

# World Journal of *Cardiology*

*World J Cardiol* 2017 April 26; 9(4): 296-395





### MINIREVIEWS

- 296 Pacemaker recycling: A notion whose time has come  
*Runge MW, Baman TS, Davis S, Weatherwax K, Goldman E, Eagle KA, Crawford TC*
- 304 Coronary artery disease detection - limitations of stress testing in left ventricular dysfunction  
*Bomb R, Kumar S, Chockalingam A*
- 312 Feature tracking cardiac magnetic resonance imaging: A review of a novel non-invasive cardiac imaging technique  
*Rahman ZU, Sethi P, Murtaza G, Virk HUH, Rai A, Mahmood M, Schoondyke J, Albalbissi K*

### ORIGINAL ARTICLE

#### Basic Study

- 320 Dissection of Z-disc myopalladin gene network involved in the development of restrictive cardiomyopathy using system genetics approach  
*Gu Q, Mendsaikhon U, Khuchua Z, Jones BC, Lu L, Towbin JA, Xu B, Purevjav E*

#### Retrospective Cohort Study

- 332 Blood conservation pediatric cardiac surgery in all ages and complexity levels  
*Karimi M, Sullivan JM, Linthicum C, Mathew A*
- 339 Bilateral vs unilateral internal mammary revascularization in patients with left ventricular dysfunction  
*Popovic B, Maureira P, Juilliere Y, Danchin N, Voilliot D, Vanhuyse F, Villemot JP*

#### Retrospective Study

- 347 QT prolongation is associated with increased mortality in end stage liver disease  
*Kim SM, George B, Alcivar-Franco D, Campbell CL, Charnigo R, Delisle B, Hundley J, Darrat Y, Morales G, Elayi SC, Bailey AL*
- 355 Determinants of percutaneous coronary intervention success in repeat chronic total occlusion procedures following an initial failed attempt  
*Cuevas C, Ryan N, Quirós A, Del Angel JG, Gonzalo N, Salinas P, Jiménez-Quevedo P, Nombela-Franco L, Nuñez-Gil I, Fernandez-Ortiz A, Macaya C, Escaned J*

#### Observational Study

- 363 Speckle tracking echocardiography to assess regional ventricular function in patients with apical hypertrophic cardiomyopathy  
*Saccheri MC, Cianciulli TF, Morita LA, Méndez RJ, Beck MA, Guerra JE, Cozzarin A, Puente LJ, Balletti LR, Lax JA*

- 371** Inter-ethnic marriages and severity of coronary artery disease: A multicenter study of Arabian Gulf States  
*Daoulah A, Al-kaabi S, Lotfi A, Al-Murayeh M, Nasser SA, Ahmed W, Al-Otaibi SN, Alama MN, Elkhateeb OE, Plotkin AJ, Malak MM, Alshali K, Hamzi M, Al Khunein S, Abufayyah M, Alsheikh-Ali AA*

**META-ANALYSIS**

- 378** Contrast use in relation to the arterial access site for percutaneous coronary intervention: A comprehensive meta-analysis of randomized trials  
*Shah R, Mattox A, Khan MR, Berzingi C, Rashid A*

**CASE REPORT**

- 384** Three-dimensional optical coherence tomography reconstruction of bifurcation stenting using the Szabo anchor-wire technique  
*Yu K, Hundal H, Zynda T, Seto A*
- 391** Conservative management of aortic root rupture complicated with cardiac tamponade following transcatheter aortic valve implantation  
*Vannini L, Andrea R, Sabaté M*

**ABOUT COVER**

Editorial Board Member of *World Journal of Cardiology*, Peter E Ong, MD, Senior Scientist, Department of Cardiology, Robert Bosch Krankenhaus, 70376 Stuttgart, Germany

**AIM AND SCOPE**

*World Journal of Cardiology (World J Cardiol, WJC)*, online ISSN 1949-8462, DOI: 10.4330) is a peer-reviewed open access journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

*WJC* covers topics concerning arrhythmia, heart failure, vascular disease, stroke, hypertension, prevention and epidemiology, dyslipidemia and metabolic disorders, cardiac imaging, pediatrics, nursing, and health promotion. Priority publication will be given to articles concerning diagnosis and treatment of cardiology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJC*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

**INDEXING/ABSTRACTING**

*World Journal of Cardiology* is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

**FLYLEAF**

**I-IV** Editorial Board

**EDITORS FOR THIS ISSUE**

**Responsible Assistant Editor:** *Xiang Li*  
**Responsible Electronic Editor:** *Ya-Jing Lu*  
**Proofing Editor-in-Chief:** *Lian-Sheng Ma*

**Responsible Science Editor:** *Jin-Xin Kong*  
**Proofing Editorial Office Director:** *Xiu-Xia Song*

**NAME OF JOURNAL**  
*World Journal of Cardiology*

**ISSN**  
ISSN 1949-8462 (online)

**LAUNCH DATE**  
December 31, 2009

**FREQUENCY**  
Monthly

**EDITORS-IN-CHIEF**  
**Jian-Jun Li, MD, PhD, Professor**, Center for Coronary Artery Disease, Fu Wai Cardiovascular Hospital, Chinese Academy of Medical Science, Beijing 100037, China

**Giuseppe De Luca, PhD**, Assistant Professor, Department of Cardiology, Piedmont University, Novara 28100, Italy

**Nathan D Wong, FACC, FAHA, PhD, Director, Professor**, Heart Disease Prevention Program, Division of Cardiology, Department of Medicine, University of California, Irvine, CA 92629, United States

sity of California, Irvine, CA 92629, United States

**EDITORIAL BOARD MEMBERS**  
All editorial board members resources online at <http://www.wjgnet.com/1949-8462/editorialboard.htm>

**EDITORIAL OFFICE**  
Xiu-Xia Song, Director  
*World Journal of Cardiology*  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLISHER**  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLICATION DATE**  
April 26, 2017

**COPYRIGHT**  
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

**SPECIAL STATEMENT**  
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

**INSTRUCTIONS TO AUTHORS**  
<http://www.wjgnet.com/bpg/gerinfo/204>

**ONLINE SUBMISSION**  
<http://www.f6publishing.com>

Retrospective Study

## QT prolongation is associated with increased mortality in end stage liver disease

Sun Moon Kim, Bennet George, Diego Alcivar-Franco, Charles L Campbell, Richard Charnigo, Brian Delisle, Jonathan Hundley, Yousef Darrat, Gustavo Morales, Samy-Claude Elayi, Alison L Bailey

Sun Moon Kim, Bennet George, Brian Delisle, Yousef Darrat, Gustavo Morales, Samy-Claude Elayi, Division of Cardiovascular Medicine, Gill Heart Institute, University of Kentucky, Lexington, KY 40509, United States

Diego Alcivar-Franco, Department of Cardiology, Summa Health System, Akron, OH 44304, United States

Charles L Campbell, Alison L Bailey, Division of Cardiovascular Medicine, Erlanger Health System, University of Tennessee College of Medicine Chattanooga, Chattanooga, TN 37403, United States

Richard Charnigo, Departments of Biostatistics and Statistics, University of Kentucky, Lexington, KY 40536, United States

Jonathan Hundley, Piedmont Transplant Institute, Atlanta, GA 30309, United States

**Author contributions:** Kim SM designed and performed the research and wrote the paper; Bailey AL and Elayi SC designed the research and supervised the report; George B, Alcivar-Franco D and Charnigo R contributed to the analysis; Campbell CL, Delisle B, Hundley J, Darrat Y and Morales G provided clinical advice.

**Institutional review board statement:** This study was reviewed and approved by the institutional review board at University of Kentucky.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used clinical data without storage of patient identifiers that were obtained after each patient agreed to treatment by written consent. Waiver of informed consent was also obtained because the research involved no more than minimal risk and met criteria specified by federal regulations.

**Conflict-of-interest statement:** The authors of this manuscript have no conflict of interest to disclose.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to:** Samy-Claude Elayi, MD, Division of Cardiovascular Medicine, Gill Heart Institute, University of Kentucky, 900 South Limestone, Room 326 Wethington Bldg, Lexington, KY 40509, United States. [samy-claude.elayi@uky.edu](mailto:samy-claude.elayi@uky.edu)  
**Telephone:** +1-859-3238040  
**Fax:** +1-859-3236475

**Received:** November 16, 2016

**Peer-review started:** November 18, 2016

**First decision:** November 30, 2016

**Revised:** January 13, 2017

**Accepted:** February 18, 2017

**Article in press:** February 20, 2017

**Published online:** April 26, 2017

## Abstract

### AIM

To determine the prevalence of QT prolongation in a large series of end stage liver disease (ESLD) patients and its association to clinical variables and mortality.

### METHODS

The QT interval was measured and corrected for heart rate for each patient, with a prolonged QT cutoff defined as QT > 450 ms for males and QT > 470 ms for females.



Multiple clinical variables were evaluated including sex, age, serum sodium, international normalized ratio, creatinine, total bilirubin, beta-blocker use, Model for End-Stage Liver Disease (MELD), MELD-Na, and etiology of liver disease.

## RESULTS

Among 406 ESLD patients analyzed, 207 (51.0%) had QT prolongation. The only clinical variable associated with QT prolongation was male gender (OR = 3.04, 95%CI: 2.01-4.60,  $P < 0.001$ ). During the study period, 187 patients (46.1%) died. QT prolongation was a significant independent predictor of mortality (OR = 1.69, 95%CI: 1.03-2.77,  $P = 0.039$ ). In addition, mortality was also associated with viral etiology of ESLD, elevated MELD score and its components ( $P < 0.05$  for all). No significant reversibility in the QT interval was seen after liver transplantation.

## CONCLUSION

QT prolongation was commonly encountered in an ESLD population, especially in males, and served as a strong independent marker for increased mortality in ESLD patients.

**Key words:** Cirrhosis; Electrophysiology; Arrhythmias; QT prolongation; Mortality; Liver transplantation

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** We performed a case-control retrospective study in a large cohort of patients with end stage liver disease (ESLD) to determine the prevalence of QT prolongation and its association to clinical variables and mortality. Our results showed a high prevalence of QT prolongation in ESLD patients (51%), especially in males, and QT prolongation was a significant independent predictor of mortality. Based on our findings, we recommend close monitoring of the QT interval in ESLD patients with increased attention to any modifiable causes for QT prolongation.

Kim SM, George B, Alcivar-Franco D, Campbell CL, Charnigo R, Delisle B, Hundley J, Darrat Y, Morales G, Elayi SC, Bailey AL. QT prolongation is associated with increased mortality in end stage liver disease. *World J Cardiol* 2017; 9(4): 347-354 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i4/347.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i4.347>

## INTRODUCTION

The QT interval on an electrocardiogram (ECG) is a measure of ventricular depolarization and repolarization. Prolongation of the QT interval is associated with ventricular arrhythmias as well as sudden cardiac death in both congenital and acquired conditions. Multiple factors are thought to be responsible for the prolongation

of the QT interval in both congenital and acquired conditions, including electrolyte abnormalities, ventricular channelopathies, myocardial ischemia, medications, alcohol toxicity, and autonomic imbalance with sympathetic nervous system hyperactivity<sup>[1-11]</sup>. Recent studies have shown that end stage liver disease (ESLD) is associated with several electrophysiological changes; specifically, an increased prevalence of QT prolongation is seen in this population<sup>[12-30]</sup>. While the exact mechanism for QT prolongation is unknown, both improvement in liver function and liver transplantation have been associated with significant shortening in the QT interval in studies with small sample sizes<sup>[25-31]</sup>. Likewise, previous studies demonstrate reduction in the QT interval for cirrhotic patients who receive beta-adrenergic blockade in both the acute and chronic settings<sup>[32-34]</sup>. Thus, this may be a modifiable condition and amenable to therapy. Although some studies suggest a prolonged QT interval is related to severity of liver disease, etiology of liver disease, and increased mortality, conflicting results exist regarding these important clinical questions<sup>[14,19,24-30,35,36]</sup>.

We aimed to determine the prevalence and variables associated with QT prolongation in ESLD patients. Furthermore, we assessed whether QT prolongation was associated with increased mortality in these patients.

## MATERIALS AND METHODS

The research study was conducted in accordance to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by approval by the institutional review board. After institutional review board approval was obtained, we performed a case-control retrospective study estimating the prevalence of QT prolongation in a cohort of cirrhotic patients with ESLD being evaluated for liver transplant. We then quantified the associations of QT prolongation with multiple clinical variables including etiology of liver disease, sex, age, Model for End-Stage Liver Disease (MELD) score, MELD-Na (MELD with incorporation of serum sodium) score, sodium level, international normalized ratio (INR), creatinine, total bilirubin, beta-blocker use, liver transplantation, and mortality. Variables were collected from the most recent labs collected (within 90 d of baseline ECG) as part of routine outpatient care. We utilized the Organ Transplant Tracking Record (OTTR) database and hospital records to identify our cohort and track their survival.

Patients included men and women above age of 18 with ESLD who were undergoing a liver transplant evaluation for any indication and had ECGs available for visual analysis. For patients who did not undergo a liver transplant, the most recent ECGs were used as baseline. For transplanted patients, the ECG prior to transplant was used as the baseline ECG while the average QT interval from the post-transplant ECGs was used to determine the effects of transplant on QT prolongation. This was done to eliminate artifacts due to the unstable or immediate post transplantation recovery period when the

patients' ECGs are vulnerable to medication changes or electrolyte imbalances. Patients without an interpretable ECG, or with conduction abnormalities, recent myocardial infarction (within the last 30 d by history), or pacemaker use, were excluded from the study.

### QT determination

For all 12 lead ECGs, the QT interval based on Bazett's principle (QT<sub>c</sub>) was obtained automatically using a computerized ECG machine (General Electronics MAC 5500 HD) to avoid interobserver variability. With Bazett's principle, the QT interval is measured from the beginning of the QRS complex to the termination of the T-wave and divided by the square root of the R-R interval in seconds<sup>[37]</sup>. A QT<sub>c</sub> > 450 ms for males and a QT<sub>c</sub> > 470 ms for females was considered abnormal or prolonged, as defined by European regulatory guidelines<sup>[38]</sup> and Goldenburg *et al.*<sup>[39]</sup> to account for gender differences. Patients with QT<sub>c</sub> prolongation were subdivided into three categories for analytic purposes: mild (451-470 ms in males; 471-490 ms in females), moderate (471-490 ms in males; 491-510 ms in females), and severe (> 490 ms in males; > 510 ms in females).

### Statistical analysis

Patients with (*n* = 207) and without QT<sub>c</sub> prolongation (*n* = 199) were compared on various clinical characteristics by *T* tests (for continuous variables and after log transformation for INR, creatinine, and bilirubin) and Fisher's exact tests (for dichotomous variables). Logistic regressions with QT<sub>c</sub> prolongation as the outcome were performed to identify significant unadjusted and adjusted associations with clinical characteristics identified in the next sentence. The first of three multivariate models included beta blocker use, etiology (viral, ethanol, non-alcohol steatohepatitis), MELD components (sodium, log INR, log creatinine, and log bilirubin), gender, and age as predictors; the second and third multivariate models replaced MELD components by total MELD score and total MELD-Na score respectively. Four logistic regressions with mortality as the outcome were also performed. The first related mortality to degree (mild, moderate, severe) of QT<sub>c</sub> prolongation. The second through fourth analyses related mortality to QT<sub>c</sub> prolongation and the aforementioned clinical characteristics, in parallel with the three multivariate models for QT<sub>c</sub> prolongation. A paired signed rank test was used to examine the change in QT<sub>c</sub> before and after surgery in a subset of patients (*n* = 74) receiving liver transplantations. Approximately 25% of the patients did not have routine outpatient labs within the 90 d of their baseline ECG. Therefore, the analyses involving the MELD components and MELD totals were performed using multiple imputation. Microsoft Excel, SAS, and R were used for data analysis and visualization. Statistical significance was declared when *P* < 0.05.

## RESULTS

### Patient characteristics

The OTTR database revealed that 729 patients were

evaluated for a liver transplant at the University of Kentucky over a recent 12-year period. Of the 729 patients, 406 met the inclusion criteria for this study. In addition, approximately 25% of the patients (102 out of 406) did not have routine outpatient labs within the 90 d of their baseline ECG. The effective sample size for comparison of QT interval pre- and post-transplantation was 74. The estimated prevalence of QT prolongation was 51.0% (207 out of 406).

Table 1 shows that the 207 patients with QT prolongation (QT<sub>c</sub> by Bazett's  $\geq$  450 for males and  $\geq$  470 ms for females) were generally similar to the 199 patients without QT prolongation based on clinical variables. However, males with QT prolongation had higher creatinine, MELD, and MELD-NA scores than males without QT prolongation. Beta-blocker use was more common in females without QT prolongation.

In logistic regression analysis with QT<sub>c</sub> prolongation as an outcome variable, there was a significant association with male sex [estimated odds ratio (OR) 3.04, 95%CI: 2.01-4.60, *P* < 0.001]. The association persisted in all three multivariate models, with adjusted OR between 3.05 and 3.09 (*P* < 0.001 in all cases); there were no other significant predictors of QT<sub>c</sub> prolongation in these models.

Of the 406 patients, 187 (46.1%) died during the study period. Any level (mild, moderate, or severe) of QT<sub>c</sub> prolongation was associated with significantly increased mortality (Table 2). However, the risk of mortality did not exhibit an increasing pattern with respect to the level of prolongation.

Figure 1 shows that QT<sub>c</sub> prolongation is a significant predictor of mortality (OR 1.69, 95%CI: 1.03-2.77, *P* = 0.039) in a multivariate model which adjusts for the components of MELD and other clinical variables. This model also reveals significant associations with mortality for viral etiology, ethanol etiology, combined viral and ethanol etiology, INR, creatinine, and bilirubin. Figure 2 depicts findings for an additional multivariate model in which MELD replaces its components, while Figure 3 pertains to a model with MELD-Na. In all the models, QT<sub>c</sub> prolongation and the aforementioned etiologies remain significant predictors of mortality.

Effective sample size for comparison of QT<sub>c</sub> interval pre- and post-transplantation was 74. Median pre-transplant QT<sub>c</sub> was 457 with interquartile range of 435-472 ms. Median post-transplant QT<sub>c</sub> was 450 with interquartile range of 429-468. Our study showed no significant change in the QT<sub>c</sub> interval after liver transplantation (*P* = 0.24).

## DISCUSSION

Electrophysiologic cardiac abnormalities are well documented in patients with ESLD. As noted in our study, QT prolongation is a common finding within this population. Although the exact mechanism for QT prolongation in ESLD remains to be established, previous studies have suggested QT prolongation in ESLD may be multifactorial

**Table 1 Patient characteristics *n* (%)**

Variable	QTc prolongation			No QTc prolongation		
	All ( <i>n</i> = 207)	Male ( <i>n</i> = 150)	Female ( <i>n</i> = 57)	All ( <i>n</i> = 199)	Male ( <i>n</i> = 92)	Female ( <i>n</i> = 107)
Beta-blocker use <sup>1</sup>	161 (77.8)	122 (81.3)	39 (68.4)	153 (77.7)	66 (71.7)	87 (82.9) <sup>3</sup>
Viral etiology	80 (38.7)	65 (43.3)	15 (26.3)	69 (34.7)	42 (45.7)	27 (25.2)
Ethanol etiology	90 (43.5)	78 (52.0)	12 (21.1)	68 (34.2)	46 (50.0)	22 (20.6)
Non-alcohol steatohepatitis etiology	47 (22.7)	28 (18.7)	19 (33.3)	57 (28.6)	13 (14.1)	44 (41.1)
Viral and ethanol etiology	35 (16.9)	32 (21.3)	3 (5.3)	24 (12.1)	17 (18.5)	7 (6.5)
Sodium <sup>2</sup>	135.6 ± 6.2	135.4 ± 6.4	136.3 ± 5.3	136.2 ± 5.6	135.4 ± 5.6	136.9 ± 5.6
INR <sup>2</sup> (logarithm)	0.39 ± 0.32	0.39 ± 0.32	0.37 ± 0.31	0.35 ± 0.34	0.31 ± 0.26	0.39 ± 0.39
Creatinine <sup>2</sup> (logarithm)	0.39 ± 0.51	0.43 ± 0.50	0.30 ± 0.53	0.30 ± 0.43	0.29 ± 0.40 <sup>3</sup>	0.31 ± 0.46
Bilirubin <sup>2</sup> (logarithm)	1.19 ± 1.05	1.18 ± 1.07	1.20 ± 0.99	1.06 ± 0.96	0.90 ± 0.86	1.20 ± 1.03
MELD-NA <sup>2</sup>	21.0 ± 9.5	21.6 ± 9.5	19.5 ± 9.3	19.3 ± 9.1	18.6 ± 7.7 <sup>3</sup>	19.8 ± 10.2
MELD <sup>2</sup>	19.0 ± 9.6	19.4 ± 9.7	18.0 ± 9.3	17.3 ± 9.0	16.0 ± 7.2 <sup>3</sup>	18.3 ± 10.1
Age	56.1 ± 9.1	56.2 ± 8.8	56.0 ± 9.7	56.7 ± 9.0	56.3 ± 9.3	57.0 ± 8.7

Entries are number (percent) or mean ± SD. <sup>1</sup>Excluded for two subjects; <sup>2</sup>Excluded for 102 subjects; <sup>3</sup>Significantly different (*P* < 0.05) *vs* patients of same gender with QTc prolongation.

**Table 2 Estimated odds ratios for mortality based on levels of QTc prolongation**

	OR	<i>P</i>	95%CI
Mild QTc prolongation <i>vs</i> none	1.67	0.045	1.01-2.76
Moderate QTc prolongation <i>vs</i> none	2.11	0.013	1.17-3.81
Severe QTc prolongation <i>vs</i> none	1.83	0.044	1.02-3.31

Mild QTc prolongation: 451-470 ms in males and 471-490 ms in females; Moderate QTc prolongation: 471-490 ms in males and 491-510 ms in females; Severe QTc prolongation: > 490 ms in males and > 510 ms in females.

and related to abnormalities in potassium channels involved in repolarization, high plasma concentrations of bile salts, and autonomic dysfunction<sup>[12-19,40]</sup>.

In our study, the majority of patients (51.0%) demonstrated QT prolongation when calculated using Bazett's formula. Of the 406 patients evaluated, 187 (46.1%) died between years 2000 to 2013, confirming the high mortality in ESLD. An increase in mortality was seen at all levels of prolonged QT. Moreover, some etiologies and MELD components, as well as total MELD and MELD-Na scores, were predictive of mortality. These findings suggest worse outcomes in patients with viral hepatitis or combined viral and ethanol etiology, and they further validate the utility of MELD, MELD-Na, and its components for predicting survival in ESLD<sup>[41,42]</sup>. Importantly, QT prolongation predicts mortality above and beyond the aforementioned factors.

A number of studies have evaluated the association between QT prolongation and severity of ESLD as measured by Child-Pugh scores<sup>[14,19,24,25,28,36]</sup>. The majority of such studies have shown an increase in QT prolongation in association with higher Child-Pugh scores with the exception of studies done by Carey *et al.*<sup>[27]</sup> and Adigun *et al.*<sup>[30]</sup>. Due to the interobserver variability and use of subjective parameters in Child-Pugh classifications, MELD and MELD-Na scores are now widely viewed as superior indices for predicting mortality and allocating

transplants<sup>[41,42]</sup>. In our study, no significant associations were seen between QT prolongation and these superior indices of ESLD, in accord with the smaller studies by Zurick *et al.*<sup>[29]</sup> and Day *et al.*<sup>[35]</sup>.

Our study is unique in that we used validated thresholds for QT prolongation. While other studies used a cutoff of 440 msec, our study uses gender specific cutoffs as suggested by Goldenberg *et al.*<sup>[39]</sup>, to account for gender differences in QT prolongation that are typically longer for females<sup>[7,38,39,43]</sup>. Given our use of higher thresholds (> 450 ms for males and > 470 for females), which allowed higher selectivity for more severe QT prolongation, we may have underestimated the prevalence of QT prolongation while overestimating its association with other variables. Although Adigun *et al.*<sup>[30]</sup> demonstrated that a physiologic gender difference in the QTc interval is abolished in cirrhosis and that gender hormone concentrations have no effect on the QTc interval, our study reports a much higher prevalence of QT prolongation among males. When QTc prolongation was a dependent variable in our logistic regression models, both unadjusted and adjusted results showed statistically significant associations between QTc prolongation and male sex, while no other variables considered were significantly associated with QTc prolongation. A potential limitation to our study and explanation for these findings may be the use of gender specific thresholds and the corresponding assumption that gender differences in QT interval exist among ESLD patients. In particular, the higher cutoff for females may tend to understate QT prolongation prevalence within that gender.

Due to their utility and wide use in portal hypertension, the effects of acute and chronic beta-blockers on QT prolongation have been evaluated, with results showing a reduced QT interval<sup>[32-34]</sup>. In addition, partial or full reversal of QT prolongation following liver transplantation has also been noted<sup>[14,26-31]</sup>. Contrary to these findings, in our study, QTc prolongation was not significantly influenced by etiology, age, beta-blocker use, or transplantation. Although beta-blocker use had a trend towards lower



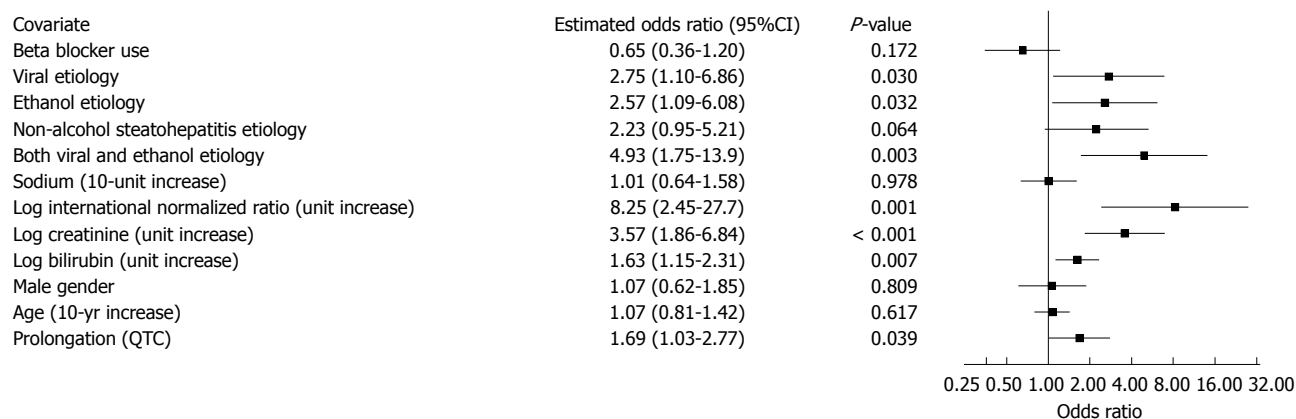


Figure 1 Association of mortality with Model for End-Stage Liver Disease components and clinical variables.

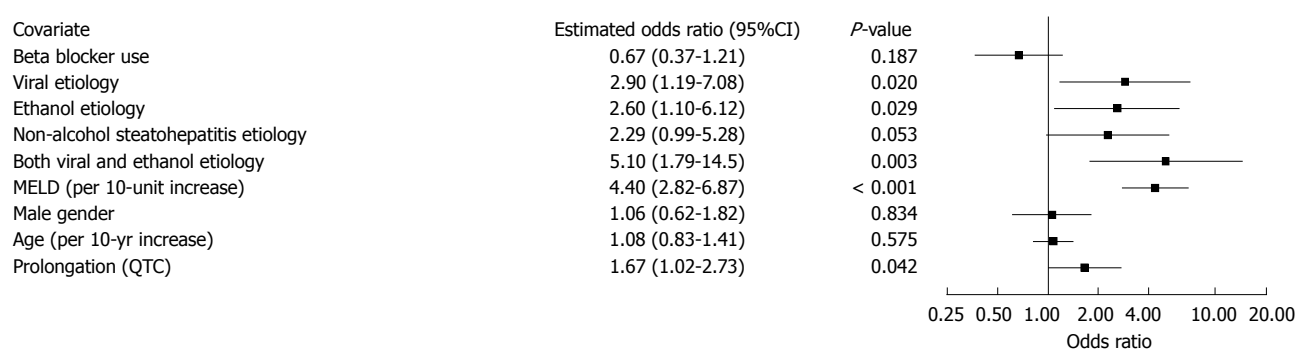


Figure 2 Association of mortality with total Model for End-Stage Liver Disease score and clinical variables.

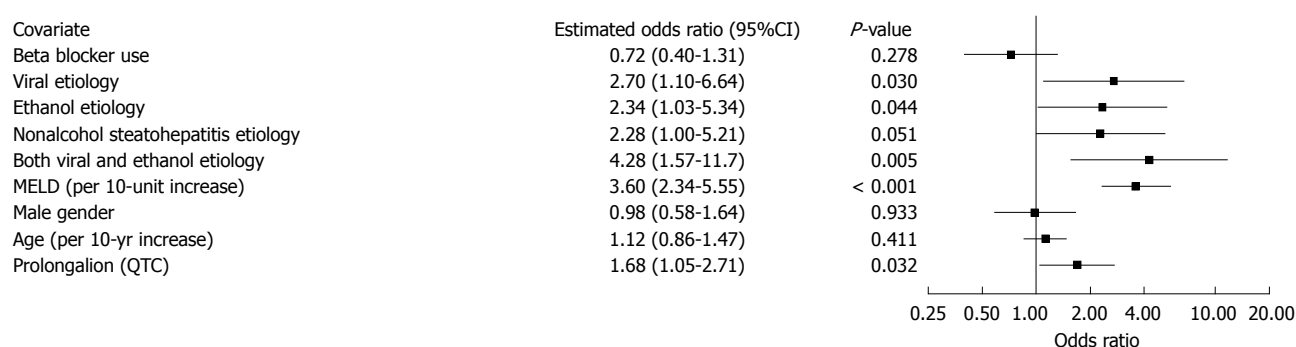


Figure 3 Association of mortality with total Model for End-Stage Liver Disease with incorporation of serum sodium score and clinical variables.

mortality, this did not meet statistical significance. The lack of reversibility in the QT interval following liver transplantation in our study may be due to our small effective sample size.

Several additional limitations need to be considered in our present investigation. As a retrospective study, our results have the potential for unintentional selection bias. Patients from our study were mostly Caucasian residing in rural areas from the state of Kentucky, which may not generalize geographically to the entire country. Our preoperative and postoperative ECGs were obtained during unspecified hospital or clinic visits, exposing our study to sampling bias related to factors such as electrolyte imbalance or concomitant use of QT

prolonging drugs. As noted above, MELD variables were unavailable from 102 out of 406 patients (25%) due to lack of outpatient labs within 90 d of their baseline ECG. Although MELD scores are frequently calculated for cirrhotics as part of their routine assessment, acute biochemical changes are often observed during inpatient hospitalizations, while labs performed outside 90 d of the baseline ECG may not accurately reflect the 90-d mortality rate assessed by MELD score in association to the observed ECG changes. Despite unavailable MELD scores on 102 patients, our analyses re-confirmed what is already well established in current literature that higher MELD scores are associated with higher mortality in ESLD patients. When the MELD components and

total score were evaluated in relation to the presence of QT prolongation, our results did show that males with QT prolongation had higher creatinine, MELD, and MELD-NA scores than males without QT prolongation (Table 1). Although males with worse MELD scores (*i.e.*, sicker patients) may have had a higher prevalence of QT prolongation, the retrospective nature of this study does not establish a cause and effect relationship, and the findings do not directly impact the main conclusion of our study where QT prolongation was an independent risk factor for mortality in ESLD.

When examining the severity of QT prolongation and its association with mortality, we defined mild, moderate, and severe levels of prolongation to categorize our patients. However, this categorization may not yield the best discriminatory power. Although the vast majority of heart rates in our study were within an acceptable range, calculation of QT intervals using Bazett's formula is thought to be less accurate with particularly low or high heart rates<sup>[44]</sup>. Furthermore, our study relies on the implicit assumptions of accurate data gathering and correct QT interval readings from our ECG machine, which may be prone to systematic error; however, the ECG machine does eliminate interobserver variability. Finally, although QT prolongation has been associated with increased mortality secondary to ventricular arrhythmias, our study did not differentiate specific causes of death.

Our study showed that QT prolongation was common, especially for male patients, in ESLD. Although an association between mortality and QTc prolongation was evident, a greater degree of QTc prolongation did not clearly portend worse outcomes. Finally, while QTc interval may be an independent risk factor for mortality in ESLD patients, the exact mechanism for the increase in mortality remains to be established. Based on our findings, it is reasonable to recommend close monitoring of the QT interval in ESLD patients with attention to any modifiable causes for QT prolongation, such as electrolyte imbalances or medications.

## COMMENTS

### Background

The QT interval on an electrocardiogram (ECG) is a measure of ventricular depolarization and repolarization. Prolongation of the QT interval is associated with ventricular arrhythmias as well as sudden cardiac death in both congenital and acquired conditions. Multiple factors are thought to be responsible for the prolongation of the QT interval in both congenital and acquired conditions, including electrolyte abnormalities, ventricular channelopathies, myocardial ischemia, medications, alcohol toxicity, and autonomic imbalance with sympathetic nervous system hyperactivity.

### Research frontiers

Recent studies have shown that end stage liver disease (ESLD) is associated with several electrophysiological changes; specifically, an increased prevalence of QT prolongation is seen in this population. While the exact mechanism for QT prolongation is unknown, improvement in liver function, beta-blocker use, and liver transplantation have been associated with shortening in the QT interval in studies with small sample sizes. Although some studies suggest a prolonged QT interval is related to severity of liver disease, etiology of liver disease, and

increased mortality, conflicting results exist regarding this important clinical question.

### Innovations and breakthroughs

The authors aimed to determine the prevalence of QT prolongation in a large series of ESLD patients and its association to clinical variables and mortality. The QT interval was measured and corrected for heart rate (QTc) for each patient, with prolongation defined as QTc > 450 ms for males and QTc > 470 ms for females. Multiple clinical variables were evaluated including sex, age, serum sodium, international normalized ratio, creatinine, total bilirubin, beta-blocker use, Model for End-Stage Liver Disease (MELD), MELD-Na, and etiology of liver disease. Among 406 ESLD patients analyzed, 207 (51.0%) had QT prolongation. The only clinical variable associated with QT prolongation was male gender (OR = 3.04, 95%CI: 2.01-4.60, *P* < 0.001). During the study period, 187 patients (46.1%) died. QT prolongation was a significant independent predictor of mortality (OR = 1.69, 95%CI: 1.03-2.77, *P* = 0.039). In addition, mortality was also associated with viral etiology of ESLD, elevated MELD score and its components (*P* < 0.05 for all). No significant reversibility in the QTc interval was seen after liver transplantation.

### Applications

QTc interval may be an independent risk factor for mortality in ESLD patients and thus the authors recommend close monitoring of the QT interval in ESLD patients and increased attention to any modifiable causes for QT prolongation such as electrolyte imbalances or medications.

### Terminology

ESLD: End stage liver disease; MELD: Model for End-Stage Liver Disease; MELD-Na: Model for End-Stage Liver Disease score with serum sodium; OTTR: Organ Transplant Tracking Record; QTc: QT interval corrected for heart rate.

### Peer-review

This is an interesting and important finding, as QT measurement is not formally considered in liver transplant clinics. The results of this study are interesting and relevant.

## REFERENCES

- 1 **Karjalainen J**, Reunanen A, Ristola P, Viitasalo M. QT interval as a cardiac risk factor in a middle aged population. *Heart* 1997; **77**: 543-548 [PMID: 9227299 DOI: 10.1136/hrt.77.6.543]
- 2 **Sawicki PT**, Dähne R, Bender R, Berger M. Prolonged QT interval as a predictor of mortality in diabetic nephropathy. *Diabetologia* 1996; **39**: 77-81 [PMID: 8720606]
- 3 **Gowda RM**, Khan IA, Wilbur SL, Vasavada BC, Sacchi TJ. Torsade de pointes: the clinical considerations. *Int J Cardiol* 2004; **96**: 1-6 [PMID: 15203254 DOI: 10.1016/j.ijcard.2003.04.055]
- 4 **Schwartz PJ**, Periti M, Malliani A. The long Q-T syndrome. *Am Heart J* 1975; **89**: 378-390 [PMID: 234667 DOI: 10.1016/0002-8703(75)90089-7]
- 5 **Surawicz B**. The QT interval and cardiac arrhythmias. *Annu Rev Med* 1987; **38**: 81-90 [PMID: 3555312 DOI: 10.1146/annurev.me.38.020187.000501]
- 6 **Schwartz PJ**, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 1978; **57**: 1074-1077 [PMID: 639227 DOI: 10.1161/01.CIR.57.6.1074]
- 7 **Straus SM**, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Deckers JW, Kingma JH, Sturkenboom MC, Stricker BH, Witteman JC. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol* 2006; **47**: 362-367 [PMID: 16412861 DOI: 10.1016/j.jacc.2005.08.067]
- 8 **Roden DM**. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; **350**: 1013-1022 [PMID: 14999113 DOI: 10.1056/NEJMr032426]
- 9 **Schooling CM**, Zhao J, Zhang Y. The association of androgens with QT interval and heart rate in US men. *Int J Cardiol* 2014; **177**: 592-594 [PMID: 25205487 DOI: 10.1016/j.ijcard.2014.08.146]
- 10 **Detta N**, Frisio G, Zullo A, Sarubbi B, Cozzolino C, Romeo E, Wang

- DW, Calabrò R, Salvatore F, George AL. Novel deletion mutation in the cardiac sodium channel inactivation gate causes long QT syndrome. *Int J Cardiol* 2013; **165**: 362-365 [PMID: 22980924 DOI: 10.1016/j.ijcard.2012.08.032]
- 11 **Tarapués M**, Cereza G, Arellano AL, Montané E, Figueras A. Serious QT interval prolongation with ranolazine and amiodarone. *Int J Cardiol* 2014; **172**: e60-e61 [PMID: 24424337 DOI: 10.1016/j.ijcard.2013.12.061]
  - 12 **Henriksen JH**, Fuglsang S, Bendtsen F, Christensen E, Møller S. Dyssynchronous electrical and mechanical systole in patients with cirrhosis. *J Hepatol* 2002; **36**: 513-520 [PMID: 11943423 DOI: 10.1016/S0168-8278(02)00010-7]
  - 13 **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 [PMID: 9277435]
  - 14 **Mohamed R**, Forsey PR, Davies MK, Neuberger JM. Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease. *Hepatology* 1996; **23**: 1128-1134 [PMID: 8621144 DOI: 10.1002/hep.510230529]
  - 15 **Theocharidou E**, Krag A, Bendtsen F, Møller S, Burroughs AK. Cardiac dysfunction in cirrhosis - does adrenal function play a role? A hypothesis. *Liver Int* 2012; **32**: 1327-1332 [PMID: 22292920 DOI: 10.1111/j.1478-3231.2011.02751.x]
  - 16 **Al Hamoudi W**, Lee SS. Cirrhotic cardiomyopathy. *Ann Hepatol* 2006; **5**: 132-139 [PMID: 17060868]
  - 17 **Lazzeri C**, La Villa G, Laffi G, Vecchiarino S, Gambilonghi F, Gentilini P, Franchi F. Autonomic regulation of heart rate and QT interval in nonalcoholic cirrhosis with ascites. *Digestion* 1997; **58**: 580-586 [PMID: 9438606 DOI: 10.1159/000201505]
  - 18 **Kempler P**, Szalay F, Váradi A, Keresztes K, Kádár E, Tanczos E, Petrik J. Prolongation of the QTc-interval reflects the severity of autonomic neuropathy in primary biliary cirrhosis and in other non-alcoholic liver diseases. *Z Gastroenterol* 1993; **31** Suppl 2: 96-98 [PMID: 7483730]
  - 19 **Bernardi M**, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, Schepis F, Mandini M, Simoni P, Contin M, Raimondo G. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology* 1998; **27**: 28-34 [PMID: 9425913 DOI: 10.1002/hep.510270106]
  - 20 **Marafioti V**, Benetti V, Montin U, Carbone V, Petrosino A, Tedeschi U, Rossi A. QTc interval prolongation and hepatic encephalopathy in patients candidates for liver transplantation: A valid inference? *Int J Cardiol* 2015; **188**: 43-44 [PMID: 25885747 DOI: 10.1016/j.ijcard.2015.04.026]
  - 21 **Møller S**, Hove JD, Diken U, Bendtsen F. New insights into cirrhotic cardiomyopathy. *Int J Cardiol* 2013; **167**: 1101-1108 [PMID: 23041091 DOI: 10.1016/j.ijcard.2012.09.089]
  - 22 **Trevisani F**, Merli M, Savelli F, Valeriano V, Zambruni A, Riggio O, Caraceni P, Domenicali M, Bernardi M. QT interval in patients with non-cirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic porto-systemic shunt. *J Hepatol* 2003; **38**: 461-467 [PMID: 12663238 DOI: 10.1016/S0168-8278(03)00057-6]
  - 23 **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 [PMID: 24708568 DOI: 10.1186/1471-230X-14-65]
  - 24 **Kosar F**, Ates F, Sahin I, Karıncaoglu M, Yildirim B. QT interval analysis in patients with chronic liver disease: a prospective study. *Angiology* 2007; **58**: 218-224 [PMID: 17495272 DOI: 10.1177/0003319707300368]
  - 25 **Mimidis KP**, Papadopoulos V, Thomopoulos K, Tziakas D, Ritis K, Dalla V, Kotsiou K, Nikolopoulou V, Hatseras D, Kartalis G. Prolongation of the QTc interval in patients with cirrhosis. *Ann Gastroenterol* 2003; **16**: 155-158
  - 26 **Finucci G**, Lunardi F, Sacerdoti D, Volpin R, Bortoluzzi A, Bombonato G, Angeli P, Gatta A. Q-T interval prolongation in liver cirrhosis. Reversibility after orthotopic liver transplantation. *Jpn Heart J* 1998; **39**: 321-329 [PMID: 9711183 DOI: 10.1536/ihj.39.321]
  - 27 **Carey EJ**, Douglas DD. Effects of orthotopic liver transplantation on the corrected QT interval in patients with end-stage liver disease. *Dig Dis Sci* 2005; **50**: 320-323 [PMID: 15745093 DOI: 10.1007/s10620-005-1603-3]
  - 28 **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 [PMID: 12895263 DOI: 10.1034/j.1600-0676.2003.00833.x]
  - 29 **Zurick AO**, Spier BJ, Teelin TC, Lorenze KR, Alberte C, Zacks S, Lindstrom MJ, Pfau PR, Selzman K. Alterations in corrected QT interval following liver transplant in patients with end-stage liver disease. *Clin Cardiol* 2010; **33**: 672-677 [PMID: 21089111 DOI: 10.1002/clc.20801]
  - 30 **Adigun AQ**, Pinto AG, Flockhart DA, Gorski JC, Li L, Hall SD, Chalasani N. Effect of cirrhosis and liver transplantation on the gender difference in QT interval. *Am J Cardiol* 2005; **95**: 691-694 [PMID: 15721125 DOI: 10.1016/j.amjcard.2004.10.054]
  - 31 **Zamirian M**, Tavassoli M, Aghasadeghi K. Corrected QT interval and QT dispersion in cirrhotic patients before and after liver transplantation. *Arch Iran Med* 2012; **15**: 375-377 [PMID: 22642249]
  - 32 **Henriksen JH**, Bendtsen F, Hansen EF, Møller S. Acute non-selective beta-adrenergic blockade reduces prolonged frequency-adjusted Q-T interval (QTc) in patients with cirrhosis. *J Hepatol* 2004; **40**: 239-246 [PMID: 14739094 DOI: 10.1016/j.jhep.2003.10.026]
  - 33 **Zambruni A**, Trevisani F, Di Micoli A, Savelli F, Berzigotti A, Bracci E, Caraceni P, Domenicali M, Felling P, Zoli M, Bernardi M. Effect of chronic beta-blockade on QT interval in patients with liver cirrhosis. *J Hepatol* 2008; **48**: 415-421 [PMID: 18194821 DOI: 10.1016/j.jhep.2007.11.012]
  - 34 **Kim YK**, Hwang GS, Shin WJ, Bang JY, Cho SK, Han SM. Effect of propranolol on the relationship between QT interval and vagal modulation of heart rate variability in cirrhotic patients awaiting liver transplantation. *Transplant Proc* 2011; **43**: 1654-1659 [PMID: 21693252 DOI: 10.1016/j.transproceed.2011.02.017]
  - 35 **Day CP**, James OF, Butler TJ, Campbell RW. QT prolongation and sudden cardiac death in patients with alcoholic liver disease. *Lancet* 1993; **341**: 1423-1428 [PMID: 8099138 DOI: 10.1016/0140-6736(93)90879-L]
  - 36 **Puthumana L**, Chaudhry V, Thuluvath PJ. Prolonged QTc interval and its relationship to autonomic cardiovascular reflexes in patients with cirrhosis. *J Hepatol* 2001; **35**: 733-738 [PMID: 11738100 DOI: 10.1016/S0168-8278(01)00217-3]
  - 37 **Bazett HC**. An analysis of the time relations of electrocardiograms. *Heart* 1920; **7**: 353-367 [DOI: 10.1111/j.1542-474X.1997.tb00325.x]
  - 38 **Committee for Proprietary Medicinal Products**. The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. London: Committee for Proprietary Medicinal Products, 1997
  - 39 **Goldenberg I**, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". *J Cardiovasc Electrophysiol* 2006; **17**: 333-336 [PMID: 16643414 DOI: 10.1111/j.1540-8167.2006.00408.x]
  - 40 **Zambruni A**, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. *J Hepatol* 2006; **44**: 994-1002 [PMID: 16510203 DOI: 10.1016/j.jhep.2005.10.034]
  - 41 **Biggins SW**, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, Benson J, Therneau T, Kremers W, Wiesner R, Kamath P, Klintmalm G. Evidence-based incorporation of serum sodium concentration into MELD. *Gastroenterology* 2006; **130**: 1652-1660 [PMID: 16697729 DOI: 10.1053/j.gastro.2006.02.010]
  - 42 **Angermayr B**, Cejna M, Kamel F, Gschwantler M, Koenig F, Pidlich J, Mendel H, Pichler L, Wichlas M, Kreil A, Schmid M, Ferlitsch A, Lipinski E, Brunner H, Lammer J, Ferenci P, Gangl A, Peck-Radosavljevic M. Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. *Gut* 2003; **52**: 879-885 [PMID: 12740346 DOI: 10.1136/gut.52.6.879]
  - 43 **Rautaharju PM**, Mason JW, Akiyama T. New age- and sex-specific criteria for QT prolongation based on rate correction formulas that minimize bias at the upper normal limits. *Int J Cardiol* 2014; **174**: 535-540 [PMID: 24825030 DOI: 10.1016/j.ijcard.2014.04.133]

- 44 **Zambruni A**, Di Micoli A, Lubisco A, Domenicali M, Trevisani F, Bernardi M. QT interval correction in patients with cirrhosis. *J*

*Cardiovasc Electrophysiol* 2007; **18**: 77-82 [PMID: 17229304 DOI: 10.1111/j.1540-8167.2006.00622.x]

**P- Reviewer:** Dourakis SP, Sinclair M **S- Editor:** Ji FF **L- Editor:** A  
**E- Editor:** Lu YJ





Published by **Baishideng Publishing Group Inc**  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.f6publishing.com>

