Cor et Vasa

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/crvasa

Původní sdělení | Original research article

Electrocardiographic findings in hepatic cirrhosis and their association with the severity of disease

Leili Pourafkari[a,b,c], Samad Ghaffari[a], Leila Nazeri[b], Janine B. Lee[c], Kourosh Masnadi-Shirazi[d], Arezou Tajlil[a], Nader D. Nader[c]

[a] *Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[b] *Department of Cardiology, Islamic Azad University (Tabriz Branch), Iran*
[c] *School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, United States*
[d] *Department of Gastroenterology, Tabriz University of Medical Sciences, Tabriz, Iran*

ARTICLE INFO

Article history:
Received: 7. 11. 2015
Received in revised form: 14. 1. 2016
Accepted: 19. 1. 2016
Available online: 10. 2. 2016

Klíčová slova:
Interval QT
Nízkovoltážní elektrokardiogram
Onemocnění jater

SOUHRN

Účel/cíl: V předchozích studiích bylo popsáno prodloužení intervalu QT u pacientů s cirhózou jater. Naším cílem bylo zkoumat změny na elektrokardiografickém (EKG) záznamu a jejich korelaci se závažností onemocnění u pacientů s cirhózou.
Metody: Ve studii bylo vyšetřeno celkem 69 pacientů s cirhózou. Prodloužení korigovaného intervalu QT a nízkovoltážní komplexy QRS na EKG záznamu byly zkříženě porovnány s klinickými a biochemickými údaji. Byla zkoumána spojitost EKG nálezů se závažností cirhózy podle Childova-Pughova skóre i skóre z modelu terminálního nemocnění jater (model for end-stage liver diseases, MELD).
Výsledky: Prodloužení intervalu QT bylo zjištěno u 63,5 % pacientů a 57,7 % jich splnilo kritéria nízkovoltážních komplexů QRS. U pacientů s prodlouženými intervaly QT sice byly zjištěny vyšší hodnoty Childova-Pughova skóre (9,58 ± 2,5, resp. 8,16 ± 2,29; $p = 0,04$), avšak při použití MELD byly hodnoty skóre při prodlouženém intervalu QT a nízkovoltážní EKG křivky podobné. Častost výskytu prodlouženého intervalu QT a nízkovoltážních komplexů QRS byla u pacientů v různých třídách Childovy-Pughovy klasifikace podobná. U pacientů s nízkovoltážní EKG křivkou byla vyšší i srdeční frekvence (89 ± 15 tepů/min, resp. 79 ± 16 tepů/min; $p = 0,01$). Průměrná voltáž komplexu QRS v prekordiálních svodech byla u pacientů s ascitem nižší (8,5 ± 2,6 mV vs. 11,8 ± 3,4 mV; $p = 0,006$).
Závěr: Změny na elektrokardiogramu jsou u cirhózy bez ohledu na závažnost onemocnění časté. Přítomnost nízkovoltážních komplexů QRS může souviset s antropomorfními změnami a s rozvojem ascitu u této skupiny pacientů.

ABSTRACT

Purpose/aim: Previous studies reported prolongation of QT interval in cirrhotic patients. We aimed to investigate the electrocardiographic changes and their correlation with the disease severity in cirrhotic patients.
Methods: Sixty-nine cirrhotic patients were examined. The prolongation of corrected QT interval and low-voltage QRS in electrocardiography were cross-examined for clinical and biochemical data. The association of electrocardiographic findings with the severity of cirrhosis, as determined by both Child-Pugh and model for end-stage liver diseases (MELD) scores, was investigated.

Address: Nader D. Nader, MD, PhD, FACC, 252 Farber Hall, Buffalo, NY 14214, United States, e-mail: nnader@buffalo.edu
DOI: 10.1016/j.crvasa.2016.01.010

Please cite this article as: L. Pourafkari, et al., Electrocardiographic findings in hepatic cirrhosis and their association with the severity of disease, Cor et Vasa 59 (2017) e105–e113 as published in the online version of *Cor et Vasa* available at http://www.sciencedirect.com/science/article/pii/S0010865016000126

Keywords:
Liver disease
Low-voltage electrocardiogram
QT interval

Results: QT-interval prolongation was detected in 63.5% patients and 57.7% met the criteria for low-voltage QRS. Patients with prolonged QT-interval had higher Child-Pugh scores (9.58 ± 2.5 vs. 8.16 ± 2.29 respectively, $p = 0.04$) but model for end-stage liver diseases scores was similar in those with prolonged QT and low-voltage electrocardiogram. The frequency of prolonged QT interval and low-voltage QRS were similar among patients with different Child-Pugh classes. Heart rate was also higher in patients with low-voltage electrocardiogram (89 ± 15 beats per minute vs. 79 ± 16 beats per minute, $p = 0.01$). Mean QRS voltage in precordial leads was lower in those with ascites (8.5 ± 2.6 mV vs. 11.8 ± 3.4 mV, $p = 0.006$).
Conclusion: Electrocardiographic changes are common in cirrhosis regardless of the disease severity. Low-voltage QRS may be related to anthropomorphic changes and development of ascites in these patients.

Introduction

Cirrhosis, which is the late stage of progressive hepatic fibrosis, makes patients susceptible to several complications [1]. Cardiac dysfunction in cirrhotic patients, which was once believed to be the result of alcoholic toxicity, is now considered because of the disease process [2,3]. Diastolic dysfunction of the left ventricle is described in majority of patients with cirrhosis. However, the other devastating consequences of cirrhosis may obscure the emergence of other cardiac complications [2,3].

Prolongation of QT-interval is a common electrocardiographic (ECG) finding in cirrhotic patients that is an indication of extended repolarization phase prolongation in cardiac muscle [2,4,5]. Prolongation of QT-interval is associated with a higher mortality rate among the affected individuals [6]. Low-voltage ECG is another finding that is rarely investigated in cirrhotic patients. A recent study has revealed that presence of low-voltage ECG in patients with no prior cardiovascular diseases increases mortality in affected individuals [7]. A low-voltage ECG in any patient may indicate the presence of another important underlying problem such as cardiac ischemia and pericardial effusion [8,9].

This study was conducted to investigate the frequency of electrocardiographic changes in cirrhotic patients and to further investigate whether these changes (QT-prolongation and or low-voltage QRS pattern) have any correlation to the severity of liver disease as assessed by Child-Pugh and model for end-stage liver disease (MELD) scores. Our primary hypothesis was that QT prolongation and the low-voltage pattern were frequently seen in patients with cirrhosis and their frequency or extent increased, as the disease process was further advanced.

Patients and methods

The study was reviewed and approved by the Institutional Review Board Committee at Tabriz University of Medical Sciences (Tabriz, Iran). Due to the retrospective design of this study involving chart reviews, which poses no more than minimal risk to the participants, the requirement for informed consent was waived. However, appropriate steps were taken to maintain complete patient privacy.

Patient population

All patients admitted to the Gastroenterology Services from March 2011 through December 2013 with a diagnosis of cirrhosis were reviewed. One hundred and ninety records were screened and 121 patients were excluded for the following reasons: cardiac related diseases including patients with a history of ischemic heart disease (history of or electrocardiographic evidence of prior myocardial infection, history of coronary revascularization) (30), congestive heart failure (9) and implantation of cardiac pacemaker (3); renal insufficiency Stage 3 or above (33 cases) and pulmonary-related disease (25 cases) as assessed by history, clinical evaluation and laboratory data. A further 21 patients were excluded for other reasons including having incomplete medical records or taking medications known to adversely affect ECG changes. After these exclusions were taken into consideration, 69 patients in total were included in this study. All patients were in normal sinus rhythm with no extrasystoles. Demographic and anthropomorphic (e.g., height, weight, BMI) data were collected from source documents and entered into the study datasheet.

The presence of cirrhosis was confirmed on clinical, biochemical, and histological grounds as available. The severity of cirrhosis was determined by two separate clinical assessments: the Child-Pugh classification and the MELD [10–12]. In terms of the Child-Pugh classification, patients were scored according to standard criteria as done in clinical practice and allocated into three groups based on their Child's class (i.e., Class A, Class B or Class C). With regard to MELD scoring, the following standard formula was used: $9.6 \times \log_e$ (creatinine mg/dL) + $3.8 \times \log_e$ (total bilirubin mg/dL) + $11.2 \times \log_e$ (INR) + 6.4. In addition, the following scoring modifications as used by the United Network for Organ Sharing (UNOS) were made: values of creatinine, bilirubin, and INR below 1 were rounded to 1, and creatinine was assigned a value of 4 if patients had received hemodialysis at least twice within the last 7 days prior to scoring. MELD scores with and without UNOS modifications were calculated and no significant difference was observed. We additionally calculated MELD-Na by adding MELD to $1.59 \times (135 - \text{Na})$ which has been shown to predict the mortality in patients with cirrhosis.

The etiology of cirrhosis, presence of ascites and hepatic encephalopathy were recorded for all patients. The various etiologies of cirrhosis were determined based on history of alcohol intake of 80 gm/day for males or 60 gm/day for females for at least 10 years for alcoholic cirrhosis, and presence of hepatitis B and C specific antigen/antibodies for post hepatitis cirrhosis and history established autoimmune disease for autoimmune causes. In the absence of any of aforementioned evidence, the etiology of cirrhosis was recorded as unknown. Ascites and hepatic encephalopathy were evaluated clinically and rated as follows: 0 = none; 1 = medically controlled; 2 = poorly controlled. Laboratory data required for clinical assessment

of cirrhosis including serum concentrations of albumin, bilirubin, prothrombin time, international normalized ratio (INR) and creatinine were also documented for all patients.

Electrocardiographic measurements

The standard 12-lead electrocardiogram tracing was recorded using a paper speed of 25 mm/s at 10 mm/mV amplitude for each patient. A cardiologist who was blinded to the medical history of the patient manually reviewed all 12-lead electrocardiographic tracing and recorded the measurements. Maximum QRS voltage in all limb (I, II, III, aVR, aVL and aVF) and precordial leads (V1–V6), as well as the intervals for P, PR, QRS, R-R and QT were measured. Both sum and mean voltage for limb leads and precordial leads were separately recorded. In leads II, V5 and V6, QT interval was measured from the beginning of QRS complex to the end point of T-wave and the longest interval was identified. If a U wave was present, the measurement of QT interval was performed to the nadir of the curve between the T wave and U wave. The average of the QT interval in 3 consecutive heartbeats in the lead with the longest QT interval was reported. The returning of T wave to isoelectric line was considered as the termination of T wave. The low-voltage ECG, defined as a QRS amplitude < 10 mm in the precordial and < 5 mm in all limb leads. QT-interval was corrected for R-R interval and recorded as QTc. The QT-interval was corrected using the standard clinical correction (Bazett's formula): $QTc = QT/\sqrt{RR}$. QT prolongation was identified when QTc values were > 440 ms (milliseconds) for males and > 460 ms for females.

Statistical analysis

Statistical software SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Electrographic measurement of QRS voltage and evidence for QT prolongation were the primary endpoints of this study. Continuous variables were presented as the mean ± standard deviation. Categorical variables were reported as frequencies and percentages. Independent t-test was used to compare the severity scores for those with and without QT prolongation. For comparison of numerical variables in polynomial groups, one-way ANOVA test was used with Bonferroni *post hoc* test to compare inter-groups variables. Categorical variables were compared between groups with chi-square test or Fisher's exact test as appropriate. Multivariate linear regression models were constructed to examine the level of contribution of independent factors on the length of QT interval. Variable selection was based on multiple univariate analysis that showed any trend toward significance with p values < 0.100. P values less than 0.05 were considered statistically significant.

Results

A total number of 69 patients with cirrhosis were studied. Forty-five of the 69 patients were male (65.2%) and the remaining 24 were female (34.8%). The mean age of all patients was 56.8 ± 16.0 years. The most common cause of cirrhosis was hepatitis B (40.6%) followed by alcoholic cirrhosis (21.7%) and hepatitis C (7.2%). In the remaining patients, the etiology was either unknown (24.6%) or due to an autoimmune process (5.8%; categorized as "Others") (Table 1). The 69 patients were divided into 3 groups according to their Child-Pugh Classification: 14 patients (20.3%) in Class A, 28 patients (40.5%) in Class B and 27 patients (39.1%) in Class C (Table 2). Severity of liver disease was confirmed by comparing mean MELD scores in each respective group (Class A: 12.9 ± 4.7; Class B: 16.3 ± 5.6; Class C: 20.6 ± 7.0, $p < 0.001$). With regards to differences in serum electrolytes between the three classes, there was a significant decrease in serum sodium with increasing Child Class and thus severity of liver disease (Class A: 142 ± 3; Class B: 139 ± 4; Class C: 136 ± 5 mEq/L, $p < 0.001$). There was no significant difference in total calcium, ionized calcium or potassium. As patients with renal insufficiency were excluded, serum creatinine did not vary significantly between the three groups (Table 2).

Various electrocardiographic findings between patients in the three Child classes were also compared (Table 3). Only the heart rate, which increased with progression of Child class severity, differed significantly (Class A: 77 ± 17; Class B: 83 ± 16; Class C: 89 ± 18 beats per minute, $p = 0.029$) (Table 3). However, approximately half of patients in each Child Class demonstrated a prolonged QTc-interval (42.9% in Child class A, 57.1% in Child class B and 48.1% in Child class C, $p < 0.644$), which reflected the proportion of patients overall with a prolonged QTc-interval (50.7% or 35/69 patients). A similar pattern was also seen with regards to low-voltage ECG findings. Approximately one-third to one-half of patients in each Child class had low-voltage ECG findings (35.7% in class A, 50% in class B and 50% in class C, $p = 0.634$), and about half of patients overall had low-voltage ECG findings either in the precordial or limb leads (46.4% or 32/69 patients). Specifically, 19 out of 69 patients (30.6%) had low-voltage ECG in precordial leads and 24 out of 69 (38.7%) had low-vol-

Table 1 – Etiology of cirrhosis according to Child-Pugh classification.

Etiology	Child-Pugh Class			
	A N = 14	B N = 28	C N = 27	Total N = 69
HBV	6 (42.9%)	12 (42.9%)	10 (37.0%)	28 (40.6%)
HCV	1 (7.1%)	3 (10.7%)	1 (3.7%)	5 (7.2%)
Alcohol	2 (14.3%)	5 (17.9%)	8 (29.6%)	15 (21.7%)
Unknown	4 (28.6%)	7 (25.0%)	6 (22.2%)	17 (24.6%)
Others	1 (7.1%)	1 (3.6%)	2 (7.4%)	4 (5.8%)

Table 2 – Demographic and laboratory findings.

	Child-Pugh Class			*p*-value
	A N = 14	B N = 28	C N = 27	
Age (year)	48.9 ± 17.0	60.1 ± 15.1	56.1 ± 14.5	***0.061***
Gender (F/M)	7/7	8/20	9/18	0.274
MELD scores	12.9 ± 4.7	16.3 ± 5.6	20.6 ± 7.0	***< 0.001***
MELD-Na	1.8 ± 6.2	10.8 ± 10.6	20.2 ± 11.3	***< 0.001***
Aspartate aminotransferase (IU/dL)	53 ± 46	101 ± 258	130 ± 164	0.499
Alanine aminotransferase (IU/dL)	40 ± 31	70 ± 196	94 ±102	0.514
Total calcium (mg/dL)	9.4 ± 1.0	9.2 ± 0.8	9.1 ± 1.6	0.603
Ionized calcium (mg/dL)	1.23 ± 0.16	1.19 ± 0.07	1.20 ± 0.15	0.518
Total bilirubin (mg/dL)	1.8 ± 1.8	4.1 ± 6.7	9.6 ± 11.1	***0.012***
Direct bilirubin (mg/dL)	0.6 ± 0.9	1.5 ± 2.9	4.7 ± 5.5	***0.005***
Indirect bilirubin (mg/dL)	1.0 ± 0.9	2.6 ± 4.0	5.2 ± 5.6	***0.015***
Serum albumin (gm/dL)	3.9 ± 0.5	3.0 ± 0.4	2.8 ± 0.4	***< 0.001***
Creatinine (mg/dL)	1.0 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.569
Sodium (mEq/L)	142 ± 3	139 ± 4	136 ± 5	***< 0.001***
Potassium (mEq/L)	4.4 ± 0.7	4.5 ± 0.6	4.1 ± 0.7	***0.063***
Platelets (× 1 000/mm^3)	89 ± 51	114 ± 68	79 ± 51	*0.051*
Prothrombin time (s)	13.9 ± 1.4	15.0 ± 3.8	19.2 ± 4.8	***< 0.001***
International normalized ratio	1.2 ± 0.2	1.5 ± 0.6	2.3 ± 1.0	***< 0.001***

MELD – Model for End-stage Liver Disease; Na – sodium. Significant *p*-values (< 0.05) are marked in a bold-italic style

Table 3 – Comparison of electrocardiographic findings in cirrhotic patients based on Child-Pugh classification.

Variables	A N = 14	B N = 28	C N = 27	*p*-value
Mean voltage limb leads	4.6 ± 1.4	5.1 ± 2.5	4.5 ± 1.4	0.473
I	5.3 ± 2.5	6.4 ± 3.5	5.4 ± 3.0	0.631
II	5.6 ± 2.4	5.4 ± 2.6	5.0 ± 2.1	0.735
III	3.9 ± 1.7	5.1 ± 3.1	4.6 ± 2.1	0.331
avR	5.1 ± 1.9	5.3 ± 3.0	4.7 ± 2.1	0.651
avL	4.1 ± 1.3	4.4 ± 3.2	4.4 ± 1.9	0.992
avF	3.9 ± 2.0	4.4 ± 2.3	3.9 ± 2.0	0.662
Sum voltage limb leads	27.8 ± 8.2	30.6 ± 15.3	28.0 ± 10.4	0.768
Mean voltage precordial leads	9.1 ± 2.5	9.3 ± 3.7	9.0 ± 3.0	0.956
V1	9.3 ± 5.8	8.1 ± 4.1	6.8 ± 3.0	0.117
V2	10.9 ± 4.7	9.7 ± 4.6	9.2 ± 4.8	0.563
V3	11.6 ± 4.3	11.2 ± 3.8	11.1 ± 4.2	0.913
V4	8.9 ± 3.6	10.5 ± 4.7	10.0 ± 3.5	0.514
V5	7.4 ± 3.2	9.1 ± 5.2	7.1 ± 2.4	0.145
V6	6.3 ± 4.3	7.7 ± 4.3	6.0 ± 2.3	0.153
Sum voltage precordial leads	54.6 ± 15.2	54.8 ± 22.2	54.0 ± 18.0	0.988
Low-voltage ECG criteria	5 (35.7%)	14 (50.0%)	13 (50.0%)	0.634
Heart rate (bpm)	77 ± 17	83 ± 16	89 ± 18	0.029
RR interval (ms)	811 ± 160	754 ± 166	703 ± 164	0.113
PR interval (ms)	149 ± 19	153 ± 53	140 ± 24	0.411
QRS duration (ms)	84 ± 12	84 ± 19	83 ± 17	0.972
QTc interval (ms)	453 ± 52	455 ± 40	449 ± 50	0.913
Prolonged QTc-interval	6 (42.9%)	16 (57.1%)	13 (48.1%)	0.644

Table 4 – Comparison of electrocardiographic findings based on the Model for End-stage Liver Disease score of 18.

Variables	MELD (low) N = 38	MELD (high) N = 31	*p*-value
QT interval, ms	455 ± 46	449 ± 46	0.587
Mean precordial leads, mV	9.0 ± 2.7	8.9 ± 3.5	0.910
Mean limb leads, mV	4.6 ± 1.4	4.9 ± 2.5	0.614
QRS duration, ms	80 ± 18	88 ± 14	***0.049***
PR interval, ms	146 ± 19	149 ± 52	0.741
Heart rate, beat/min	84 ± 15	84 ± 20	0.950

MELD – Model for End-stage Liver Disease; Na – sodium. Significant *p*-values (< 0.05) are marked in a bold-italic style

Table 5 – Demographic and laboratory data among the patients with and without QT prolongation.

Variables	Normal QT interval (N = 34)	Prolonged QT (N = 35)	*p*-value
Age (years)	57 ± 16	56 ± 16	0.942
Gender (female/male)	14/20	10/25	0.199
Serum sodium (mmol/l)	139 ± 6	138 ± 5	0.816
Serum potassium (mmol/l)	4.3 ± 0.7	4.3 ± 0.7	0.912
Total calcium (mg/dL)	9.4 ± 1.4	9.1 ± 0.9	0.282
Ionized calcium (mmol/l)	1.2 ± 0.2	1.2 ± 0.1	0.584
Creatinine (mg/dL)	1.2 ± 0.3	1.0 ± 0.3	***0.013***
International normalized ratio	1.7 ± 0.8	1.7 ± 0.8	0.838
Total bilirubin (mg/dL)	5.5 ± 9.6	6.4 ± 8.3	0.699
Direct bilirubin (mg/dL)	2.6 ± 4.7	2.8 ± 4.1	0.851
Indirect bilirubin (mg/dL)	3.3 ± 5.1	3.5 ± 4.3	0.817
Platelets (× 1 000/μL)	95 ± 60	91 ± 62	0.708
Aspartate aminotransferase (IU/L)	100 ± 151	106 ± 232	0.894
Alanine aminotransferase (IU/L)	70 ± 95	76 ± 175	0.868
Albumin (gm/dL)	3.1 ± 0.6	3.1 ± 0.6	0.885
MELD score (UNOS)	18.5 ± 8.1	17.9 ± 9.9	0.423
MELD-Na	11.67 ± 9.97	11.09 ± 13.00	0.835
Child class A	8 (23.5%)	6 (17.1%)	0.452
Child class B	12 (35.3%)	16 (45.7%)	0.405
Child class C	14 (41.2%)	13 (37.2%)	0.090
Child score	8.6 ± 2.4	8.9 ± 2.5	0.548
Ascites	18 (52.9%)	22 (62.9%)	0.278
Icteric	13 (38.2%)	16 (45.7%)	0.622
Encephalopathy	9 (27.3%)	4 (13.8%)	0.162
Heart rate (beat/min)	82 ± 15	85 ± 15	0.121

MELD – Model for End-stage Liver Disease; Na – sodium. Significant *p*-values (< 0.05) are marked in a bold-italic style.

tage ECG in limb leads. Finally, there was no significant difference in mean or sum voltages in either the limb or precordial leads between the three groups, nor was there a significant difference in mean QTc-intervals.

Patients were also divided into two groups based on the cutoff MELD score of 18, which was repeatedly shown to be associated with 3-month mortality in a group of 180 cirrhotic patients [13,14]. Patients with scores equal to or greater than 18 were categorized as MELD-High and patients with scores less than 18 as MELD-Low (Table 4). The duration of QRS was in average 8 ms longer in patients with lower MELD scores compared to those with MELD scores > 18 ($p = 0.049$). The rest of the ECG findings including the heart rate, the mean QTc-interval and presence of low-voltages in limb or precordial leads were not significantly different between these two groups.

Table 6 – Multivariate linear regression model for QT interval (ms).

Model	Unstandardized coefficients		Standardized coefficients	t	*p*-values
	B	Std. error	Beta		
Constant	282.1	348.3		0.810	0.421
Age	–0.80	0.41	–0.269	–1.941	0.057*
Bilirubin (mg/dL)	–0.133	0.73	–0.030	–0.181	0.857
AST (IU)	0.04	0.11	0.175	0.400	0.690
ALT (IU)	–0.004	0.15	–0.013	–0.028	0.977
Total calcium (mg/dL)	–7.58	4.97	–0.194	–1.527	0.132
Serum albumin (g/dL)	–1.17	12.1	–0.017	–0.097	0.923
Creatinine (mg/dL)	13.5	6.40	0.318	2.103	0.040**
Sodium (mEq/L)	2.29	2.51	0.234	0.915	0.364
Potassium (mEq/L)	–8.49	7.68	–0.139	–1.106	0.274
Prothrombin time	–1.44	1.60	–0.171	–0.901	0.372
Child-Pugh Score	2.32	3.71	0.130	0.624	0.535
MELD-Na	0.51	1.10	0.150	0.465	0.643

* A trend *p*-value between 0.05 and 0.10.
** A *p*-value < 0.05.

Table 7 – Comparison of patients with and without low-voltage electrocardiogram.

Variables	Normal voltage (N = 36)	Low-voltage (N = 32)	*p*-value
Age (years)	53.2 ± 17.7	60.2 ± 12.3	***0.049***
Gender (female/male)	14/22	9/23	0.249
Serum sodium (mmol/L)	139 ± 5	138 ± 4	0.493
Serum potassium (mmol/L)	4.3 ± 0.3	4.5 ± 0.9	0.127
Total calcium (mg/dL)	9.5 ± 1.2	8.9 ± 0.9	0.061
Ionized calcium (mmol/L)	1.2 ± 0.1	1.2 ± 0.1	0.596
Creatinine (mg/dL)	1.0 ± 0.4	1.1 ± 1.4	0.389
International normalized ratio	1.8 ± 1.0	1.9 ± 0.8	0.625
Total bilirubin (mg/dL)	6.6 ± 10.7	5.3 ± 8.9	0.585
Direct bilirubin (mg/dL)	2.8 ± 5.1	2.2 ± 4.1	0.605
Indirect bilirubin (mg/dL)	3.6 ± 5.9	4.0 ± 3.1	0.715
Platelets (× 1 000/μL)	99 ± 64	92 ± 53	0.642
Aspartate aminotransferase (IU/L)	96 ± 145	113 ± 241	0.372
Alanine aminotransferase (IU/L)	62 ± 86	87 ± 186	0.469
Albumin (gm/dL)	3.3 ± 0.6	2.9 ± 0.5	***0.045***
MELD-Na	9.33 ± 7.46	13.46 ± 9.43	***0.048***
MELD score (UNOS)	17.8 ± 6.2	21.1 ± 7.2	***0.038***
Child class A	9 (25.0%)	5 (15.6%)	0.228
Child class B	14 (38.9%)	14 (43.8%)	0.834
Child class C	13 (36.1%)	13 (40.6%)	0.490
Child-Pugh Score	8.6 ± 2.7	9.3 ± 2.4	0.312
Ascites	20 (55.6%)	19 (59.4%)	0.472
Jaundice	17 (47.2%)	12 (37.5%)	0.715
Encephalopathy	7 (20.6%)	5 (18.5%)	0.551

MELD – Model for End-stage Liver Disease; Na – sodium. Significant *p*-values (< 0.05) are marked in a bold-italic style.

Patients in our study were also grouped into two classes based on the absence or presence of a prolonged QT-interval, and the two groups were compared in terms of laboratory values, clinical features, ECG findings and severity of cirrhosis (Table 5). Patients with a prolonged QTc--interval had a significantly lower serum creatinine than patients with a normal QTc-interval (1.0 ± 0.3 vs 1.2 ± 0.3, $p = 0.013$). There were no significant differences between the two groups in terms of other findings including serum electrolytes, mean heart rate, and mean Child and MELD scores ($p > 0.05$ for all variables). In linear regression models, serum creatinine is the only independent factor that significantly correlates with QT interval. For every 1 mg/dL of serum creatinine concentration, Q interval prolongs 13.5 ms ($p = 0.040$) (Table 6).

Patients were then allocated into two groups based on the absence or presence of low-voltage ECG, and similar to the previous analysis, the two groups were compared in terms of laboratory, clinical and ECG findings. When compared to patients with normal ECG voltage, patients with low ECG voltage had a significantly higher mean MELD score (21.1 ± 7.2 vs 17.8 ± 6.2 mV, $p = 0.038$) as well as lower serum albumin levels (2.9 ± 0.5 vs. 3.3 ± 0.6 mV, $p = 0.045$). Patients with low-voltage ECG also had significantly higher heart rates (89 ± 18 vs. 80 ± 15 beats per minute, $p = 0.030$) and were significantly older (60.2 ± 12.6 vs. 53.2 ± 17.7 years, $p = 0.049$). In contrast to patients with a prolonged QTc-interval, patients with low-voltage ECG did not demonstrate a significant difference in serum creatinine levels from patients with normal voltage (1.1 ± 1.4 vs. 1.0 ± 0.4, respectively; $p = 0.39$). There was also no difference in mean Child scores or serum electrolytes between the two groups. The presence of ascites also occurred in similar proportions of patients with or without low-voltage ECG (59.4% vs. 55.6%, respectively; $p = 0.47$) (Table 6).

By excluding the patients with low-voltage limb leads, the mean QRS voltage in precordial limbs was significantly lower in patients with ascites (8.8 ± 2.7 mV vs. 11.1 ± 3.4 mV, $p = 0.018$). However, the reverse was not true and by excluding the patients with low-voltage precordial leads, there was no difference in mean limb lead voltage in patients with and those without ascites (4.6 ± 1.4 mV vs. 5.5 ± 2.7 mV, respectively; $p = 0.118$).

Discussion

ECG abnormalities have been commonly seen with cirrhosis [5]. Prolongation of the QT-interval and low-voltage of QRS complex were thought to reflect cardiac dysfunction secondary to cirrhosis through undetermined mechanisms [2,15]. A direct correlation was described between the QT--prolongation and the ventricular loading in patients with severe cirrhosis [16]. In this study, QTc-prolongation was present in approximately 50% of the patients regardless of disease severity. This finding indicates that QTc-prolongation can be found in early, well-compensated cirrhosis as well as late stages of the disease.

Additionally, our study showed that Child-Pugh scores tend to be higher in patients with QT-prolongation although there was no difference in QT-interval and the frequency of QT-prolongation among difference classes of cirrhosis. A retrospective review of 48 cirrhotic patients described that the prevalence of QTc-prolongation rose from 19% in Class A 86% in Class C.[17] However, when the patients were analyzed according to etiology, they found that 15 out of 18 or 83% of patients with alcoholic cirrhosis had a QTc > 440 ms, whereas only 20% of patients with post-viral cirrhosis had the same abnormality. Furthermore, they noted that the severity of the disease was higher in patients with alcoholic cirrhosis. In a study of 94 cirrhotic patients, the prevalence of abnormal QTc rose from 25% in Class A to 60% in Class C and QTc-interval correlated with Child-Pugh scores [5]. Although the prevalence of prolonged QTc or its duration did not differ between patients with alcoholic versus nonalcoholic cirrhosis, the authors could not rule out the role of alcohol toxicity in QT-prolongation.

In other studies that also noted a correlation between cirrhosis severity and QTc-prolongation, alcoholic etiology similarly played a confounding role. Majority of patients (85.7%) with Class C and 53.4% in Class B had alcohol--related cirrhosis compared with only 15.4% of patients in Class A. In addition when the slope of the regression line QT/RR was calculated, patients with alcoholic cirrhosis had a steeper QT/RR slope than patients with viral cirrhosis, indicating that QTc was prolonged to a greater extent as the heart rate decreased [18]. Likewise, in a study by Bal and Thuluvath, QTc prolongation was more commonly seen in patients with alcoholic cirrhosis (60%) as compared with non-alcoholic cirrhosis, and alcoholic etiology was an independent predictor of QT-interval prolongation [4]. In contrast, Pozzi et al. found that the structural heart abnormalities were present more frequently even in pre-cirrhotic patients with HCV infection [19].

Electrolyte abnormalities are common in cirrhotic patients and lower calcium level described in cirrhotic patients with QT-prolongation [17]. Genovesi et al. noted that the three Child groups had modest but significant difference in calcium levels [17]. Calcium levels decreased from 1.25 mg/dL in Class A to 1.22 mg/dL in Class C and the QTc-interval duration was inversely correlated with plasma calcium ion concentration. Thus, serum concentrations of ionized calcium confound the positive association between QTc--prolongation and Child class. In this study, patients with ionized calcium abnormality were all excluded to eliminate the role of serum calcium. This may suggest the contribution of other intrinsic cardiac factors rather than electrolyte disturbance in pathogenesis of cardiac abnormalities.

Similar to our findings, in a prospective study of 48 cirrhotics, Henriksen et al. showed an increased prevalence of QTc-prolongation in cirrhotics without any correlation to the severity [20]. They claimed that this higher prevalence was due to the fact that a majority of the patients had alcoholic liver cirrhosis (43/48). However, alcoholic etiology was considerably less common among our patients despite the higher prevalence of QT-prolongation. These authors did observe, however, that patients with cirrhosis have deranged hemodynamics and abnormal coupling of electrical and mechanical systole and proposed that this finding may be due to mechanical cardiac defects due to portal hypertension.

Lastly, Kosar et al. also investigated the relationship between QT-dispersion and Child-Pugh Class, and found that

QT-dispersion increased from Class A to Class C but was not different between Class A and Class B [6]. This study is mainly limited by the fact that the reliability of QT-dispersion is significantly lower than that of the QT-interval, and QT-dispersion is considered a crude reflection of ventricular repolarization abnormalities as shown by others [21]. As such, only grossly abnormal values (> 100 ms) may have practical value, whereas authors of this study used a much lower cut-off (> 70 ms). Patel et al., similarly reported higher INR in patients with prolonged QT-interval [22], while another group found no relationship between the severity of liver disease as determined by the MELD and QT-prolongation among 117 cirrhotic patients [23].

In our study, neither the mean QTc-interval duration nor the prevalence of QTc-prolongation correlated with Child Class severity. The difference between these findings and those of previous studies may be explained by the absence of specific confounders and limitations as mentioned above. In this study, the proportion of patients with alcoholic cirrhosis did not differ significantly between the three classes and did not differ between patients with or without QT-prolongation, which minimizes the confounding influence of alcohol toxicity. Separating the effects of alcohol is critical because it is well established that harmful levels cause cardiac dysfunction and QT-prolongation independent of liver cirrhosis. Patients with low calcium were also excluded in this study, elimination the effect of this electrolyte abnormality on ventricular repolarization. Furthermore, regardless of correlation to Child score, the prevalence of QT-interval in well-compensated cirrhosis is not negligible, both in the aforementioned studies as well as in this one [4,6]. The consistency of this finding strongly suggests the potential role of other underlying factors in developing cardiac abnormalities beside liver disease severity.

Another important finding in this study is the attenuation of QRS voltage in both precordial and limb leads in a relatively high proportion of cirrhotic patients. As with QT-prolongation, the presence of low-voltage QRS complex in ECG is associated with impaired cardiac function and increased mortality [8]. Both cardiac and extra-cardiac etiologies including peripheral edema, ascites, hypovolemia and various pulmonary diseases can potentially affect the electrical conductivity of tissue and pericardial fluid.

Similar to QT-prolongation, while low-voltage was common in cirrhosis, there was no correlation to disease severity. This finding strengthens the notion that cardiac dysfunction may be present even in early stages of the disease. Furthermore, when patients were grouped by the presence or absence of low-voltage, patients with low-voltage have significantly lower serum albumin concentrations as well significantly higher MELD and MELD-Na scores. Lower serum albumin may contribute to and exacerbate peripheral edema while hyponatremia, which is caused by solute-free water retention, is considered an indirect marker of portal hypertension. Serum sodium concentration was found to be a sensitive, independent predictor of mortality with decreases as little as 1 mEq significantly affecting survival in cirrhosis. Indeed, MELD-Na captures a subset of patients with refractory ascites and low sodium that are typically underscored by MELD but have a high risk of early death.

Madias reported low-voltage ECG in two patients with cirrhosis, ascites and peripheral edema who were closely followed for a number of years [24]. They noted that low-voltage state became more profound with fluid overload and responded well to diuresis. Repeated abdominal paracentesis (up to 10 L ascites removed) did not affect the QRS voltage, they suggested that low-voltage was not associated with ascites and was likely due to peripheral edema alone. On the other hand, in 20 patients with ascites (of which half were cirrhosis-related) and showed that low-voltage was seen in both limb and precordial leads [25]. They proposed that low-voltage was due to upwards displacement of the heart by increased intra-abdominal pressure and could be temporarily corrected by more cranially placing the precordial leads.

In our study population, patients with ascites had similar rates of low-voltage criteria that include patients with low QRS voltage in either limb or precordial leads. However, by considering the patients with low-voltages in only the precordial limbs, patients with ascites had significantly lower voltage in precordial leads as compared to those without ascites, confirming Cuculi's finding. This may suggest a different pathophysiological process for developing low-voltage ECG in limb and precordial leads as Cuculi pointed out, with low-voltages in the precordial leads more specific for ascites than peripheral edema. While we did not find a significant difference between low ECG voltages in the limb leads, QRS attenuation can be a normal variant particularly in the limb leads. Additionally, patients with refractory ascites typically have the poorest prognosis.

The present study is limited by its retrospective design. Automatic QTc measurement by ECG device may not be accurate partly because of the inconsistency between algorithms used for interval calculations [26]. Accordingly manual reading is preferred and was utilized in this study. The findings in our study are important and clinically significant for several reasons. First, we confirm previous studies that ECG abnormalities are common in cirrhotic patients. In addition, our findings serve to help clarify the controversy regarding the effect of cirrhosis severity and related clinical symptoms on the emergence of cardiac complications [4,27,28]. Our results show that both QTc-prolongation and attenuation of QRS voltage are not related to liver severity and that these ECG changes are present even in well-compensated cirrhosis. Whether screening stable compensated patients for prolongation of QT interval influence the survival of the patients needs to be determined.

Conflict of interest
No conflict of interest.

Funding body
None.

Ethical statement
I declare, on behalf of all authors that the research was conducted according to Declaration of Helsinki.

Informed consent
I declare, on behalf of all authors that the informed consent was obtained from all patients participating in this study.

References

[1] R. Bataller, D.A. Brenner, Liver fibrosis, Journal of Clinical Investigation 115 (2005) 209–218.
[2] S.K. Baik, T.R. Fouad, S.S. Lee, Cirrhotic cardiomyopathy, Orphanet Journal of Rare Diseases 2 (2007) 15.
[3] Y.Y. Yang, H.C. Lin, The heart: pathophysiology and clinical implications of cirrhotic cardiomyopathy, Journal of the Chinese Medical Association 75 (2012) 619–623.
[4] J.S. Bal, P.J. Thuluvath, Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation, Liver International 23 (2003) 243–248.
[5] M. Bernardi, S. Calandra, A. Colantoni, et al., Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors, Hepatology 27 (1998) 28–34.
[6] F. Kosar, F. Ates, I. Sahin, et al., QT interval analysis in patients with chronic liver disease: a prospective study, Angiology 58 (2007) 218–224.
[7] A.O. Usoro, N. Bradford, A.J. Shah, E.Z. Soliman, Risk of mortality in individuals with low QRS voltage and free of cardiovascular disease, American Journal of Cardiology 113 (2014) 1514–1517.
[8] J.E. Madias, Low QRS voltage and its causes, Journal of Electrocardiology 41 (2008) 498–500.
[9] J.E. Madias, Low voltage ECG in myocarditis: peripheral edema as a plausible contributing mechanism, Pacing and Clinical Electrophysiology 30 (2007) 448–452.
[10] R.B. Freeman Jr., R.H. Wiesner, A. Harper, et al., The new liver allocation system: moving toward evidence-based transplantation policy, Liver Transplantation 8 (2002) 851–858.
[11] M. Malinchoc, P.S. Kamath, F.D. Gordon, et al., A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts, Hepatology 31 (2000) 864–871.
[12] R.N. Pugh, I.M. Murray-Lyon, J.L. Dawson, et al., Transection of the oesophagus for bleeding oesophageal varices, British Journal of Surgery 60 (1973) 646–649.
[13] L. Amitrano, M.A. Guardascione, R. Bennato, et al., MELD score and hepatocellular carcinoma identify patients at different risk of short-term mortality among cirrhotics bleeding from esophageal varices, Journal of Hepatology 42 (2005) 820–825.
[14] G. D'Amico, Developing concepts on MELD: delta and cutoffs, Journal of Hepatology 42 (2005) 790–792.
[15] S.A. Alqahtani, T.R. Fouad, S.S. Lee, Cirrhotic cardiomyopathy, Seminars in Liver Disease 28 (2008) 59–69.
[16] A. Moaref, M. Zamirian, M. Yazdani, et al., The correlation between echocardiographic findings and QT interval in cirrhotic patients, International Cardiovascular Research Journal 8 (2014) 39–43.
[17] S. Genovesi, D.M. Prata Pizzala, M. Pozzi, et al., QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium, Clinical Science 116 (2009) 851–859.
[18] C. Lazzeri, G. La Villa, G. Laffi, et al., Autonomic regulation of heart rate and QT interval in nonalcoholic cirrhosis with ascites, Digestion 58 (2009) 580–586.
[19] M. Pozzi, E. Redaelli, L. Ratti, et al., Time-course of diastolic dysfunction in different stages of chronic HCV related liver diseases, Minerva Gastroenterologica e Dietologica 51 (2005) 179–186.
[20] J.H. Henriksen, S. Fuglsang, F. Bendtsen, et al., Dyssynchronous electrical and mechanical systole in patients with cirrhosis, Journal of Hepatology 36 (2002) 513–520.
[21] M. Malik, B. Acar, Y. Gang, et al., QT dispersion does not represent electrocardiographic interlead heterogeneity of ventricular repolarization, Journal of Cardiovascular Electrophysiology 11 (2000) 835–843.
[22] D. Patel, P. Singh, W. Katz, et al., QT interval prolongation in end-stage liver disease cannot be explained by nonhepatic factors, Annals of Noninvasive Electrocardiology 19 (2014) 574–581.
[23] S. Tarique, S. Sarwar, Correlation of prolonged QT interval and severity of cirrhosis of liver, Annals of King Edward Medical University 17 (2011) 103–107.
[24] J.E. Madias, Attenuation of ECG voltage in cirrhotic patients, Europace 9 (2007) 175–181.
[25] F. Cuculi, P. Jamshidi, R. Kobza, et al., Precordial low voltage in patients with ascites, Europace 10 (2008) 96–98.
[26] I. Goldenberg, A.J. Moss, W. Zareba, QT interval: how to measure it and what is normal, Journal of Cardiovascular Electrophysiology 17 (2006) 333–336.
[27] E. Hajiani, A. Masjedizadeh, K. Ahmadi, The prevalence of corrected QT interval in ECG and the severity of cirrhosis, Journal of Research in Medical Sciences 7 (2003) 319–321.
[28] S. Hansen, S. Moller, F. Bendtsen, et al., Diurnal variation and dispersion in QT interval in cirrhosis: relation to haemodynamic changes, Journal of Hepatology 47 (2007) 373–380.