The Importance of Corrected QT Interval for Predicting of Mortality in Patients with Severe Coronavirus Disease 2019

Şiddetli Coronavirüs Hastalığı 2019 Olan Hastalarda Mortaliteyi Öngörmede Düzeltilmiş QT Aralığının Önemi

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19), which started in Wuhan, China in December 2019, soon turned into a pandemic that severely affected the countries ' health and economic systems. COVID-19 can lead to death, especially in patients with lung involvement and cardiac injury. We aimed to determine whether baseline repolarization parameters provide prognostic information in patients admitted to intensive care unit (ICU) with COVID-19.

Methods: In this retrospective cohort study, we included 135 adult patients (median age 61 years, 52% men, 51% hypertension, 43% diabetes mellitus, 32% coronary artery disease) with confirmed COVID-19 who were followed in the intensive care unit (ICU). Data of patients were extracted from the electrical medical records and compared between the survivors and the non-survivors.

Results: : In follow-up, of whom 80 were discharged, 55 died in hospital. Multivariate logistic regression analysis showed that the corrected QT interval (QTc) longer than ≥457 msn on admission (odds ratio (OR) =6.433, 95% CI 1.539-26.970, p=0.01), the age older than 65 years (OR=2.848, 95% CI: 1.003-8.091, p=0.04) and heart rate greater than 99 bpm (OR=9.180, 95% CI: 3.037-27.749, p=0.0001) were independent risk factors for mortality in hospital. In addition, corrected the peak of T wave to the end of T wave interval (Tpec) was statistically longer in patients who died than those who lived.

Conclusion: The QTc value measured on admission, age and heart rate and can help to predict mortality in hospital. Additionally, Tpec can provide about the risk of mortality in COVID-19 patients.

Key words: Coronavirus disease 2019, mortality, ventricular repolarization

ÖZET

Giriş: Aralık 2019'da Çin'in Wuhan kentinde başlayan Coronavirus 2019 (COVID-19) hastalığı, kısa sürede ülkelerin sağlık ve ekonomik sistemlerini ciddi şekilde etkileyen bir pandemiye dönüştü. COVID-19, özellikle akciğer tutulumu ve kalp hasarı olan hastalarda ölüme neden olabilir. COVID-19 ile yoğun bakım ünitesine (YBÜ) kabul edilen hastalarda başlangıç repolarizasyon parametrelerinin prognostik bilgi sağlayıp sağlamadığını belirlemeyi amaçladık.

Yöntemler: Bu retrospektif kohort çalışmasına, YBÜ'de takip edilen ve doğrulanmış COVID-19'lu 135 yetişkin hastayı (ortanca yaş 61, %52 erkek, %51 hipertansiyon, %43 diabetes mellitus, %32 koroner arter hastalığı) dahil ettik. Hastaların verileri elektronik tıbbi kayıtlarından çıkarıldı ve hayatta kalanlar ile hayatta kalmayanlar arasında karşılaştırıldı.

Bulgular: 80'i taburcu olan hastaların takiplerinde 55'i hastanede öldü. Çok değişkenli lojistik regresyon analizi, kabulde düzeltilmiş QT aralığının (QTc) ≥457 msn'den uzun olduğunu gösterdi (olasılık oranı (OR) =6.433, %95 GA 1.539-26.970, p=0.01), 65 yaşından büyük (OR= 2.848, %95 GA: 1.003-8.091, p=0.04) ve 99 bpm'den yüksek kalp hızı (OR=9.180, %95 GA: 3.037-27.749, p=0.0001) hastanede mortalite için bağımsız risk faktörleriydi. Ayrıca düzeltilmiş T dalgasının sonuna kadar T dalga aralığı (Tpec) ölen hastalarda yaşayanlara göre istatistiksel olarak daha uzundu.

Sonuç: Başvuru, yaş ve kalp hızında ölçülen QTc değeri hastanede mortaliteyi tahmin etmeye yardımcı olabilir. Ayrıca Tpec, COVID-19 hastalarında ölüm riski hakkında bilgi verebilir.

Anahtar Kelimeler: Koronavirüs hastalığı 2019, mortalite, ventriküler repolarizasyon

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has rapidly become a global pandemic after the first cases were reported in Wuhan, Hubei Province, in China on December 2019 (1). Although COVID-19 mainly affects the respiratory system, cardiac injury is also common and is associated with high mortality (2, 3). Hypoxia, myocarditis, ischemia, myocardial strain, intravascular volume imbalances, abnormal host response and side effects of drugs used for COVID-19 may lead to cardiac arrhythmias by causing cardiac injury (4).

Abnormal increases in repolarization heterogeneity may cause life-threatening ventricular arrhythmias and sudden cardiac death (SCD) (5-6). Ventricular repolarization heterogeneity can be evaluated with surface ECG parameters such as QT interval (QT), corrected QT interval (QTc), dispersion of QT interval (QTd), the peak and the end of the T wave interval (Tpe) and corrected the peak and the end of the T wave interval (Tpec). Previous studies showed that increase in QT, QTc, QTd, Tpe and Tpec is associated with increased risk of ventricular arrhythmias and SCD (7-9). In patients with COVID-19, cardiac injury and antiviral drug-related QT/QTc prolongation may increase mortality (10-12).

In this study, we sought to study whether baseline repolarization parameters provide prognostic information in patients admitted to intensive care unit (ICU) with COVID-19.

METHODS

Study Population

This is a retrospective observational cohort study. We studied patients with COVID-19 admitted to our intensive care unit (ICU) between dates 18 March 2020 and 30 August 2020. COVID-19 diagnosis was confirmed by real-time reverse-transcriptase polymerase chain reaction (PCR) on nasopharyngeal swabs. A low dose computerized tomography (CT) of thorax revealed lung lesion typical for COVID-19 in all patients. Patients who had ECG at or near to the time of their admission were included in our study.

During the study period, 335 patients with COVID-19 were admitted to our ICU. Among 335 patients with COVID-19, 255 patients (76%) had an ECG on the first day of hospitalization. 3 patients with cardiac pacemaker, 105 patients taking drugs that prolong QT interval (including hydroxychloroquine and azithromycin), and 12 patients with low ejection fraction (EF) at the time of admission were excluded from the study. Finally, remaining 135 patients constituted our study population. Data from patients who survived (the survivor group) were compared with data from patients who died (the non-survivor group) during hospitalization. Patient data were retrieved from the electronic hospital and national health registry database. All data were checked by two physicians (OP and BP). All patients received standard treatment protocols for COVID-19 as proposed by the National Department of Health. All surviving patients were seen at our outpatient clinic for the follow-up. This study was approved by local ethics committee and Ministry of Health Scientific Research Platform.

Electrocardiography

ECGs that were taken on the first day of hospitalization were used for evaluation for all patients. All measurements were performed by two independent investigators (OP and OK), who were blinded as to the clinical status of the patients. In case of disagreement between the ECG measurements of the investigators, it was resolved by consensus. PR interval, RR interval, QRS duration, QT interval, and Tpe interval were measured manually by using EP calipers application (© 2015 – 2020 EP Studios, Inc.). PR interval was defined as the time from the onset of P wave to the onset of

Table 1. Baseline Clinical Characteristics of Patients, Overall and by Survival Status

Variables		All (n=135)	Survivor (n=80)	Non-survivor (n=55)	*Odds Ratio*	*95% CI*	*p value*
Preoperative							
Age, n (%)	**<65**	73 (54.1%)	54 (67.5%)	19 (34.5%)	3.935	1.903-8.137	**<0.001**
	≥65	62 (45.9%)	26 (32.5%)	**36 (65.5%)**			
Sex, n (%)	**female**	65 (48.1%)	38 (47.5%)	27 (49.1%)	0.938	0.472-1.865	0.856
	male	70 (51.9%)	42 (52.5%)	28 (50.9%)			
CHF, n (%)	**Yes**	4 (3.0%)	1 (1.3%)	3 (5.5%)	0.219	0.022-2.167	0.157
	No	131 (97.0%)	79 (98.7)	52 (94.5%)			
CAD, n (%)	**Yes**	43 (31.9%)	20 (25.0%)	**23 (41.8%)**	0.464	0.222-0.969	**0.039**
	No	92 (68.1%)	60 (75.0%)	32 (58.2%)			
HT, n (%)	**Yes**	69 (51.1%)	28 (35.0%)	**41 (74.5%)**	0.184	0.086-0.394	**<0.001**
	No	66 (48.9%)	52 (65.0%)	14 (25.5%)			
HL, n (%)	**Yes**	41 (30.4%)	21 (26.3%)	20 (36.4%)	0.623	0.297-1.308	0.209
	No	94 (69.6%)	59 (73.8%)	35 (63.6%)			
DM, n (%)	**Yes**	58 (43.0%)	26 (32.5%)	**32 (58.2%)**	0.346	0.170-0.705	**0.003**
	No	77 (57.0%)	54 (67.5%)	23 (41.8%)			
Smoking, n (%)	**Yes**	43 (31.9%)	24 (30.0%)	19 (34.5%)	0.812	0.390-1.690	0.578
	No	92 (68.1%)	56 (70.0%)	36 (65.5%)			
ACEIs./ARBs, n (%)	**Yes**	56 (41.5%)	26 (32.5%)	**30 (54.5%)**	0.401	0.198-0.814	**0.011**
	No	79 (58.5%)	54 (67.5%)	25 (45.5%)			
Beta blockers, n (%)	**Yes**	43 (31.9%)	23 (28.8%)	20 (36.4%)	0.706	0.340-1.469	0.351
	No	92 (68.1%)	57 (71.3%)	35 (63.6%)			
	No	129 (95.5%)	77 (96.3%)	52 (94.5%)			
	No	127 (94.1%)	77 (96.3%)	50 (90.9%)			

Abb. CI, *confidence interval;* ***CHF****, congestive heart failure;* ***CAD****, coronary artery disease;* ***HT****, hypertension;* ***HL****, hyperlipidemia;* ***DM****, diabetes mellitus;* ***ACEIs/ARBs****, Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers*

QRS. The onset of QRS wave was defined as first visible deflection from baseline and the end of QRS wave defined as return to baseline. QT interval was defined as the time from the onset of the QRS to the point at which T wave returns to baseline. QTc interval was calculated by using the Bazett's formula (13). QTd was calculated by subtracting the shortest QT value from the longest QT value, which was measured in all derivations on a 12-channel ECG. Tpe interval was measured from the peak of T wave to the end of T wave in leads V_2 to V_5 and these values were averaged. The end of the T was defined as intersection of tangent to the downslope of T wave and isoelectric line. Tpec was also calculated by using the Bazett's formula (13).

Statistical analysis

All statistical analyses were performed using SPSS 23.0 Statistical Package Program for Windows (SPSS Inc. Chicago, IL, USA). Continuous variables were characterized by using mean, maximum and minimum values, and percentage values were used for categorical variables. Normal distributions were expressed as mean ± SD and Student t-test was used for comparisons between groups. Pearson chi-square test was used to analyze qualitative variables. Nonparametric continuous variables were expressed as median and intermittent distributions and were compared using Mann-Whitney U tests. $p < 0.05$ value was accepted statistically significant. Parametric and nonparametric values were compared for patients who developed mortality in hospital. ECG values were evaluated with ROC curves, and areas below the curve (area under curve=AUC) were evaluated. In multi-variable analysis, the evaluation was carried out by only

Table 2. On Admission Electrocardiographic Characteristics of Patients Hospitalized Overall and by Survival Status

Variables	Mean±SD	Survivor (n=80)	Non-survivor (n=55)	*p value*
Heart rate, bpm±SD	92.7±23.1	86.2±16.8	102.2±27.5	**<0.001**
QRS, msn±SD	105.0±20.2	103.2±17.5	107.6±23.6	0.600
QT interval, msn±SD	376.6±51.9	378.5±50.0	373.8±54.8	0.601
QTc, msn±SD	454.9±42.1	446.7±35.9	467.0±40.6	**0.001**
QTd, msn±SD	78.5±26.9	76.9±25.1	80.8±29.3	0.566
Tpe interval, msn±SD	90.9±14.0	90.7±13.8	91.3±14.4	0.791
Tpec, msn±SD	111.4±19.9	107.7±16.6	116.6±22.9	**0.011**
Variables	**Total**	**Survivor (n=80)**	**Non-survivor (n=55)**	***p value***
Atrial fibrillation or flutter,n(%)	6	3 (3.7%)	3 (5.5%)	0.637
Atrial premature contractions(%)	8	3 (3.8%)	5 (9.1%)	0.197
Ventricular premature contractions(%)	16	6 (7.5%)	10 (18.2%)	0.101

Abb. QTc, corrected QT interval; QTd, QT dispersion, Tpec, corrected Tpe interval

using variables which were statistically demonstrated to have an effect on mortality in single-variable analysis, and which were significant in terms of threshold values. Finally, independent risk factors were determined.

RESULTS

80 patients (59.3%) survived and constituted our "survivor group" and 55 (40.7%) patients who died during hospitalization constituted our "non-survivor group". Baseline clinical characteristics of the groups are shown in the Table 1.

Mortality rate was higher in patients over 65 years of age (OR=3.935, 95%CI: 1.903-8.137, p<0.001). Mean age was significantly higher in the non-survivor group (65.0±15.5 vs 57.8±15.4, p=0.005). Moreover, HT (OR=0.184, 95%CI: 0.086-0.394, p<0.001), CAD (OR=0.464, 95%CI: 0.222-0.969, p=0.03), DM (OR=0.346, 95%CI: 0.170-0.705, p=0.003) and ACEIs/ARBs drug use (OR=0.401, 95%CI: 0.198-0.814, p=0.01) were significantly higher in the non-survivor group.

Heart rate (102.2±27.5 vs 86.2±16.8, p <0.001), QTc (467.0±40.6 vs 446.7±35.9, p = 0.001) and Tpec (116.6±22.9 vs 107.7±16.6, p = 0.01) were higher in the non-survivor group. QRS duration (107.6±23.6 vs 103.2±17.5, p=0.600), QT (373.8±54.8 vs 378.5±50.0, p=0.601), QTd (80.8±29.3 vs 76.9±25.1, p=0.566) and Tpe (91.3±14.4 vs 90.7±13.8, p = 0.791) values were similar between the groups (Table 2).The relationship between hospitalization ECG data and mortality was considered in conjunction with ROC analysis (Table 3).

Table 3. Results obtained after examining the reliability of admission ECG data in predicting mortality with ROC curves

	AUC	95% CI	Cutoff	Sensitivity	Specificity	p value
HR	0.695	0.610-0.772	99	56.3%	84.8%	**<0.0001**
QRS	0.527	0.438-0.614	126	20.3%	93.6%	0.608
QT	0.527	0.439-0.613	343	36.3%	75.9%	0.613
QTc	0.667	0.580-0.746	457	67.2%	69.6%	**0.0006**
QTd	0.529	0.441-0.616	90	38.1%	70.8%	0.569
Tpe	0.513	0.426-0.601	101	23.6%	83.5%	0.793
Tpec	0.630	0.542-0.711	112	60.0%	64.5%	**0.009**

ROC analizi.
***Abb. AUC**, Area Under Curve; **CI**, Confidence interval;*
***QT,** QT interval; **QTc**, corrected QT interval; **QTd**, QT dispersion; **Tpe**, Tpe interval, **Tpec**, corrected Tpe interval; **HR**, heart rate.*

ECG parameters that predict mortality were QTc interval (p=0.0006) and heart rate (p<0.0001). Tpec interval (P=0.009) QRS, QT, QTd, and Tpe interval were not significant in predicting mortality. Patients with values higher than and lower than the threshold value were grouped separately by using the cut-off values

determined for ECG parameters which proved to be significant predictors of mortality (Table 4). After grouping all significant predictors (heart rate, QTc, Tpec) determined in Tables 3 and 4, mortality was found to be higher in patients with higher values than the threshold values for all these parameters.

Table 4. Comparison of mortality rates using threshold values determined in Roc analysis of parameters determined to be significant predictors for mortality

	Mortality Rate	Odds Ratio	95% CI	p value
Heart rate				
<99 (n=92)	24 (26.1%)	7.319	3.247-16.499	**<0.001**
≥99 (n=43)	31 (72.1%)			
QTc				
<457 (n=74)	18 (24.3%)	4.796	2.291-10.041	**<0.001**
≥457 (n=61)	37 (60.7%)			
Tpec				
<112 (n=71)	21 (29.6%)	2.698	1.330-5.476	**0.005**
≥112 (n=64)	34 (53.1%)			

Abb. CI, *confidence interval****; QTc****, corrected QT interval;* ***Tpec****, corrected Tpe interval*

A multivariate analysis was done by using the demographic parameters (age, CAD, HT, DM, ACE/ARB usage), and ECG parameters (heart rate, QTc, and Tpec) that significantly affect mortality. By using our multivariate analysis model, age older than 65 years (OR=2.848, 95% CI: 1.003-8.091, p=0.04), heart rate greater than 99 bpm (OR=9.180, 95% CI: 3.037-27.749, p=0.0001) and QTc longer than 457 msec (OR=3.314, 95% CI: 1.265-8.679, p=0.01) were found to be independent risk factors for mortality (Table 5).

DISCUSSION

The main finding of our study is that baseline QTc longer than 457 msec, heart rate greater than 99 bpm and age older than 65 years are independent risk factors for mortality in adult COVID-19 patients admitted to ICU. To the best of our knowledge, our study is the first relatively large study in which ventricular repolarization was evaluated with QTc, QTd, Tpe and Tpec in critical COVID-19 patients. We found that patients with a baseline QTc longer than 457 msec measured at the time of admission have 3.3 fold higher risk of mortality during hospitalization. Our finding of the close association of QTc with mortality is an important finding. We provide a unique QTc cut-off value for the first time.

Table 5. Multivariate Logistic Regression Analysis for mortality

Variables	Odds Ratio	95% CI	p value
Age range	2.848	1.003-8.091	**0.04**
CAD	0.863	0.282-2.639	0.797
HT	3.275	0.831-12.904	0.08
DM	2.003	0.750-5.345	0.165
ACEIs/ARBs	0.667	0.172-2.587	0.558
Heart Rate ≥99	9.180	3.037-27.749	**0.0001**
QTc ≥457	3.314	1.265-8.679	**0.01**
Tpec ≥112	1.226	0.461-3.261	0.682

Abb. CI, *confidence innterval;* ***CAD,*** *coronary artery disease;* ***HT****, hypertension;* ***DM****, diabetes mellitus;* ***ACEIs/ARBs****, Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers;* ***QTc****, corrected QT interval;* ***Tpec****, corrected Tpe interval.*

Cardiac arrhythmias are common in critically ill COVID-19 patients. Cardiac injury secondary to hypoxia, myocarditis, ischemia, myocardial strain, intravascular volume imbalances, abnormal host response, ACE2-receptors downregulation and side effects of drugs used for COVID-19 may be responsible for the development of arrhythmias (4). Guo et. al. reported the incidence of malignant arrhythmia including ventricular tachycardia and fibrillation in hospitalized patients as 5.9% (3). Some outpatient COVID-19 patients with mild symptoms found dead at home while in quarantine (14). These deaths may be SCD secondary to COVID-19 (14). QTc, QTd, Tpe and Tpec are used for ventricular repolarization evaluation and may predict malignant ventricular arrhythmia development and SCD (7-9). We used QTc, QTd, Tpe and Tpec to evaluate ventricular repolarization. Furthermore, we also determined that prolonged Tpec is associated with increased the risk of mortality in severe COVID-19 patients. Bertini et. Al.

have reported significantly prolonged QTc on admission ECG in older COVID-19 patients (15). In addition, in a study involving 756 patients, prolonged QT was more common in the group of patients who died (16). Hypoxia that occurs in severe COVID-19 patients can activate anaerobic glycolysis, reduce intracellular pH, and thus increase cytosolic calcium levels. As a result, it may lead to early and late depolarizations, as well as causing temporal changes in action potential duration (17). In addition, the increase in extracellular potassium levels caused by hypoxia reduces the depolarization threshold and accelerates electrical conduction (17). Furthermore, during myocarditis which is a common finding in COVID-19 patients, viral and host factors can lead to structural and electrophysiological remodeling, which can cause abnormal calcium processing and down-regulation of potassium channels, leading to prolonged repolarization and abnormal conduction (18). Another mechanism for the prolongation of the ventricular action potential is that cytokines including interleukin (IL) 6, tumor necrosis factor-a, and IL-1 that increase along with inflammation can affect the function and expression of potassium and calcium channels (19). We consider that Tpec can identify COVID-19 patients with a high risk of death and ventricular arrhythmic events.

Increased heart rate is a common finding during a systemic infection. Heart rate increases as a response to inflammation and infection, especially in patients with increased fever. In general, there is a linear relationship between fever and infection severity, as the severity of infection increases, the heart rate also increases (20). COVID patients that admitted to ICU frequently have advanced degree of lung involvement and pneumonia (21). Furthermore, these patients have low oxygen saturation. This is another mechanism of increased heart rate. Zhao et al. have reported that increased heart rate was an independent risk factor for mortality in critically COVID-19 illness (22). Similarly, we found that mortality is increased 9.9 fold in patients with heart rate greater than 99 bpm at the time of admission.

Previous studies on COVID-19 have reported that older age is an independent predictor of mortality (23, 24)**.** In our study, we found that age older than 65 years is associated with 2.8 fold increase in mortality. It has been reported that, T cell and B cell functions and overproduction of Type 2 cytokines can drive to longer-term proinflammatory responses and lead to a lack of control of viral replication and is associated with potentially poor outcomes in older patients with infectious diseases (25). Furthermore, the prevalence of comorbidities like CAD, HT, and DM is higher in older patients (26). Previous studies showed that CAD, HT, and DM are related to increased mortality in COVID-19 (27-29). Similarly, our study showed that CAD, HT and DM have also been found to be associated with increased mortality.

Our study has some limitations. First, given that not all patients had previous ECGs, we were unable to compare the presentation ECG with previous ECGs to assess the presence of new findings. Second, echocardiographic evaluation was not possible for most patients due to viral exposure. The measured values, especially the EF, were not included in the study because they were also suboptimal. Finally, our study is a retrospective study, and larger and prospective studies are needed to determine the effect of ventricular repolarization parameters on predicting mortality in critical COVID-19 patients.

CONCLUSION

We found that the prolonged QTc on admission ECG is an independent predictor of mortality. Furthermore, older age and heart rate are also independent predictors of mortality in these patients.

Conflict of Interest: There are no conflicts of interest to declare.

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