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Predictive value of Tp-e interval, Tp-e/QT, and Tp-e/QTc for disease severity in patients with liver cirrhosis

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Abstract. – OBJECTIVE: The cardiovascular system is one of the most affected systems in the liver cirrhosis (LC) process, especially due to the tendency to arrhythmia. Since the data about the relationship between LC and novel electrocardiography (ECG) indexes are lacking, we aimed to investigate the association between LC and Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio.

PATIENTS AND METHODS: The study included 100 patients in the study group (56 male, median age 60) and 100 in the control group (52 female, 60 median age) between January 2021 and January 2022. ECG indexes and laboratory findings were analyzed.

RESULTS: The patient group had significantly higher heart rate (HR), Tp-e, Tp-e/QT, and Tp-e/QTc compared to the control group ($p < 0.001$ for all). There was no difference in terms of QT, QTc, QRS (depolarization of ventricles, involving Q, R, and S waves on ECG) duration, and ejection fraction between the two groups. Kruskal-Wallis test results revealed that there was a significant difference between Child stages in terms of HR, QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc, and QRS duration. There was also a significant difference between the model for end-stage liver disease (MELD) score groups in terms of all these parameters except for Tp-e/QTc. In the ROC analyses of Tp-e, Tp-e/QT and Tp-e/QTc to predict the Child C, the AUC values were 0.887; (95% CI: 0.853-0.921), 0.730; (95% CI: 0.680-0.780), and 0.670; (95% CI: 0.614-0.726), respectively. Similarly, AUC values for the MELD score > 20 were 0.877; (95% CI: 0.854-0.900), 0.935; (95% CI: 0.918-0.952), and 0.861; (95% CI: 0.835-0.887); ($p < 0.001$ for all).

CONCLUSIONS: Tp-e, Tp-e/QT, and Tp-e/QTc values were significantly higher in patients with LC. These indexes can be useful for arrhythmia risk stratification and to predict the end-stage of the disease.

Key Words:
Liver cirrhosis, Arrhythmia, Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio.

Introduction

Liver cirrhosis (LC) is a characteristic result of a chronic inflammation due to several infectious, toxic, metabolic, or autoimmune conditions such as viral hepatitis, alcoholism, non-alcoholic steatohepatitis (NASH), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), hemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency[1,2]. LC is still one of the most important causes of mortality and morbidity worldwide. According to the Global Burden of Disease (GBD) report, LC caused more than one million death worldwide in 2010, compared with 676,000 deaths in 1980[3].

LC may lead to many fatal complications such as electrolyte imbalance, spontaneous bacterial peritonitis, hepato-renal syndrome, hepato-pulmonary syndrome, gastroesophageal varice-related or non-related gastrointestinal system bleeding, hepatic encephalopathy, portal hypertension, portal vein thrombosis, and hepatocellular carcinoma[4-8]. It is well known that one of the most affected systems in the LC process is the cardiovascular system, and one of the most affected organs in cardiovascular system disorders is the liver[9]. LC causes increased mortality by affecting the cardiovascular system in many ways such as cardiomyopathy, prolongation of QT duration, arrhythmia, autonomic dysfunction, decreased peripheral vascular resistance, inflammation, and hyperdynamic circulation[10,11]. The presence of cardiomyopathy, remodeling of ion channels, electrolyte imbalance, autonomic nervous system dysfunction, hepatorenal syndrome, and altered liver anabolic and catabolic processes are the main factors increasing the risk of arrhythmia in LC patients[12]. Moreover, the alcohol itself may incre-

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ase sudden cardiac death, especially by triggering ventricular arrhythmias in patients with alcoholic cirrhosis[13].

To date, several studies[14-16] have been conducted investigating the association between LC and arrhythmia, and most of them have focused on prolonging the QT interval (QT). T wave peak-to-end (Tp-e) interval, Tp-e/QT ratio, and Tp-e/QTc are novel electrocardiography (ECG) parameters reflecting cardiac repolarization abnormalities as well as QT and corrected QT interval (QTc). The number of studies[17] showing the relationship between these markers and LC is limited and includes relatively few patients. In our study, we aimed to investigate the association of QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc, and the severity of LC.

Patients and Methods

This single-center, retrospective study was approved by the local Ethics Committee of Kırıkkale University Hospital in terms of compliance with the Helsinki principles (Decision number: 2022.06.19) and informed written consent was obtained from all participants. The study included 100 patients diagnosed with LC and 100 healthy subjects recruited from both the cardiology and gastroenterology outpatient clinics between January 2021 and January 2022. Patients with coronary artery disease, valvular heart disease, atrial fibrillation, uncontrolled hypertension, left/right bundle branch block, ST-T changes on electrocardiography, permanent pacemaker, left ventricular hypertrophy, use of drugs that may a possible effect on QT or Tp-e (except for the propranolol use due to LC), spontaneous bacterial peritonitis, upper gastrointestinal bleeding, hepatocellular carcinoma, sepsis, and chronic inflammatory disease were excluded from the study. The data about patients' demographics, Child stage, medical history, laboratory parameters, radiological, and clinical outcome data were obtained through the electronic patient database.

Clinical Criteria for Diagnosis of Cirrhosis

The diagnosis of LC was made based on a combination of clinical features, blood profile, and radiological imaging. Clinical features were the presence of signs of portal hypertension such as ascites and/or gastrointestinal varices. The blood profile included evidence of thrombocytopenia and/or coagulopathy. Radiological features were a shrunken liver with or without splenomegaly and intra-abdominal varices on imaging with transabdominal ultrasound, MRI, or computed tomography[18-20].

The Child-Pugh classification and the model for end-stage liver disease (MELD) score were used to assess the severity of LC. Child A was defined as mild, Child B as moderate, and Child C as severe LC, respectively[21]. Patients were also classified based on MELD scores as low (< 10), intermediate (10-19), and high (≥ 20)[22].

Echocardiographic Measurements

Standard 2-dimensional echocardiography was performed on all subjects lying in the left lateral decubitus position with a Vivid 7 Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway) using a 3.5-MHz transducer. Echocardiographic measurements were made according to ACC and AHA standard protocols[23]. Two-dimensional and M-mode echocardiography was applied to assess ejection fraction (EF). An EF of less than 50% was defined as heart failure.

Electrocardiography

A 12-lead electrocardiogram with standard chest and limb leads was used to evaluate Tp-e and QTc intervals. The 12- lead ECG was recorded at a paper speed of 50 mm/s in the supine position. The QT interval was measured from the beginning of the QRS complex to the end of the T wave and corrected for heart rate using the Bazett formula: $cQT=QT\sqrt{}$ (R-R interval). Tp-e interval was defined as the interval between the peak and the end of the T wave. Measurements of the Tp-e interval were performed from precordial leads. Tp-e/QTc ratio was calculated from these measurements. Measurements of Tp-e intervals and QTc were calculated by two cardiologists who were blinded to patient data.

Statistical Analysis

SPSS 25.0 (IBM Corp., Armonk, NY, USA) program was used in the analysis of the variables. Quantitative variables with a non-normal distribution were specified as the median (1^{st} quartile/3^{rd} quartile) and categorical variables were specified with the number and percentage values. The normality of the data was evaluated by Shaphiro-Wilk's test. Mann-Whitney U test (for 2 groups) and Kruskal-Wallis' test (for 3 groups) were used for the comparison of non-normal numerical variables between groups. The Chi-square test was used to evaluate the relationship

between categorical variables. The ROC curves were used to determine the cut-off values of Tp-e, Tp-e/QT, and Tp-e/QTc to end-stage LC (Child C or MELD score ≥ 20). A *p*-value of < 0.05 was considered statistically significant.

Results

A total of 200 patients were analyzed in our study, including 108 (54 %) males and 92 (46 %) females with a median age of 61.0 (55.3-69.0) years. The basic demographic profile, ECG, and laboratory findings were presented in Table I. Both groups were similar in terms of gender, age, and smoking status. Fifty (50%) patients were using beta blockers.

Regarding ECG parameters, the patient group had significantly higher heart rate, Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio compared to the control group ($p < 0.001$ for all). However, there was no difference in terms of QT, QTc, QRS duration, and ejection fraction between the two groups. As laboratory findings, international normalized ratio (INR) ($p<0.001$), total protein ($p = 0.005$), aspartate aminotransferase (AST) ($p < 0.001$), total bilirubin ($p < 0.001$), and direct bilirubin ($p < 0.001$) levels were higher whereas hemoglobin ($p < 0.001$), platelet ($p < 0.001$), and albumin ($p < 0.001$) levels were lower in the patient group compared to control group. There was no significant difference in terms of potassium and alanine transaminase (ALT) levels and glomerular filtration rate (GFR) between the two groups.

Table II presents the Kruskal-Wallis's test results of the ECG parameters of the patient group, grouped according to the Child stages and MELD scores. The subgroup analysis demonstrated that there was a significant difference between Child stages in terms of heart rate (A *vs.* C, $p = 0.024$; A *vs.* B, $p = 0.011$; B *vs.* C, $p = 0.77$), QT duration (A *vs.* C, $p = 0.002$; A *vs.* B, $p = 0.13$; B *vs.*

Table I. Basic demographic profile, ECG, and laboratory findings of patients.

	Patient (n=100) Median [25-75%]	Control (n=100) Median [25-75%]	*p*
Age, years	60 (25-82)	60 (27-81)	0.840
Gender, male (%)	56 (56)	52 (52)	0.570
Smoking, n (%)	25 (25)	23 (23)	0.741
ECG parameters			
HR, bpm	82 [71.5-95.5]	72.5 [70-80.5]	**0.001***
QT, ms	391 [364-409]	400 [388-402.5]	0.096
QTc, ms	444 [414.5-480]	443.5 [415-458.5]	0.144
Tp-e, ms	75 [70-85]	60 [55-65]	**0.001***
Tp-e/QT, ms	0.2 [0.19-0.22]	0.16 [0.15-0.17]	**0.001***
Tp-e/QTc, ms	0.17 [0.16-0.19]	0.14 [0.13-0.15]	**0.001***
QRS, ms	85 [80-92]	85 [80-90]	0.919
Ejection fraction, n %	60 [55-60]	58 [55-60]	0.212
Beta blocker use, n %	50 (50)	-	-
Laboratory findings			
INR	1.43 [1.24-1.76]	0.9 [0.9-1]	**0.001***
Hemoglobin, g/dL	11.6 [10.1-12.65]	14.1 [13.25-15]	**0.001***
Platelet, 10*9/L	102 [73.5-147.5]	242 [201-294]	**0.001***
GFR, mL/min/1.73 m^2	93 [75.5-105]	94 [81-110]	0.100
Potassium, mmol/L	4.38 [4.01-4.74]	4.5 [4.06-4.74]	0.832
Total protein, mg/dL	6.95 [6.4-7.65]	6.6 [6.3-6.78]	**0.005***
Albumin, mg/dL	3.1 [2.8-3.7]	3.8 [3.6-4.1]	**0.001***
AST, U/L	39 [29-52]	24 [21-28]	**0.001***
ALT, U/L	24.5 [16-32]	23 [21-28]	0.748
Total bilirubin, mg/dL	1.64 [0.96-2.3]	0.4 [0.31-0.75]	**0.001***
Direct bilirubin, mg/dL	0.54 [0.31-0.83]	0.13 [0.1-0.17]	**0.001***

Shown as median (1^{st} quartile/3^{rd} quartile) for non-normally distributed data, and n (%) for categorical data. Mann-Whitney U test. *Statistically significant. ALT: Alanin aminotransferase, AST: Aspartate aminotransferase, ECG: Electrocardiography, GFR: Glomerular filtration rate, HR: Heart rate, INR: international normalized ratio, QRS: Depolarization of ventricles, involving Q,R, and S waves on ECG.

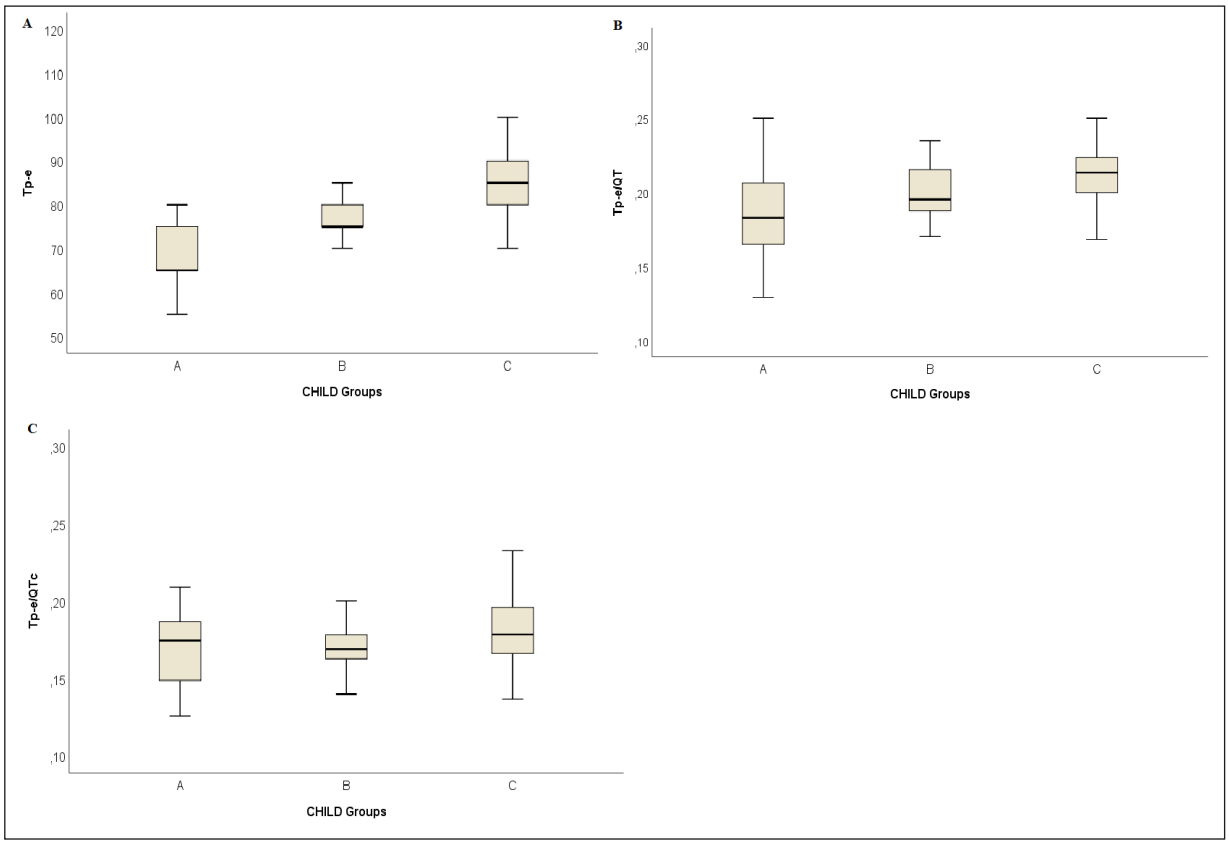

Figure 1. Boxplot of Tp-e (**A**), Tp-e/QT (**B**), and Tp-e/QTc (**C**) indexes according to Child stages.

C, $p = 0.08$), QTc duration (A *vs.* C, $p < 0.001$; A *vs.* B, $p < 0.001$; B *vs.* C, $p = 0.09$), Tp-e interval ($p < 0.001$ for all), Tp-e/QT (A *vs.* C, $p < 0.001$; A *vs.* B, $p = 0.052$; B *vs.* C, $p = 0.02$), Tp-e/QTc ratio (A *vs.* C, $p = 0.018$; A *vs.* B, $p = 0.98$; B *vs.* C, $p = 0.015$), and QRS duration (A *vs.* C, $p = 0.002$; A *vs.* B, $p = 0.013$; B *vs.* C, $p = 0.58$). There was also a significant difference between MELD score groups in terms of QT (low *vs.* intermediate, $p = 0.019$; low *vs.* high, $p < 0.001$; intermediate *vs.* high, $p = 0.055$), QTc (low *vs.* intermediate, $p < 0.001$; low *vs.* high, $p < 0.001$; intermediate *vs.* high, $p = 0.07$), Tp-e interval ($p < 0.001$ for all), Tp-e/QT (low *vs.* intermediate, $p = 0.059$; low *vs.* high, $p = 0.006$; intermediate *vs.* high, $p = 0.21$), and QRS duration (low *vs.* intermediate, $p < 0.001$; low *vs.* high, $p = 0.09$; intermediate *vs.* high, $p = 0.16$) (Figure 1-2).

In the ROC analysis of Tp-e interval, Tp-e/QT and Tp-e/QTc ratios designed to estimate the end-stage (Child C) LC, the area under the curve (AUC) values were 0.887; (95% CI: 0.853-0.921; $p < 0.001$), 0.730; (95% CI: 0.680-0.780; $p < 0.001$), and 0.670; (95% CI: 0.614-0.726; $p < 0.001$), respectively. Similarly, the ROC analyzes of Tp-e interval, Tp-e/QT and Tp-e/QTc ratios designed to estimate the end-stage (MELD score ≥ 20) LC, the AUC values were 0.877; (95% CI: 0.854-0.900; $p < 0.001$), 0.935; (95% CI: 0.918-0.952; $p < 0.001$), and 0.861; (95% CI: 0.835-0.887; $p < 0.001$) (Table III) (Figure 3-4).

Discussion

The main findings of this study are as follows: i) patients with LC had a significantly longer Tp-e interval and Tp-e/QT and Tp-e/QTc ratio compared to control subjects, ii) higher values of QT, QTc, Tp-e, Tp-e/QT, and QRS duration was associated with higher MELD score and advanced Child stage. Tp-e/QTc was also associated with advanced Child stage, iii) Tp-e, Tp-e/QT, and Tp-e/QTc are useful parameters to predict end-stage (Child C, MELD score ≥ 20) in patients with LC.

QT and QTc, which are indicators of abnor-

Table II. Kruskal-Wallis' test results of the ECG parameters of the patient group, grouped according to the CHILD stages and MELD scores.

	Child A (n=32) Median [25-75%]	Child B (n=34) Median [25-75%]	Child C (n=34) Median [25-75%]	*p*	MELD < 10 (n=26) Median [25-75%]	MELD 10-19 (n=48) Median [25-75%]	MELD ≥ 20 (n=26) Median [25-75%]	*p*
HR, bpm	72 [63-83]	86 [74-97]	84 [75-96]	**0.022***	75.5 [70-97]	85.5 [73-96]	81 [72-95]	0.482
QT, ms	375 [320-400]	391 [360-410]	400 [380-423]	**0.007***	369 [320-392]	392 [362-412]	400 [384-424]	**0.001***
QTc, ms	406 [397-426]	457.5 [429-480]	477 [438-506]	**0.001***	406 [399-433]	448 [420.5-482.5]	470 [449-495]	**0.001***
Tp-e, ms	65 [65-75]	75 [75-80]	85 [80-90]	**0.001***	65 [65-75]	77.5 [75-80]	85 [80-90]	**0.001***
Tp-e/QT, ms	0.18 [0.16-0.21]	0.2 [0.19-0.22]	0.21 [0.2-0.22]	**0.001***	0.19 [0.16-0.21]	0.2 [0.19-0.22]	0.21 [0.2-0.22]	**0.021***
Tp-e/QTc, ms	0.17 [0.15-0.19]	0.17 [0.16-0.18]	0.18 [0.17-0.2]	**0.021***	0.17 [0.15-0.19]	0.17 [0.16-0.19]	0.18 [0.17-0.19]	**0.061**
QRS, ms	80 [76.5-88]	86.5 [84-90]	87 [80-104]	**0.006***	80 [78-84]	88 [84-97]	85 [80-92]	**0.004***
EF, %	60 [55-60]	60 [53-60]	58 [55-60]	0.713	60 [55-60]	58 [53-60]	60 [55-60]	0.226

Shown as median (1st quartile/3rd quartile) for non-normally distributed data. Kruskal-Wallis' test. *Statistically significant. ECG: Electrocardiography, EF: Ejection fraction, HR: Heart rate, QRS: Depolarization of ventricles, involving Q,R, and S waves on ECG..

Table III. ROC analysis results of patients.

	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	*p*
Child stage C						
Tp-e	0.887	0.853-0.921	> 80	73.5	92.5	**<0.001**
Tp-e/QT	0.730	0.680-0.780	> 0.192	91	50	**<0.001**
Tp-e/QTc	0.670	0.614-0.726	> 0.161	85	33.5	**<0.001**
MELD score ≥20						
Tp-e	0.877	0.854-0.900	> 65	80	80	**<0.001**
Tp-e/QT	0.935	0.918-0.952	> 0.175	84	90	**<0.001**
Tp-e/QTc	0.861	0.835-0.887	> 0.157	78	83	**<0.001**

AUC: Area under the curve; CI: Confidence interval; hs-TnI: High-sensitivity cardiac troponin I; NT-proBNP: N-terminal brain-type natriuretic peptide.

mal repolarization, are the main traditional clinical markers for arrhythmic risk estimation. Prolonged QT interval length has been associated with an increased risk of total, cardiovascular, coronary, and sudden cardiac death mortality[24]. However, due to the limitations of using QTc alone in predicting arrhythmogenicity, new parameters such as Tp-e, Tp-e/QT, and Tp-e/QTc have been used recently[25]. Tp-e is defined as the interval between the peak of the T wave and the end of the T wave and represents the repolarization distribution. Studies[25,26] have shown that it is a marker of global repolarization distribution rather than transmural repolarization and prolongation of the Tp-e interval is associated with malignant ventricular arrhythmias. The Tp-e/QT ratio is used as

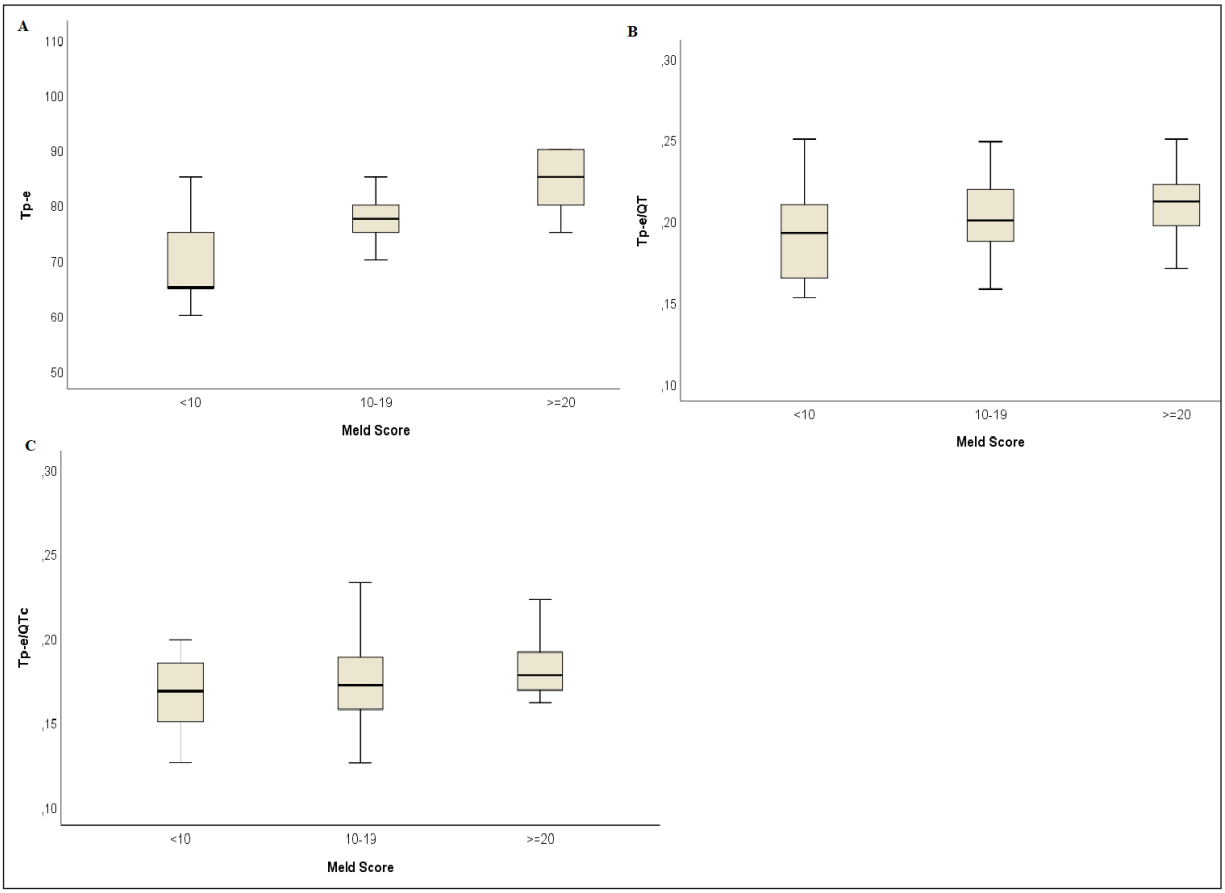

Figure 2. Boxplot of Tp-e (**A**), Tp-e/QT (**B**), and Tp-e/QTc (**C**) indexes according to MELD scores.

an electrocardiographic arrhythmogenesis index to evaluate the risk of both hereditary ion channel pathologies such as long QT and Brugada syndrome, and acquired ion channel pathologies such as acute myocardial infarction, leading to ventricular arrhythmias[26]. The role of these parameters has been investigated[27-33] in many diseases that affect the electrophysiological state of the heart and lead to mortality and morbidity, such as coronary artery disease, Fabry disease, hypertrophic cardiomyopathy, hypothyroidism, diabetes mellitus, acute pulmonary embolism, and vasculitis.

LC may predispose to arrhythmia by causing electrophysiological changes in the heart during the course of the disease. The mechanisms leading to arrhythmia are the following: i) induction of atrial arrhythmias by the toxic effect of an excess of serum bile acids[34]; ii) dysfunction of membrane potassium channels, hyperreactivity of sympathetic-adrenergic discharges, and downregulation of beta-adrenergic receptors defined as ion channel remodelling[35]; iii) chronic alcohol consumption can lead to arrhythmia through myocardial toxic effect, myocardial dysfunction, and segmental delays in electrical intracardiac conduction[36]; iv) autonomic system dysfunction[34]; v) chronic inflammation[34]; vi) electrolyte imbalance due to the disease itself or spironolactone use[12]; vii) hepatorenal syndrome[12]. All these factors directly affect QT, Tp-e, and QRS parameters, which are the parameters related to ventricular repolarization and depolarization in ECG, and may cause increased morbidity and mortality by inducing ventricular arrhythmia. Importantly, since the autono-

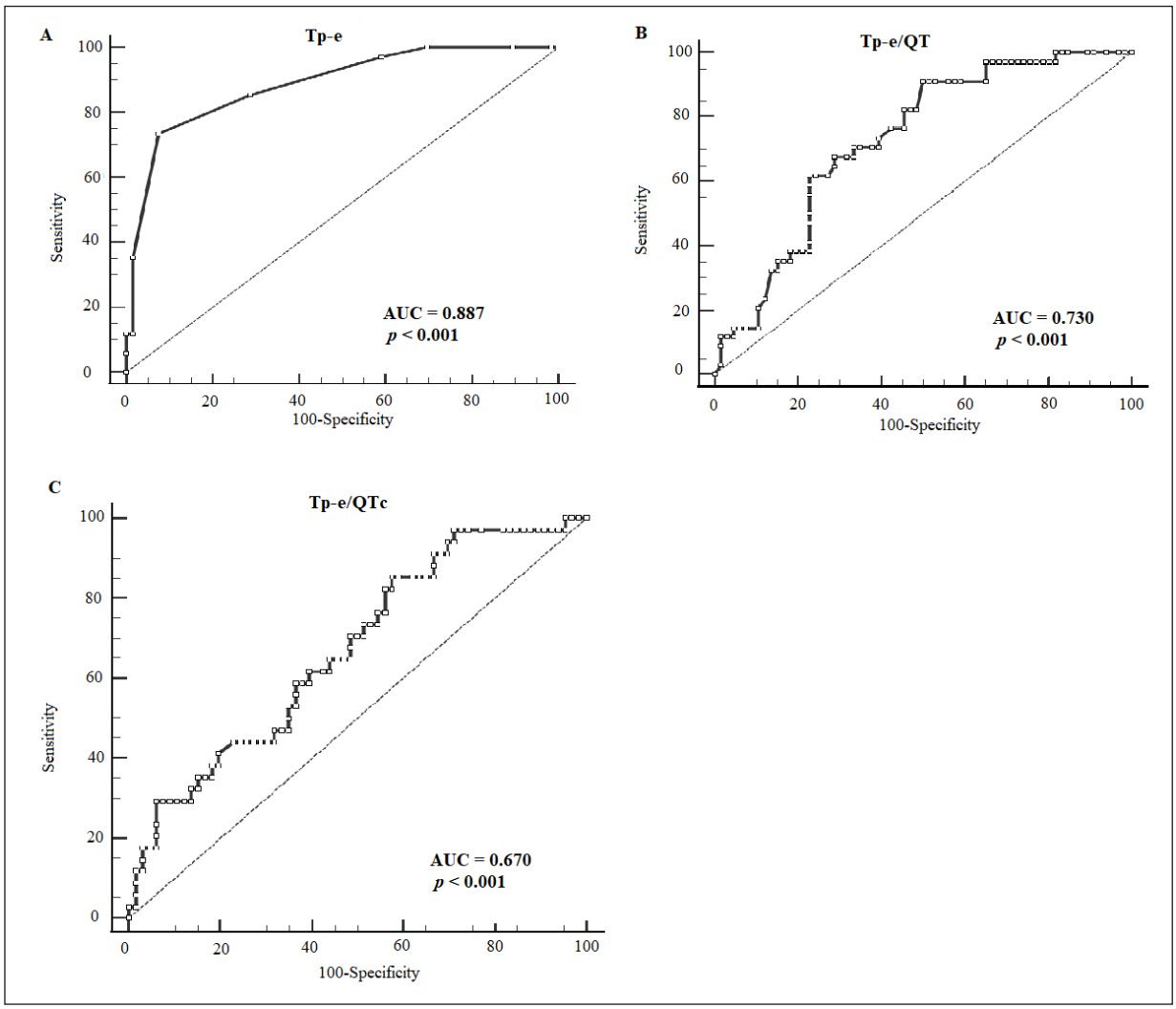

Figure 3. ROC cırves for Tp-e (**A**), Tp-e/QT (**B**), and Tp-e/QTc (**C**) indexes according to Child stages.

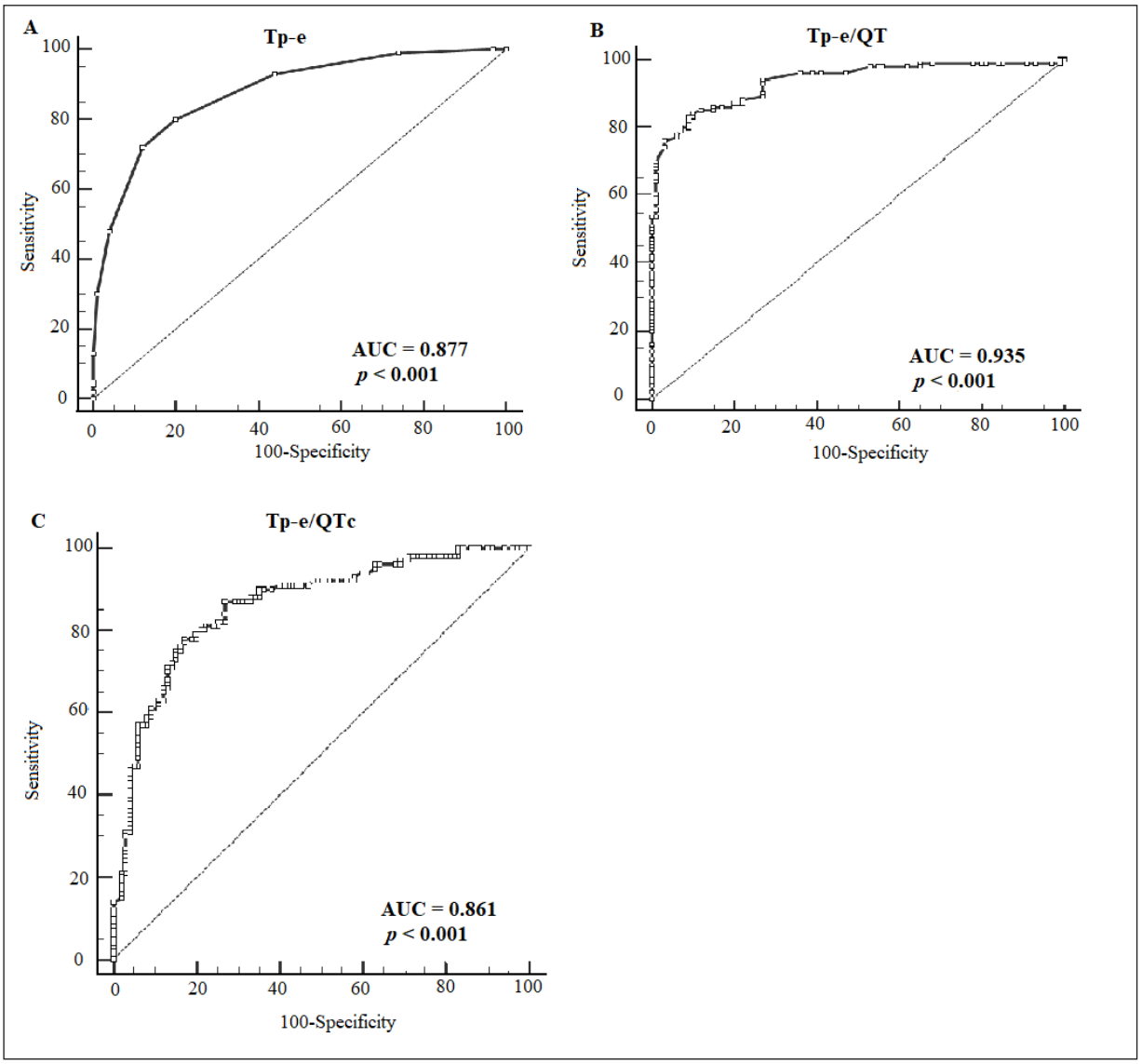

Figure 4. ROC curves for Tp-e (**A**), Tp-e/QT (**B**), and Tp-e/QTc (**C**) indexes according to MELD scores.

mic dysfunction is permanent, the risk of arrhythmia may remain, even if cirrhotic cardiomyopathy improves after liver transplantation[12]. In a recent study[37] including 406 patients with end-stage LC, no significant change in the QT interval was observed after liver transplantation in patients.

There are very few studies[14,17] investigating the relationship between the combination of QT, QTc, Tp-e interval, Tp-e/QTc parameters, and LC. Akboga et al[17] compared 88 patients diagnosed with LC and 73 control subjects and showed that the Tp-e interval, Tp-e/QTc ratio, and the rate of fragmented QRS were increased in parallel with the severity of the disease in the LC group. In support of this study, we found that the Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were higher in the patient group compared to the control group. There was also a significant difference between the Child stage and MELD score groups. Similarly, QT and QTc were higher in the patient group as expected. Tsiompanidis et al[14] compared 51 patients diagnosed with cirrhosis and 51 control subjects and found that QT was prolonged in the patient group. Moreover, decompensated patients tended to have longer QTc. In contrast, in our study, there was no difference in terms of QT and QTc between the two groups. The use of propranolol can be shown as an important reason why

there was no difference between the two groups in terms of these parameters. Because propranolol significantly shortens the QT, it is even used in the treatment of long QT syndrome[38]. In our study, 50% of the patient group was using propranolol. Another reason is that the number of patients in the study was less than ours and the patients using propranolol were excluded from the study.

Our study has a different aspect from previous studies[14,17,34]. Importantly, we presented the cut-off values of Tp-e, Tp-e/QT, and Tp-e/QTc parameters to distinguish end-stage (Child C or MELD score > 20) patients. This may be important in determining the degree of liver dysfunction in patients and the risk of arrhythmia while waiting for organ transplantation. In addition, to the best of our knowledge, our study is the largest study in which the combination of Tp-e, Tp-e/QT, and Tp-e/QTc parameters related to arrhythmia risk in LC patients has been investigated to date.

Limitations of the Study

The study has several limitations. First of all, the study was designed retrospectively and included a relatively small number of patients. Second, the use of beta-blockers may have affected the more objective evaluation of data on the parameter related to ventricular repolarization. Third, due to the cross-sectional nature of the study, patients in whom the relationship between ventricular arrhythmias and Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio could not be determined were not followed-up for future arrhythmic attacks.

Conclusions

LC has an association with significantly higher Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio indices, which are ECG parameters related to ventricular arrhythmia risk, compared to normal healthy individuals, and there is also a significant association between end-stage LC and electrophysiological abnormalities. The prognostic significance of these indices in patients with LC needs further evaluation, and if confirmed by larger studies, they can be used as an important prognostic marker, especially in patients with Child C stage or high MELD score.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was approved by the local Ethics Committee of Kırıkkale University (Decision number: 2022.06.19).

Informed Consent

Informed written consent was obtained from all participants.

Availability of Data and Materials

Data and materials used during the current study are available from the corresponding author upon request.

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None.

Authors' Contributions

Concept: İ.H.İ, S.B; Design: İ.H.İ, S.B, C.Ş, E.P; Supervision: S.B, İ.H.İ, Materials: S.B, İ.H.İ; Data Collection and/or Processing: S.B, C.Ş, E.P; Analysis and/or Interpretation: S.B, İ.H.İ, C.Ş, E.P; Literature Review: İ.H.İ, E.P; Writing: İ.H.İ ; Critical Review: S.B, İ.H.İ, C.Ş, E.P.

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