Tp-e Interval, Tp-e/QTc Ratio, and Fragmented QRS Are Correlated with the Severity of Liver Cirrhosis

Mehmet Kadri Akboga, M.D.,* Mahmut Yuksel, M.D.,†
Kevser Gulcihan Balci, M.D.,* Mustafa Kaplan, M.D.,† Serkan Cay, M.D.,*
Volkan Gokbulut, M.D.,† Cagri Yayla, M.D.,* Ahmet Goktug Ertem, M.D.,*
Meral Akdogan Ayhan, M.D.,† Serkan Topaloglu, M.D.,* and Dursun Aras, M.D.*

From the *Department of Cardiology, *Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey*, and
†Department of Gastroenterology, *Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey*

Background: Arrhythmias and electrocardiographic changes are reported in several noncardiac diseases, including liver cirrhosis (LC). We intended to evaluate the interval from the peak to the end of the electrocardiographic T wave (Tp-e), Tp-e/QTc ratio, and fQRS as presumed markers of arrhythmias in LC.

Methods: In this cross-sectional study, a total of 88 consecutive patients with LC according to clinical, biological, ultrasonographic, or histological criteria and 73 control subjects were enrolled. The severity of cirrhosis was classified according to Pugh-Child's classification and Model for End-Stage Liver Disease (MELD) score. Tp-e interval, Tp-e/QTc ratio, and fQRS rates were measured from the 12-lead electrocardiogram.

Results: Tp-e interval, Tp-e/QTc ratio and fQRS rates were significantly increased in parallel to the severity of LC ($P < 0.001$, $P < 0.001$, and $P = 0.003$, respectively). In correlation analysis, Pugh-Child stage showed a significantly positive correlation with Tp-e interval ($r = 0.462$, $P < 0.001$), QTc interval ($r = 0.373$, $P < 0.001$), Tp-e/QTc ratio ($r = 0.352$, $P < 0.001$), and fQRS ($r = 0.407$, $P < 0.001$). Furthermore, Tp-e interval ($r = 0.414$, $P < 0.001$) and Tp-e/QTc ratio ($r = 0.426$, $P < 0.001$) had significant positive correlation with MELD score.

Conclusions: Our study demonstrated that Tp-e interval, Tp-e/QTc ratios, and fQRS rates were significantly increased in parallel to the severity of LC. Thus, these findings may implicate that Tp-e interval, Tp-e/QTc ratio, and fQRS may be novel and useful indicators for prediction of arrhythmias in LC.

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Tp-e interval; Tp-e/QTc ratio; fragmented QRS; arrhythmias; liver cirrhosis

INTRODUCTION

Cirrhotic cardiomyopathy is a clinical condition characterized by impaired diastolic relaxation and contractility with electrophysiological abnormalities. Cirrhotic patients with cardiac abnormality have higher mortality rates compared to patients without cardiomyopathy.¹ The suggested pathophysiologic mechanisms of cirrhotic cardiomyopathy are; alterations in the beta-adrenergic signaling pathway and cardiomyocyte membrane

fluidity, myocardial fibrosis formation, sympathetic nervous system activation and changes in ion channels.²⁻⁴ As a component of cirrhotic cardiomyopathy, prolongation of the corrected QT (QTc) interval has been documented most of the cases with liver cirrhosis (LC) and its prevalence increases with the severity of the disease.⁵ It may signify either ventricular repolarization abnormality with an arrhythmogenic tendency or the presence of cirrhotic cardiomyopathy.

In the literature, studies conducted on patients

Address for correspondence: Mehmet K. Akboga, M.D., Department of Cardiology, *Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey*. E-mail: mkakboga@yahoo.com

with LC mainly focused on QT interval,⁵⁻⁷ and the value of additional electrocardiographic (ECG) parameters were not evaluated. Recently, Tp-e interval and Tp-e/QTc ratio were used as novel indices to detect ventricular repolarization abnormalities.^{8,9} Tp-e interval, the interval between the peak and the end of the T wave represents the total dispersion of repolarization (TDR).¹⁰ In the recent reports a link between prolonged Tp-e and sudden cardiac death has been reported.^{8,9,11} Also, fragmented QRS complexes (fQRS) which reflect abnormal cardiac depolarization were found related to worse outcomes in patients with cardiomyopathy.¹²

The aims of the present study were (1) to assess the repolarization dispersion represented by Tp-e interval and Tp-e/QTc ratio in patients with LC, (2) to evaluate if fQRS which is an arrhythmogenic ECG marker is associated LC and whether the disease severity has an impact on ventricular repolarization abnormalities.

METHODS

Study Population

Between May 2013 and December 2014, 88 consecutive patients with LC and 73 control subjects were enrolled in this single-center study after excluding the patients who had a history of revascularization (coronary artery bypass graft, or percutaneous coronary intervention), documented significant coronary artery disease, severe valvular heart disease, segmental wall motion abnormality or left ventricular ejection fraction (LVEF) below 50% in echocardiography, complete or incomplete bundle branch block, preexcitation syndromes, atrioventricular block, atrial fibrillation, and pacemaker rhythm on ECG. Patients diagnosed with renal dysfunction, hematological disease, and the presence of malignancy were also excluded from the study. All patients were in sinus rhythm at admission, and none was taking any medicine that could affect the Tp-e or QT interval.

The diagnosis of LC was based on clinical diagnosis, biochemistry, ultrasound and liver biopsy when performed. The severity of LC was classified according to Pugh-Child's classification (stage) and Model for End-Stage Liver Disease (MELD) score.^{13,14} The Child-Pugh score uses five clinical measurements of liver disease; total bilirubin

(<2, 2-3, >3 mg/dL), serum albumin (>3.5, 2.8-3.5, <2.8 g/dL), international normalized ratio [INR] (<1.7, 1.7-2.3, >2.3), ascites (none, mild, moderate to severe), and hepatic encephalopathy (none, grade I-II, grade III-IV). Each measure is scored from 1 to 3, following the order in parentheses above. The MELD score was calculated according to the following formula: $MELD = (3.78 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[INR] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43) \times 10$.

Baseline demographic characteristics, electrocardiographic findings, and the main clinical events such as ascites, hepatic encephalopathy, or other signs of hepatic deterioration were evaluated and reviewed carefully. Transthoracic echocardiography was performed in all patients, and LVEF was calculated using modified Simpson method. The study was in compliance with the principles outlined in the Declaration of Helsinki and approval for the study was obtained from the institutional review board and ethics committee of our hospital.

Electrocardiography

A 12-lead electrocardiogram with standard chest and limb leads was used to evaluate the Tp-e interval, QTc interval, and presence of fQRS. The 12-lead ECG was recorded at a paper speed of 50 mm/s in the supine position. To decrease the error measurements, all of the ECGs were scanned and transferred to a personal computer and then used for $\times 400\%$ magnification by Adobe Photoshop software. ECG measurements of QTc and Tp-e intervals were performed by two cardiologists who were blinded to the patient data. Subjects with U waves on their ECGs were excluded from the study. An average value of three readings was calculated for each lead. 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: $cQT = QT / \sqrt{RR \text{ interval}}$. The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave. Measurements of the Tp-e interval were performed from precordial leads.¹ The Tp-e/QT ratio was calculated from these measurements. Interobserver and intraobserver coefficients of variation were 3.4% and 2.7% respectively. Fragmentation of QRS was defined as the presence of various RSR' patterns with different

Table 1. Clinical Characteristics and Electrocardiographic Findings of the Study Population

Parameters	Control group (n = 73)	Pugh-Child A (n = 26)	Pugh-Child B (n = 39)	Pugh-Child C (n = 23)	P Value
Age (years)	52.7 ± 9.1	48.5 ± 12.4	52.3 ± 13.7	50.7 ± 12.0	0.413
Gender, male n (%)	40 (54.8)	16 (61.5)	22 (56.4)	17 (73.9)	0.419
Etiology					
Viral	–	13 (50.0)	16 (41.0)	12 (52.2)	
Alcoholic	–	6 (23.1)	10 (25.6)	4 (17.4)	
Others	–	7 (26.9)	13 (33.3)	7 (30.4)	
Ascites	–	7 (26.9)	35 (89.7)	22 (95.7)	
Encephalopathy	–	1 (3.8)	6 (15.4)	12 (52.2)	
MELD score	–	12.0 ± 4.7	13.1 ± 3.7	15.8 ± 2.9	
Creatinine (mg/dL)	0.78 ± 0.17	0.75 ± 0.19	0.80 ± 0.21	0.86 ± 0.27	0.267
Tp-e interval (ms)	66.6 ± 15.3	73.8 ± 15.3	81.9 ± 13.8	86.2 ± 16.5	<0.001
QTc interval (ms)	391 ± 33	428 ± 32	427 ± 30	435 ± 34	<0.001
Tp-e/QTc ratio	0.16 ± 0.04	0.17 ± 0.04	0.19 ± 0.03	0.20 ± 0.04	<0.001
Heart rate (beat/min)	74 ± 13	76 ± 14	76 ± 15	75 ± 14	0.949
LVEF (%)	61.4 ± 3.4	61.8 ± 3.6	59.8 ± 3.9	60.7 ± 3.9	0.335
fQRS, n (%)	0	2 (7.7)	5 (12.8)	5 (21.7)	0.003

Data were given as mean ± SD or %. fQRS = fragmented QRS; LVEF = left ventricular ejection fraction; MELD score = Model for End-Stage Liver Disease score; Tp-e = T wave peak to end interval; QTc = corrected QT.

Table 2. Baseline Demographic Characteristics and Electrocardiographic Findings of the Cirrhosis Patients According to the MELD Score

Parameters	MELD ≤ 10	MELD 11–19	MELD ≥ 20	P Value
Age (years)	50.2 ± 13.1	50.0 ± 13.3	54.8 ± 10.4	0.472
Gender, male n (%)	16 (53.3)	31 (68.9)	8 (61.5)	0.394
Tp-e interval (ms)	74.2 ± 14.3	81.2 ± 14.2	93.6 ± 15.6	0.001
QTc interval (ms)	424 ± 29	432 ± 31	435 ± 41	0.475
Tp-e/QTc ratio	0.18 ± 0.03	0.19 ± 0.04	0.21 ± 0.04	0.007
Heart rate (beat/min)	75 ± 13	77 ± 16	73 ± 19	0.733
LVEF (%)	62.0 ± 4.4	59.8 ± 3.4	61.5 ± 4.1	0.222
fQRS, n (%)	3 (10.0)	6 (13.3)	3 (23.1)	0.516

Data were given as mean ± SD or %. fQRS = fragmented QRS; LVEF = left ventricular ejection fraction; MELD score = Model for End-Stage Liver Disease score; Tp-e = T wave peak to end interval; QTc = corrected QT.

morphologies of QRS complexes. Various RSR' patterns included additional R wave (R'), notching of the R wave or the S wave, or the presence of >1 R' (fragmentation) without a typical bundle branch block in 2 contiguous leads corresponding to a major lead set for major coronary artery territory. Any QRS morphology with a QRS duration >120 ms, including bundle branch block or intraventricular conduction delay, was excluded.

Statistical Analysis

In all statistical analysis SPSS 20.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used. Kolmogorov-Smirnov test was used to test normality of distribution. Quantitative variables with a normal distribution were specified as the mean ± standard deviation and categorical

variables were shown as number and percentage values. Categorical variables were compared with chi-square test. ANOVA test was used to compare continuous variables according to Pugh-Child stage. Pearson correlation analysis was performed to examine association of MELD score with Tp-e and Tp-e/QTc. Pearson correlation analysis was also performed to examine association of Pugh-Child stage with potential continuous variables. A P value of <0.05 was accepted as statistically significant.

RESULTS

The study population was categorized into 4 groups as according to the severity of LC (Pugh-Child A (n = 26), Pugh-Child B (n = 39),

Table 3. Baseline Demographic Characteristics and Electrocardiographic Findings of the Cirrhosis Patients According to the Etiology

Parameters	Alcoholic (n = 20)	Nonalcoholic (n = 68)	P Value
Age (years)	51.2 ± 12.2	50.6 ± 13.1	0.855
Gender, male n (%)	13 (65.0)	42 (61.8)	0.793
Ascites	16 (80.0)	48 (70.6)	0.406
Encephalopathy	3 (15.0)	16 (23.5)	0.415
MELD score	12.5 ± 2.9	13.8 ± 4.3	0.196
Tp-e interval (ms)	77.6 ± 15.7	81.5 ± 15.5	0.329
QTc interval (ms)	436 ± 35	427 ± 30	0.298
Tp-e/QTc ratio	0.18 ± 0.04	0.19 ± 0.04	0.212
Heart rate (beat/min)	75 ± 16	79 ± 15	0.291
LVEF (%)	60.4 ± 4.4	60.7 ± 3.6	0.847
fQRS, n (%)	2 (10.0)	10 (14.7)	0.590

Data were given as mean ± SD or %. fQRS = fragmented QRS; LVEF = left ventricular ejection fraction; MELD score = Model for End-Stage Liver Disease score; Tp-e = T wave peak to end interval; QTc = corrected QT.

Figure 1. Comparison of Tp-e interval and Tp-e/QTc ratio with the severity of liver cirrhosis according to Pugh-Child stage.

and Pugh-Child C (n = 23) and as a control group (n = 73). Baseline clinical characteristics and electrocardiographic findings of the study population were shown in Table 1. There was no significant difference between groups regarding age and gender ($P > 0.05$). Serum creatinine, mean heart rate, and LVEF were similar between the groups ($P > 0.05$). In addition, we presented the baseline clinical characteristics and electrocardiographic findings of the study population according to the MELD score and the etiology of LC in Tables 2 and 3.

It was demonstrated that Tp-e interval (66.6 ± 15.3 ms in the control group, 73.8 ± 15.3 ms in the Pugh-Child A group, 81.9 ± 13.8 ms in the Pugh-Child B group, 86.2 ± 16.5 ms in the Pugh-Child C group, $P < 0.001$) and Tp-e/QTc ratio

Table 4. Pearson's Correlation Analysis of Pugh-Child Stage with Potential Continuous Variables

Variables	r	P Value
Tp-e interval	0.462	<0.001
QTc interval	0.373	<0.001
Tp-e/QTc ratio	0.352	<0.001
fQRS	0.407	<0.001
MELD score	0.440	<0.001

fQRS = fragmented QRS; LVEF = left ventricular ejection fraction; MELD score = Model for End-Stage Liver Disease score; r = correlation coefficient; Tp-e = T wave peak to end interval; QTc = corrected QT.

(0.16 ± 0.04 , 0.17 ± 0.04 , 0.19 ± 0.03 , 0.20 ± 0.04 , $P < 0.001$, respectively) were significantly prolonged in parallel to the severity of LC according to Pugh-Child stage (Fig. 1). Also, the presence

Figure 2. Correlation of MELD score with Tp-e interval and Tp-e/QTc ratio.

of fQRS (0, 7.7%, 12.8%, 21.7%, $P = 0.003$, respectively) was significantly higher in parallel to the severity of LC. In Pearson correlation analysis, Pugh-Child stage showed a significantly positive correlation with Tp-e interval, QTc interval, Tp-e/QTc ratio, fQRS, and MELD score (Table 4). Moreover, Tp-e interval ($r = 0.414$, $P < 0.001$) and Tp-e/QTc ratio ($r = 0.426$, $P < 0.001$) had a positive correlation with MELD score as illustrated in Figure 2.

DISCUSSION

This study showed that patients with LC had longer QTc interval, Tp-e interval, and Tp-e/QTc ratio compared to control subjects, and the presence of fQRS on ECG was related to LC. Moreover, all of the ECG indices of the arrhythmia risk determination had a significant relation parallel with the severity of LC represented by Pugh-Child and MELD scores.

Increased dispersion of repolarization showing heterogeneity of repolarization is a sign for lethal ventricular arrhythmias.¹⁵ QT/QTc interval and T wave analyzes are commonly used for ventricular repolarization assessment, and uneven distribution of sympathetic nervous system activity on heart causes prolonged QT interval.¹⁶ In cirrhotic cardiomyopathy high levels of circulating catecholamines, due to enhanced activation of the sympathetic nervous system may lead QT prolongation. Also, functional remodeling in

potassium channels in cardiac plasma membranes has a possible role in electrophysiological abnormalities seen in the clinical course of the LC.¹⁷ QT is almost approximated with the mid-myocardial cell (M cell) action potential duration,¹⁸ and Tp-e interval shows the TDR (transmural, apicobasal, and global).¹⁰ However, both QT and Tp-e intervals may vary according to the body weight and heart rate that makes these indices less sensitive for predicting arrhythmogenesis.¹⁹ In this context, using the Tp-e/QTc ratio is more favored compared to a single assessment of either Tp-e or QT intervals because this ratio remains steady regardless of the dynamic variations in heart rate.^{19,20}

In LC posttransplant and gastrointestinal bleeding related mortalities are related to abnormal ECG parameters.^{21,22} In one study, patients with LC and longer QT interval who admitted with gastrointestinal bleeding had higher bleeding-induced mortality and QT prolongation independently predicted mortality in such patients.²¹ Moreover, baseline QT prolongation on ECG increases the posttransplant cardiac events.²² Recently it has been evidenced that there is a relation between prolonged Tp-e, arrhythmia, and mortality.^{8,23} Moreover, in patients with left ventricular hypertrophy (LVH) increased ventricular repolarization, Tp-e/QT ratio, QT, and Tp-e intervals have been reported.²⁴ However, to date, it has not been investigated in patients with LC. We observed that the prolongation of Tp-e and Tp-e/QT ratio showed a positive correlation with the severity of the disease. Although, prolonged Tp-

e and QT intervals are related to arrhythmic deaths, their prognostication in LC needs to be validated. We think that LVH being frequently seen in LC, and both metabolic and electrochemical alterations influence action potentials causing repolarization anomalies represented by QT, Tp-e, and Tp-e/QT. However, there are no prospective randomized studies evaluating the significance of these ECG parameters, and the actual incidence of arrhythmic events is unclear. Besides, if these patients should be followed with frequent ECG monitoring, or beta-blocker treatment is solely able to shorten QT interval and lessen arrhythmogenesis is debatable. Further studies aiming the utility of ECG monitoring in patients with LC may provide valuable information.

fQRS is described as multiple deflections within the QRS complex and presence of fQRS reflects heterogeneous myocardial electrical activation.²⁵ It has been suggested that irregular and erratic conduction arose from the scarred, or fibrotic myocardium generates fQRS on surface ECG.²⁶ Besides, recent studies have shown that fQRS is a predictor for arrhythmic events and sudden cardiac death in various diseases.^{27,28} Noteworthy, in the present study, we observed that the presence of fQRS was significantly related to LC and the severity of the disease. Current data supports that there is a catecholamine-induced cardiac fibrosis in cirrhotic cardiomyopathy.²⁹ Moreover, cirrhotic patients experience an increment in left ventricular mass which in turn cause abnormal filling of the ventricle.³⁰ Therefore, altered characteristics of the myocardial tissue may lead heterogeneous electrophysiological properties and a possible source of arrhythmias. In the literature, there is no report regarding the relation between LC and fQRS. A previous study investigating the effects of LC in ECG parameters reported reduced QRS voltage in patients with ascites, but they did not evaluate fragmentation in QRS complexes.³¹ Another study reported a higher occurrence of post-transplant cardiac events if there was a Q wave in the QRS complexes.²² We observed that in advanced LC frequent fQRS complexes are seen on surface ECG. It can be concluded that fQRS may show structural changes of the myocardium including fibrosis, cardiac edema, and increased cardiac wall thickness indirectly. Although, fQRS is related to arrhythmic deaths, the application of this information to patients with LC in clinical practice is not clear.

Study Limitation

The main limitation of this study is the limited number of patients that may have affected the statistical power of the study. Also, due to the cross-sectional nature of the study, the patients were not followed for future arrhythmic episodes that the relation between ventricular arrhythmias with Tp-e interval, Tp-e/QTc ratio, and fQRS could not be evaluated.

CONCLUSION

In conclusion, LC is associated with prolongation of the ECG indices of ventricular arrhythmogenesis, and there was a positive correlation between the disease severity and the electrophysiological abnormalities. The prognostic significance of longer Tp-e interval and Tp-e/QTc ratio, and frequent fQRS in patients with LC needs further evaluation. If these results confirmed with prospective and larger studies and if a higher mortality risk is reported for patients with advanced disease and waiting lengthy time for liver transplantation, pretransplant implantable cardioverter defibrillator indication may arise.

REFERENCES

1. Karagiannakis DS, Papatheodoridis G, Vlachogiannakos J. Recent advances in cirrhotic cardiomyopathy. *Dig Dis Sci* 2015;60:1141-1151.
2. Ma Z, Miyamoto A, Lee SS. Role of altered beta-adrenoceptor signal transduction in the pathogenesis of cirrhotic cardiomyopathy in rats. *Gastroenterology* 1996;110:1191-1198.
3. Ward CA, Liu H, Lee SS. Altered cellular calcium regulatory systems in a rat model of cirrhotic cardiomyopathy. *Gastroenterology* 2001;121:1209-1218.
4. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. *Gut* 2008; 57: 268-278.
5. Fede G, Privitera G, Tomaselli T, et al. Cardiovascular dysfunction in patients with liver cirrhosis. *Ann Gastroenterol* 2015;28:31-40.
6. Bernardi M, Calandra S, Colantoni A, et al. Q-T interval prolongation in cirrhosis: Prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology* 1998;27:28-34.
7. Bal JS, Thuluvath PJ. Prolongation of QTc interval: Relationship with etiology and severity of liver disease, mortality and liver transplantation. *Liver Int* 2003;23:243-248.
8. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, et al. T peak-T end and T peak-T end dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol* 2006;47:1828-1834.
9. Smetana P, Schmidt A, Zabel M, et al. Assessment of repolarization heterogeneity for prediction of mortality in cardiovascular disease: Peak to the end of the T

- wave interval and nondipolar repolarization components. *J Electrocardiol* 2011;44:301–308.
10. Antzelevitch C, Sicouri S, Di Diego JM, et al. Does T peak-T end provide an index of transmural dispersion of repolarization? *Heart Rhythm* 2007;4:1114–1116.
 11. Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged T peak-to-Tend interval on the resting ECG Is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol* 2011; 4:441–447.
 12. Rosengarten JA, Scott PA, Morgan JM. Fragmented QRS for the prediction of sudden cardiac death: A meta-analysis. *Europace* 2015;17:969–977.
 13. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646–649.
 14. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000;31:864–871.
 15. Antzelevitch C. Role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes. *Am J Physiol Heart Circ Physiol* 2007;293:H2024–H2038.
 16. Arı H, Arı S, Coşar S, et al. The effect of varenicline on Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in healthy smokers and nonsmokers. *Cardiol J*. 2015;22:551–556.
 17. Ward CA, Ma Z, Lee SS, Giles WR. Potassium currents in atrial and ventricular myocytes from a rat model of cirrhosis. *Am J Physiol* 1997;273:G537–G544.
 18. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. *Circulation* 1998; 98:1928–1936.
 19. Gupta P, Patel C, Patel H, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. *J Electrocardiol* 2008;41:567–574.
 20. Karaman K, Altunkaş F, Çetin M, et al. New markers for ventricular repolarization in coronary slow flow: Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. *Ann Noninvasive Electrocardiol* 2015;20:338–344.
 21. Trevisani F, Di Micoli A, Zambruni A, et al. QT interval prolongation by acute gastrointestinal bleeding in patients with cirrhosis. *Liver Int* 2012;32:1510–1515.
 22. Josefsson A, Fu M, Björnsson E, Kalaitzakis E. Prevalence of pre-transplant electrocardiographic abnormalities and post-transplant cardiac events in patients with liver cirrhosis. *BMC Gastroenterol* 2014;14:65.
 23. Erikssen G, Liestøl K, Gullestad L, et al. The terminal part of the QT interval (T peak to T end): A predictor of mortality after acute myocardial infarction. *Ann Noninvasive Electrocardiol* 2012;17:85–94.
 24. Zhao Z, Yuan Z, Ji Y, et al. Left ventricular hypertrophy amplifies the QT, and Tp-e intervals and the Tp-e/QT ratio of left chest ECG. *J Biomed Res* 2010;24:69–72.
 25. Morita H, Kusano KF, Miura D, et al. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation* 2008;118:1697–1704.
 26. Das MK, Suradi H, Maskoun W, et al. Fragmented wide QRS on a 12-lead ECG: A sign of myocardial scar and poor prognosis. *Circ Arrhythm Electrophysiol* 2008;1:258–268.
 27. Brenyo A, Pietrasik G, Barsheshet A, et al. QRS fragmentation and the risk of sudden cardiac death in MADIT II. *J Cardiovasc Electrophysiol* 2012;23:1343–1348.
 28. Akgul O, Uyarel H, Pusuroglu H, et al. Predictive value of a fragmented QRS complex in patients undergoing primary angioplasty for ST elevation myocardial infarction. *Ann Noninvasive Electrocardiol* 2015;20:263–272.
 29. Bos R, Mougnot N, Findji L, et al. Inhibition of catecholamine-induced cardiac fibrosis by an aldosterone antagonist. *J Cardiovasc Pharmacol* 2005;45:8–13.
 30. Merli M, Calicchia A, Ruffa A, et al. Cardiac dysfunction in cirrhosis is not associated with the severity of liver disease. *Eur J Intern Med* 2013;24:172–176.
 31. Cichoż-Lach H, Tomaszewski M, Kowalik A, et al. QT interval prolongation and QRS voltage reduction in patients with liver cirrhosis. *Adv Clin Exp Med* 2015;24:615–622.