

IBM SPSS Statistics for Windows, Version 18.0 (IBM Corp.,) was used to perform the statistical analysis. Shapiro-Wilk test was used to assess the normality of distribution of the variables. Quantitative variables with a normal distribution were specified as the mean ± standard deviation and non-normally distributed variables were specified as median (25%-75%quartile). Categorical variables were shown as numbers and percentage values. The non-normally distributed variables were assessed with the Mann–Whitney U test, while normally distributed variables were assessed with an independent sample Student’s t-test. The categorical variables were analyzed with a chi-squared test and Fisher exact test. Correlation analysis was used to examine the relationships between Tp-e interval, CRP, length of hospital stay, length of stay in intensive care unit (ICU), age, D-dimer, EF, and hs troponin I. The uni- and multivariate regression analysis were used to compare length of stay in ICU with Tp-e interval, age, EF, CRP, and D-dimer.

3 | RESULTS

The average age of group 1 was 65 years, group 2 was 59.6 years and there was not a significant difference. In group 1, 31 (62%) individuals consisted of male patients. In group 2, 74 (74%) of the patients were male, and the two groups were considered similar in this respect. In group 1, 50 (100%) patients had positive nasal swabs on the other hand lung involvement on non-contrast thoracic tomography was typical for COVID 19 pneumonia in 43 (86%) patients. The groups were compared in terms of chronic disease history. The data of other demographics and disease history are summarized in Table 1.

| Parameters | Group 1 (n = 50) | Group 2 (n = 100) | p |
|------------|-----------------|-----------------|---|
| Age (year) | 65 (49–80)      | 59.6 (48–65)    | .470 |
| Male       | 31 (62%)        | 74 (74%)        | .094 |
| Smoking    | 17 (34%)        | 46 (46%)        | .109 |
| COVID-19 test results | | | |
| CT(+)      | 43 (86%)        | -               | |
| Swap (+)   | 50 (100%)       | -               | |
| Intubation | 5 (10%)         | 5 (5%)          | .206 |
| Length of stay in intensive care unit (Day) | 4.33±3.55 | 2.66±2.4 | .003 |
| Length of stay in hospital (Day) | 8.6±6.9 | 5.02±4.04 | <.001 |

Ischemic heart disease

| Parameters | Group 1 (n = 50) | Group 2 (n = 100) | p |
|------------|-----------------|-----------------|---|
| CABG       | 7 (14%)         | 6 (6%)          | .094 |
| PCI        | 26 (52%)        | 55 (55%)        | .127 |
| Diabetes mellitus | 24 (48%) | 33 (33%) | .118 |
| Hypertension | 32 (64%)    | 66 (66%)        | .106 |
| Chronic kidney disease | 0 (0%) | 3 (3%) | .574 |
| Cerebrovascular Event | 2 (4%) | 1 (1%) | .436 |

Abbreviations: CABG, Coronary artery bypass graft; CT, Computed tomography; PCI, Percutaneous coronary intervention.

The groups were compared in terms of laboratory test results. Hemoglobin, lymphocyte count, total cholesterol and triglyceride levels were higher in the group 2 (p = .041; <.001; .018; .050, respectively). In group 1, the CRP, and D-dimer were higher (p <.001; .032 respectively), which led to a significant statistical
result. Other laboratory results are summarized in Table 2. The patients were also compared in terms of coronary angiographic characteristics. 42 (84%) of the patients in the group 1 and 74 (74%) of the group 2 presented with NSTEMI. On the other hand, 9 patients (18%) of group 1 and 26 patients (26%) of group 2 were presented with STEMI. There was no statistical difference between the groups in terms of these characteristics (p > .050). Other angiographic features are summarized in Table 3.

The patients were also compared in terms of echocardiographic and ECG data. Systolic pulmonary artery pressure was higher in group 2 (p = .050). In group 1, Tp-e / QTc ratio was higher and QT interval, QTc interval, and Tp-e were longer (p = < .001; .014; .018; < .001, respectively). Other results are summarized in Table 3.

Table 4 summarizes whether there is a correlation between CRP, procalcitonin, D-dimer, hs troponin I, EF, age, length of the hospital—ICU stay, and Tp-e interval. There was a significant correlation between Tp-e and CRP, D-dimer.

Table 5 summarizes the univariate and multivariate regression analyses results between length of ICU stay and D-dimer, age, Tp-e interval, CRP, and EF. The length of stay in ICU and age were independent predictor of prolonged Tp-e in univariate analysis. However, length of stay in ICU was only an independent predictor of prolonged Tp-e interval in multivariate regression analysis.

| Parameters | Group 1 (n = 50) | Group 2 (n = 100) | p   |
|------------|-----------------|------------------|-----|
| Type of MI  |                 |                  |     |
| NSTEMI     | 42 (84%)        | 74 (74%)         | .188|
| STEMI      | 9 (18%)         | 26 (26%)         |     |
| Decision of Procedure |  |                  |     |
| Medical    | 15 (30%)        | 24 (24%)         | .103|
| CABG       | 9 (18%)         | 7 (7%)           |     |
| PCI        | 26 (52%)        | 69 (69%)         |     |
| >50% occlusion |  |                  |     |
| LMCA       | 4 (8%)          | 5 (5%)           | .376|
| LAD        | 30 (60%)        | 60 (60%)         | .857|
| CX         | 24 (48%)        | 46 (46%)         | .330|
| RCA        | 19 (38%)        | 47 (47%)         | .421|
| IM         | 1 (2%)          | 5 (5%)           | .933|
| Body temperature at admission to hospital (°C) | 37.0 ± 1.12 | 36.7 ± 1.01 | .071 |
| Heart rate (per minute) | 77.03 ± 1.88 | 74.38 ± 1.34.5 | .415 |
| PR duration (ms) | 147.27 ± 27.56 | 157.45 ± 25.18 | .096 |
| QRs (ms)   | 92.85 ± 19.57  | 93.86 ± 20.02   | .261|
| QT dispersion (ms) | 32.7 ± 6.57  | 33.92 ± 7.02   | .083|
| fQRS       | 7 (17.5%)       | 19 (19%)        | .387|
| QT interval (ms) | 392.52 ± 38.3 | 370.64 ± 39.37 | .014 |
| QTc interval (ms) | 453.76 ± 34.61 | 434.67 ± 35.87 | .018 |
| Tp-e interval (ms) | 103.52 ± 26.3 | 78.38 ± 13.28 < .001 |
| Tp-e/QTc   | 0.2 ± 0.06      | 0.14 ± 0.06     | < .001|
| In hospital mortality | 4 (10%) | 2 (2%) | .097 |

Abbreviations: CABG, Coronary artery bypass grafting; QTc, corrected QT duration; CX, Circumflex artery; fQRS, Fragment QRS; IM, Intermediate artery; LAD, Left anterior descending; LMCA, Left main coronary artery; LBBB, Left bundle branch block; Myocardial infarctus; mm Hg, millimeter mercury; ms, milisecond; NSTEMI, non ST elevation myocardial infarctus; PCI, Percutaneous coronary intervention; RBBB, Right bundle branch block; RCA, Right coronary artery; STEMI, ST elevation myocardial infarctus; Tp-e, Tpeak-end.

Table 4  Correlation analysis between Tp-e interval and some clinical, laboratory, demographic and electrocardiographic features.

| Parameters     | p     | r     |
|----------------|-------|-------|
| Length of hospital stay | .257 | .103 |
| Length of ICU stay     | .124 | .139 |
| Age                   | .782 | -.025 |
| Procalcitonin         | .774 | .054 |
| CRP                   | .021 | .224 |
| Hs-Troponin I         | .672 | .039 |
| D-Dimer               | .002 | .418 |
| EF                    | .039 | -.187 |

Abbreviations: CRP, C reactive protein; EF, Ejection fraction; Hs-Troponin I, High sensitive troponin I; ICU, Intensive care unit; r, Rho; Tp-e, Tpeak-Tend.

## DISCUSSION

This study summarises the data of ACS patients with and without COVID-19 who were admitted to our primary percutaneous intervention center and underwent coronary angiography. The main finding of our study is that in the ACS patients with COVID-19, Tp-e interval and Tp-e/QTc ratio were increased, with prolonged QT, and QTc interval. The lengths of stay in the hospital and ICU were longer in group 1. In addition, prolonged Tp-e was one of the independent predictors of prolongation in the length of stay in ICU. To the best of our knowledge, this is the first study to show increased Tp-e interval and Tp-e/QTc ratio, which are ventricular repolarisation parameters, in patients with COVID-19 and ACS.

Despite the improvements in medical and revascularization therapies, coronary artery diseases are still the most common causes of death worldwide. Therefore, several methods have been developed to predict the risk of mortality in patients with ACS. Ventricular repolarisation parameters such as Tp-e interval, QTc interval, and Tp-e/QTc ratio can be used for this purpose. Haarmark et al. measured Tp-e interval in 101 patients with ST-segment elevation myocardial infarction (STEMI) who underwent percutaneous coronary intervention (PCI). They found no association between post-PCI Tp-e interval and mortality. However, they found a significant
correlation between pre-PCI Tp-e and mortality. In another study, a correlation was found between short-term arrhythmia and Tp-e. In the same study, a significant decrease was found in the Tp-e interval after successful revascularization. In the study of Tatlısu et al., 488 consecutive patients with STEMI treated with PCI were included and followed up for 21.1 ± 10.2 months. The authors found that the Tp-e interval was associated with not only in-hospital VT/VF and target vessel revascularization but also death. Tp-e interval was found to be an important predictor of long-term mortality.

COVID-19 infection may cause cardiomyopathy by involving the myocardium and/or pericardium, and ACS by involving vascular structures. During the course of these clinical scenarios, sudden cardiac death may occur by triggering arrhythmic events. Cardiac involvement can be measured using cardiac biomarkers, and conduction system pathologies may be detected on ECG as abnormal repolarisation parameters. COVID-19 infection may also present arrhythmogenic features. Öztürk et al. compared 51 patients with COVID-19 with 40 controls in terms of ECG results. Although no significant differences were found between the groups in terms of heart rate, QT interval, or Tp-e interval. However, the groups showed differences in QTc interval and Tp-e/QTc. In another study, patients with COVID-19 and severe pneumonia showed increased Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio, without prolonged QT and QTc intervals. Furthermore, in the study of Yenercag et al., a positive correlation was found between ventricular repolarisation parameters and CRP level. In another study, multivariate analyses demonstrated that age, D-dimer, high-sensitivity troponin I, Tp-e and Tp-e/QTc ratio statistically significant independent predictors in terms of determining mortality. The difference among our study and other studies is that we investigated whether COVID-19 infection affects ventricular repolarisation parameters such as Tp-e, QTc, and Tp-e/QTc in patients with ACS. QT interval, QTc interval, Tp-e, and Tp-e/QTc were higher in the ACS patients with COVID-19. Moreover, a positive correlation was observed between Tp-e and CRP and D-dimer levels. The univariate and multivariate regression analyses revealed that prolonged Tp-e interval was one of the independent predictors of prolonged stay in the ICU.

Cardiac injury secondary to COVID-19 infection, could be causing electrical disturbances leading to arrhythmias. Cardiac injury in patients with COVID-19 could be attributed to myocardial stress. The myocardial stress could be caused by metabolic and electrolyte abnormalities, hypoxia, increased endogenous catecholamine release, inflammation of myocardial cells, whether the patient has preexisting coronary artery disease or not. Our univariate analysis revealed that age was an independent predictor of Tp-e. An increase in age may increase the Tp-e. This means that the risk of arrhythmias may increase.

### 4.1 Study limitations

The small number of patients in the study is its greatest limitation. The patients included in the study were not divided into non-STEMI and STEMI groups. Moreover, whether arrhythmias develop during follow-up after discharge remains unknown.

### 4.2 Conclusions

Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios, which are used to evaluate ventricular repolarisation, are easily accessible, inexpensive, repeatable, and non-invasive ECG parameters. To our knowledge, this is the first study to evaluate ventricular repolarisation using Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios in patients with COVID-19 and ACS. In this study, Tp-e interval and Tp-e/QTc ratios were found to be increased before treatment in the ACS patients with COVID-19. Moreover, prolonged Tp-e interval was one of the independent predictors of prolonged stay in the ICU. Large-scale long-term studies are needed to support our data.

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None.

### CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

### ETHICS STATEMENT

The study was reviewed and approved by the Institutional Review Board of our institution Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital on September 09, 2021 (no:2021/187) by the Declaration of Helsinki and other.
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