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Research Article

Effect of systemic inflammatory response syndrome on ventricular repolarization parameters in COVID-19 patients

COVID-19 hastalarında sistemik inflamatuar yanıt sendromunun ventriküler repolarizasyon parametreleri üzerindeki etkisi

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Abstract

Aim: Malignant ventricular arrhythmia is a significant cause of mortality in COVID-19 patients. We aimed to investigate ventricular repolarization parameters that predict the risk of malignant ventricular arrhythmia in COVID-19 patients who developed systemic inflammatory response syndrome (SIRS).

Material and Methods: Our study included 533 COVID-19 patients, divided into two groups: those who developed SIRS (n=197) and those without SIRS (n=336). ECG measurements were taken for QRS, QT, QTc, Tp-e intervals, Tp-e/QTc, Tp-e/QT, QT/QRS (Index of Cardiac Electrophysiological Balance, İCEB) and QTc/QRS (ICEBc), and these values were compared between groups.

Results: The mean age of the study population was 62 years, and 49% (261) were female. The ICEBc was 5.1 for the SIRS group and 4.98 for the non-SIRS group (p=0.004). The QTc interval was 450 ms in the SIRS group and 427 ms in the non-SIRS group (p=0.001), indicating a substantially higher QTc interval in the SIRS group. Multivariable linear regression analysis revealed a significant correlation between ICEBc and SIRS, age, gender, and C-reactive protein (CRP). ROC analysis showed that ICEBc was a more significant predictor of in-hospital mortality than QTc (ICEBc: 64.5% sensitivity, 50.4% specificity; QTc: 56.4% sensitivity, 53.9% specificity).

Conclusion: ICEBc and QTc were significantly higher in COVID-19 patients with SIRS compared to those without SIRS. ICEBc, known to be related to malignant arrhythmias on ECG in SIRS patients, may aid in predicting and preventing arrhythmic events. Additionally, ICEBc was found to be a better predictor of in-hospital mortality than QTc.

Keywords: ICEB, SIRS, COVID-19, ventricular arrhythmia

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Öz

Amaç: Malign ventriküler aritmi, COVID-19 hastalarında önemli bir mortalite nedenidir. Sistemik inflamatuar yanıt sendromu (SIRS) gelişen COVID-19 hastalarında malign ventriküler aritmi riskini öngören ventriküler repolarizasyon parametrelerini araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmamıza 533 COVID-19 hastası dahil edildi ve hastalar iki gruba ayrıldı: SIRS gelişenler (n=197) ve gelişmeyenler (n=336). QRS, QT, QTc, Tp-e intervalleri, Tp-e/QTc, Tp-e/QT, QT/QRS (Kardiyak Elektrofizyolojik Denge İndeksi, İCEB) ve QTc/QRS (ICEBc) için EKG ölçümleri alındı ve bu değerler gruplar arasında karşılaştırıldı.

Bulgular: Çalışma grubunun ortalama yaşı 62 olup, %49'u (261) kadındı. ICEBc, SIRS grubunda 5,1, SIRS olmayan grupta ise 4,98 olarak bulundu (p=0,004). QTc aralığı, SIRS grubunda 450 ms, SIRS olmayan grupta ise 427 ms olarak bulundu (p=0,001). Bu da SIRS grubunda önemli ölçüde daha yüksek bir QTc aralığı olduğunu göstermektedir. Çok değişkenli doğrusal regresyon analizi, ICEBc ile SIRS, yaş, cinsiyet ve C-reaktif protein (CRP) arasında anlamlı bir korelasyon olduğunu ortaya koymuştur. ROC analizi, ICEBc'nin hastane içi mortaliteyi QTc'den daha anlamlı bir öngörücü olduğunu göstermiştir (ICEBc: %64,5 duyarlılık, %50,4 özgüllük; QTc: %56,4 duyarlılık, %53,9 özgüllük).

Sonuç: ICEBc ve QTc, SIRS gelişen COVID-19 hastalarında, SIRS gelişmeyen hastalara kıyasla anlamlı derecede yüksekti. SIRS hastalarında EKG'de malign aritmilerle ilişkili olduğu bilinen ICEBc, aritmik olayların öngörülmesine ve önlenmesine yardımcı olabilir. Ayrıca, ICEBc'nin QTc'den daha iyi bir hastane içi mortalite öngörücüsü olduğu bulunmuştur.

Anahtar Kelimeler: ICEB, SIRS, COVID-19, ventriküler aritmiü

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes coronavirus disease-2019 (COVID-19), was first identified on December 31, 2019, in Wuhan, Hubei Province, China [1]. Cardiac involvement can occur in COVID-19, with systemic inflammatory response, adrenergic stimulation, hypoxia, hypotension, myocardial damage, and microthrombogenesis playing roles in its pathophysiology [2]. Additionally, studies have shown that COVID-19 can lead to arrhythmias, cardiac block, myocarditis, cardiac failure, and sudden death [3,4].

Recent studies suggest that the Index of Cardiac Electrophysiological Balance (ICEB), measured by QTc/QRS, and the left ventricular repolarization transmural dispersion (TDR), measured by T peak to end (Tp-e) and Tp-e/QTc, are associated with the risk of malignant arrhythmias and sudden death [4-7]. ICEB, a new noninvasive marker, can predict the risk of malignant ventricular arrhythmias and is considered equivalent to the cardiac wavelength λ (effective refractory period × conduction velocity). Consequently, both increased and decreased ICEB values are linked to the risk of ventricular arrhythmia [8].

Arrhythmias are a common cause of death in critically ill COVID-19 patients. A study comparing intensive care unit (ICU) patients with non-ICU patients found a two-fold higher rate of arrhythmic events in the ICU group [9]. Therefore, our study aimed to evaluate ventricular repolarization parameters that predict the risk of malignant arrhythmia and sudden death in COVID-19 patients who developed systemic inflammatory response syndrome (SIRS).

Material and Methods

Our study is a single-center retrospective analysis. We excluded patients with negative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) results, complete or incomplete bundle branch block, pre-excitation syndrome, AV block, pacing rhythm, atrial fibrillation, and those using medications that prolong the QT interval before admission. After applying these exclusion criteria, 533 out of 980 patients diagnosed with SARS-CoV-2 at our hospital between August 20, 2020, and October 20, 2020, were included in the study (Figure 1). Among these, 197 patients developed systemic inflammatory response syndrome (SIRS), and 336 did not. All COVID-19 diagnoses were confirmed using RT-PCR tests from nasopharyngeal swabs. SIRS was defined as the presence of at least two of the following criteria: temperature >38°C or <36°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or PaCO2 <32 mm Hg, WBC >12,000/mm^3 or <4,000/mm^3, or >10% bands [10]. Myocardial damage was defined as having at least one cardiac troponin value above the 99th percentile upper reference limit [11]. Baseline clinical characteristics, including age, gender, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, chronic renal failure (CRF), and heart failure, were obtained from hospital and Ministry of Health databases. Approval for our study was obtained from the ethics committee of University of Health Sciences Diyarbakır Gazi Yaşargil Education and Research Hospital. 02/07/2021/84). Our study protocol adheres to the Declaration of Helsinki.

/Electrocardiogram Examinati/on

Electrocardiograms (ECGs) for the COVID-19 patients involved in the study were obtained after hospitalization and before the initiation of treatment. Recordings were performed using a 12-lead ECG device (Nihon Kohden, Tokyo, Japan) at a speed of 25 millimeters/second and a calibration of 10 millimeters/millivolt. All ECGs were transferred to a computer and evaluated by two cardiologists using Adobe Photoshop software at 400% magnification. In cases of disagreement, a third cardiologist was consulted to reach a consensus. All measurements were done manually.

The QT interval was measured in milliseconds from the beginning of the QRS complex to the end of the T wave, defined as the point where the tangent of the isoelectric line intersects with the maximal downward slope of the T wave. When U waves were present, the end of the T wave was defined as the nadir of the curve between the T and U waves. The longest QT interval was used for measurements, taken from leads V5 and DII. The QRS duration was calculated in milliseconds from the beginning of the Q or R wave to the end of the R or S wave. The Tp-e interval was measured in milliseconds from the peak of the T wave to its end. QT intervals were corrected using the Bazett formula (QTc = QT/√RR) and recorded as QTc. These measurements were used to calculate the Tp-e/QTc, Tp-e/QT, QTc/QRS (ICEBc), and QT/QRS ratios.

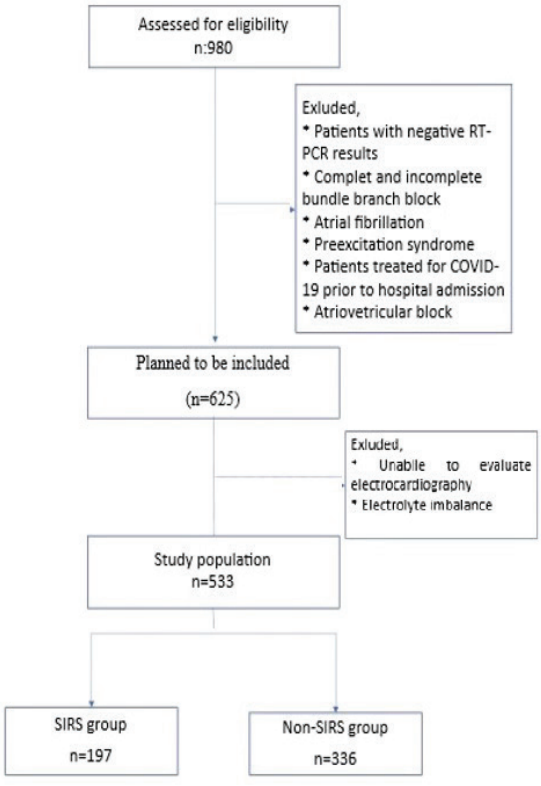

Figure 1. Flowchart of patient selection.

Statistical Analysis

Constant variables were presented as median values with interquartile ranges (IQRs) (25–75%) due to their non-normal distribution. Normality of the data was assessed using histograms and the Shapiro-Wilk test. Categorical variables were expressed as percentages. Comparisons of continuous variables were performed using the Mann-Whitney U test, while categorical variables were compared using the chi-square test or Fisher's exact test. Multivariable linear regression analysis was used to evaluate the relationship between ICEBc and clinical variables, including age, gender, potassium levels, corrected calcium levels, SIRS, congestive heart failure (CHF), myocardial injury, beta-blocker use, chronic renal failure (CRF), and C-reactive protein (CRP). Receiver operating characteristic (ROC) curve analysis was conducted to determine the area under the curve (AUC) for ICEBc and QTc in predicting in-hospital mortality. A p-value <0.05 was considered statistically significant for all analyses. Data were analyzed using SPSS version 24 (Statistical Package for the Social Sciences for Windows).

Results

A total of 533 COVID-19 patients were included in the study, with 197 patients in the SIRS group and 336 in the non-SIRS group. The mean age of the study population was 62 years (range: 49-72), and 49% (261) were female. Demographic, clinical, and laboratory parameters are summarized in Table 1.

There were no significant differences between the two groups regarding age, gender, hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease. However, myocardial damage ($p < 0.001$) and mortality ($p < 0.001$) were significantly higher in the SIRS group.

Electrocardiographic findings are detailed in Table 2. The QTc interval was significantly prolonged in the SIRS group, with a median of 450 ms (422-474), compared to 427 ms (407-447) in the non-SIRS group ($p < 0.001$). The ICEBc was also significantly higher in the SIRS group at 5.1 (4.65–5.66), compared to 4.98 (4.49–5.45) in the non-SIRS group ($p = 0.004$). The Tp-e interval and QRS duration were not statistically significant between the groups (p-values of 0.963 and 0.460, respectively). The Tp-e/QTc ratio was substantially lower in the SIRS group [0.186 (0.164-0.208)] compared to the non-SIRS group [0.194 (0.175-0.220)] ($p < 0.001$).

Table 1. Demographic characteristics, clinical and laboratory findings of the patients.				
	Total (n=533)	SIRS (n=197)	Non SIRS (n=336)	p
Age, years	62 (49-72)	65 (53-73)	46 (60-71)	0.110
Gender (female), n (%)	261 (49)	84 (43)	178 (53)	0.210
Hypertension, n (%)	197 (39)	84 (43)	123 (37)	0.168
Diabetes mellitus, n (%)	140 (26)	59 (30)	81 (24)	0.139
Chronic renal failure, n (%)	23 (4)	17 (9)	6 (2)	<0.001
Congestive heart failure, n (%)	18 (3)	9 (5)	9 (3)	0.359
Coronary artery disease, n (%)	81 (15)	34 (17)	47 (14)	0.310
COPD, n (%)	24 (5)	8 (4)	16 (5)	0.465
Myocardial injury, n (%)	33 (6)	24 (12)	9 (3)	<0.001
Mortality, n (%)	110 (21)	90 (46)	20 (6)	<0.001
Beta blocker use, n (%)	69 (13)	34 (17)	35 (10)	0.024
ICU admission, n (%)	140 (26)	111 (56)	29 (9)	<0.001
Loop diuretic use, n (%)	11 (2)	3 (2)	8 (2)	0.754
Temperature, °C	36.7 (36.4-36.9)	36.8 (36.4-37.3)	36,6 (36.4-36.8)	<0.001
Systolic blood pressure, mmHg	120 (110-130)	120 (110-130)	120 (110-125)	0.151
Diastolic blood pressure, mmHg	70 (65-80)	70 (67-80)	70 (60-80)	0.053
White blood cell, 10^3/µL	6.94 (5.19-9.51)	7.96 (4.86-12,7)	6.59 (5.25-8.43)	<0.001
Neutrophil, 10^3/µL	5.18 (3.52-7.8)	6,58 (3.7-1.71)	4,.8 (3.52-6.59)	<0.001
Lymphocyte, 10^3/µL	1.1 (0.78-1.44)	0.96 (0.69-1.24)	1.21 (0.87-1.52)	<0.001
Hemoglobin, g/dL	13.3 (12.2-14.4)	13.1 (12-14.4)	13.4 (12.4-14.4)	0.703
C-reactive protein, mg/L	80 (35.9-129.4)	105 (48.5-168.7)	65.1 (28.3-113.4)	<0.001
NLR	4.5 (2.8-8.6)	6.3 (3.7-11.7)	3.9 (2.6-6.6)	<0.001
Procalsitonin, ng/mL	0.11 (0.05-0.27)	0.18 (0.07-0.59)	0.1 (0.04-0.18)	<0.001
Ferritin, ng/mL	218 (424-839)	625 (261-1153)	371 (191-653)	<0.001
D-dimer, ng/mL	274 (168-443)	352 (204-680)	240 (162-351)	<0.001
Creatinine, mg/dl	0.91 (0.76-1.18)	0.97 (0.77-1.41)	0.9 (0.75-1.11)	0.008
Albumin, g/L	33 (29-36)	31 (28-35)	34 (31-37)	<0.001
Aspartate aminotransferase, IU/l	32 (23-47)	37 (24-50)	29 (23-45)	0.030
Alanine aminotransferase, IU/	24 (17-39)	28 (18-43)	22 (16-36)	0.060
Potassium, mmol/L	4.14 (3.82-4.49)	4.13 (3.79-4.52)	4.14 (3.84-4.45)	0.832
Correct calsium, mmol/L	8.74 (8.40-9.10)	8.78 (8.36-9.12)	8.71 (8.40-9.09)	0.816
Abbrev.: COPD; chronic obstructive pulmonary disease, NIRL; neutrophil lymphocyte ratio, ICU: Intensive care unit				

Table 2. Electrocardiographic findings of patients.				
	Total (n=533)	SIRS (n=197)	Non SIRS (n=336)	p value
Heart rate, beat/min	92 (82-100)	98 (93-106)	86 (78-96)	<0.001
QRS duration, ms	85 (80-96)	86 (80-100)	85 (80-95)	0.460
QT interval, ms	360 (330-380)	346 (320-380)	360 (340-380)	0.020
QTc interval, ms	435 (413-458)	450 (422-474)	427 (407-447)	<0.001
QT/QRS ratio (İCEB)	4.00 (3.65-4.45)	4.00 (3.60-4,46)	4.10 (3.75-4.50)	0.022
QTc/QRS ratio (İCEBc)	5.02 (4.56-5.50)	5.10 (4.65-5.66)	4.98 (4.49–5.45)	0.004
Tp-e interval	80 (80-94)	80 (80-95)	80 (80-93)	0.963
Tp-e/QT ratio	0.235 (0.211-0.264)	0.236 (0.213-0.267)	0.234 (0.210-0.263)	0.162
Tp-e/QTc ratio	0.192 (0.171-0.215)	0.186 (0.164-0.208)	0.194 (0.175-0.220)	<0.001

Multivariable linear regression analysis indicated a significant relationship between ICEBc and SIRS, age, gender, and CRP, with the following results: β = 2.372 (95% CI: 0.028-0.302, p = 0.024), β = 2.265 (95% CI: 0.001-0.009, p = 0.024), β = 2.079 (95% CI: 0.008-0.270, p = 0.018), and β = 2.077 (95% CI: 0.001-0.002, p = 0.038), respectively (Table 3).

Table 3. Multivariable linear regression analysis between the ICEBc (QTc/QRS) and clinical variable.

	β-coefficient	CI 95%	P value
Age (year)	2.265	0.001-0.009	0.024
Gender (female)	2.079	0.008-0.270	0.018
CHF	-0.718	-0.520-0.240	0.473
CRP	2.077	0.001-0.002	0.038
SIRS	2.372	0.028-0.302	0.018
Myocardial injury	0.560	-0.193-0.347	0.575
CAD	1.446	-0.550-0.364	0.149
Beta blocker	-0.220	-0.243-0.194	0.830
Corected Calcium(mg/dL)	-1.345	-0.192-0.360	0.830
Potassium (mmol/L)	0.811	-0.073-0.175	0.418
CRF	0.723	-0.205-0.444	0.470

Abbrev.: CAD: Coronary artery disease, CHF: chronic heart failure, CRP: C-reactive protein, CRF: chronic renal failure, CI: Confidence interval, SIRS: Systemic inflammatory response syndrome

ROC curve analysis for ICEBc in predicting in-hospital mortality showed an optimal cut-off value of 4.99, with an area under the curve (AUC) of 0.598 (95% CI: 0.538-0.657, p = 0.002). This cut-off value had 64.5% sensitivity and 50.4% specificity. For QTc, the ROC analysis identified a cut-off value of 436 ms, with an AUC of 0.574 (95% CI: 0.514-0.634, p = 0.017), and 56.4% sensitivity and 53.9% specificity (Table 4, Figure 2).

Ventricular arrhythmia, including ventricular fibrillation, was observed in a total of 18 patients, with 14 in the SIRS group and 4 in the non-SIRS group.

Table 4: Receiver operating characteristic (ROC) curve comparison of ICEBc and QTc interval predicting in-hospital mortality COVID-19

RİSK FACTOR	AUC (95%)	Cut off	p	Sensitivity (%)	Specificity(%)
In-hospital mortality					
ICEB	0.598 (0.538-0.657)	4.99	0.002	64.5	50.4
QTc interval, ms	0.574 (0.514-0.634)	436	0.017	56.4	53.9

Area Under the ROC curve (AUC), sensitivity and specificity by the optimized Cutoff points for ICEB and QTc interval predicting in-hospital mortality

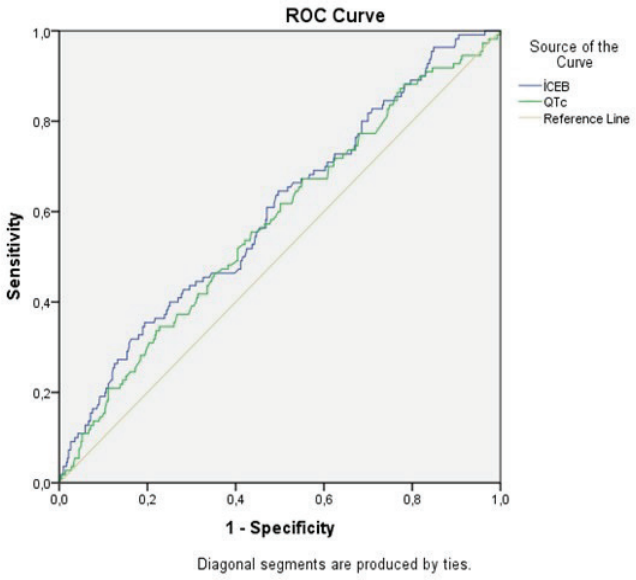

Figure 2. ROC curve analysis for ICEBc and QTc interval to predict in-hospital mortality (Area Under the ROC curve (AUC), sensitivity and specificity by the optimized Cutoff points for ICEBc and QTc interval predicting in-hospital mortality).

Discussion

To our knowledge, this is the first study to evaluate the effect of systemic inflammatory response syndrome (SIRS) on ventricular repolarization parameters during hospitalization in COVID-19 patients. Our main finding is that both ICEBc and QTc intervals were significantly higher in the SIRS group compared to the non-SIRS group. Additionally, SIRS, age, gender, and C-reactive protein (CRP) levels were significantly associated with ICEBc in the multivariable linear regression analysis.

Arrhythmias in COVID-19 patients are related to disease severity and systemic inflammation. A previous study reported malignant ventricular arrhythmias in 16.6% of hospitalized patients and 44.4% of ICU patients [12]. CRP and the neutrophil-to-lymphocyte ratio (NLR) are key indicators of systemic inflammation in COVID-19 [13]. Systemic inflammation can lower the arrhythmogenic threshold in susceptible patients. Our study found higher CRP and NLR levels in the SIRS group. Although COVID-19 can induce severe immune responses, systemic inflammation independently contributes to QTc prolongation [14-16]. Cytokines affect the action potential by altering calcium and potassium channel expression and

function [17]. Increased pro-inflammatory cytokines during SIRS may prolong QTc through myocardial damage [18]. Notably, every 10 ms of QTc prolongation is associated with an 8.3% increase in mortality [19]. Our findings align with this, as QTc was significantly prolonged in the SIRS group.

In cardiac electrophysiology, the repolarization phase of the action potential is crucial for predicting ventricular arrhythmia risk. ICEB, a novel parameter representing the balance between ventricular depolarization and repolarization, provides additional information beyond traditional ECG parameters like QT and QTc intervals [20]. ICEB has been shown to be a useful marker for predicting ventricular arrhythmia and sudden death [21]. Increased ICEB is associated with torsades de pointes, while decreased ICEB is linked to ventricular tachycardia or fibrillation. The distribution of ventricular repolarization, as reflected by ICEB, is associated with malignant arrhythmias and sudden cardiac death [22]. The Tp-e interval, indicating transmural dispersion of ventricular repolarization, predicts arrhythmias and sudden death even in patients with normal QTc intervals [23]. Yenerçağ et al. and Öztürk et al. observed increased transmural dispersion in recently diagnosed COVID-19 patients compared to healthy controls [4,25]. Alareedh et al. found lower TDR in COVID-19 patients compared to non-SIRS groups, with higher ICEB in critical cases [26].

In our study, Tp-e and Tp-e/QTc were lower in the SIRS group compared to the non-SIRS group. Other studies typically compared COVID-19 patients to healthy controls, with COVID-19 patients in our study showing higher Tp-e values than those reported for healthy controls [4,25,27]. Although Tp-e values were not statistically significant between groups in our study, the lower Tp-e/QTc ratio in the SIRS group suggests that QTc increases more than Tp-e in severe inflammation. This finding may explain the higher mortality and more severe disease course observed in the SIRS group.

Shaghee et al. reported QTc sensitivity and specificity for predicting in-hospital mortality as 70% and 32%, respectively, while ICEB had 70% sensitivity and 33% specificity [28].In our study, ICEBc had 64.5% sensitivity and 50.4% specificity, and it was a better predictor of in-hospital mortality compared to QTc. The higher ICEB in the SIRS group underscores its potential role in understanding the mechanisms leading to sudden cardiac death and ventricular arrhythmia in COVID-19 patients with SIRS.

Limitation of the study

The primary limitation of this study is its retrospective design. Additional limitations include the absence of pre-COVID-19 ECG data for patients and the reliance on manual rather than computer-assisted measurements. Furthermore, the potential for electrolyte imbalances in patients with SIRS and the pro-arrhythmic effects of antibiotics administered during treatment are also limitations of this study.

In conclusion, CEBc and QTc intervals were significantly higher in COVID-19 patients with SIRS compared to those without SIRS. Therefore, assessing ICEBc and QTc, which are associated with malignant ventricular arrhythmias on ECG, may aid in predicting and preventing arrhythmic events in patients with SIRS. Our findings also suggest that ICEBc is a better predictor of in-hospital mortality than QTc.

Ethics Approval

The study was approved by the ethics committee of University of Health Sciences Diyarbakır Gazi Yaşargil Education and Research Hospital. 02/07/2021/84).

Conflict of Interest

The authors declare no conflict of interest.

Funding Statement

This research received no external funding.

Authors' contributions

ÖB, MÇ conceived and supervised the study; ET, FI, BA, MO, MZK and HY were responsible for data collection. HA, EE, and ŞK analyzed and interpreted the data. All authors provided comments on the manuscript at various stages of development. All authors read and approved the final manuscript.

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