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QT Prolongation is Associated with Increased Mortality in End Stage Liver Disease

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Retrospective Study

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

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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

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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^[1-11]. 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^[12-30]. 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^[25-31]. Likewise, previous studies demonstrate reduction in the QT interval for cirrhotic patients who receive beta-adrenergic blockade in both the acute and chronic settings^[32-34]. 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^[14,19,24-30,35,36].

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_c) 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^[37]. A QT_c > 450 ms for males and a QT_c > 470 ms for females was considered abnormal or prolonged, as defined by European regulatory guidelines^[38] and Goldenburg *et al.*^[39] to account for gender differences. Patients with QT_c 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_c 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_c 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_c prolongation. The second through fourth analyses related mortality to QT_c prolongation and the aforementioned clinical characteristics, in parallel with the three multivariate models for QT_c prolongation. A paired signed rank test was used to examine the change in QT_c 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_c by Bazett's ≥ 450 for males and ≥ 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_c 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_c prolongation in these models.

Of the 406 patients, 187 (46.1%) died during the study period. Any level (mild, moderate, or severe) of QT_c 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_c 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_c prolongation and the aforementioned etiologies remain significant predictors of mortality.

Effective sample size for comparison of QT_c interval pre- and post-transplantation was 74. Median pre-transplant QT_c was 457 with interquartile range of 435-472 ms. Median post-transplant QT_c was 450 with interquartile range of 429-468. Our study showed no significant change in the QT_c 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 (n = 207)	Male (n = 150)	Female (n = 57)	All (n = 199)	Male (n = 92)	Female (n = 107)
Beta-blocker use ¹	161 (77.8)	122 (81.3)	39 (68.4)	153 (77.7)	66 (71.7)	87 (82.9) ³
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 ²	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 ² (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 ² (logarithm)	0.39 + 0.51	0.43 + 0.50	0.30 + 0.53	0.30 + 0.43	0.29 + 0.40 ³	0.31 + 0.46
Bilirubin ² (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 ²	21.0 + 9.5	21.6 + 9.5	19.5 + 9.3	19.3 + 9.1	18.6 + 7.7 ³	19.8 + 10.2
MELD ²	19.0 + 9.6	19.4 + 9.7	18.0 + 9.3	17.3 + 9.0	16.0 + 7.2 ³	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. ¹Excluded for two subjects; ²Excluded for 102 subjects; ³Significantly 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	P	95%CI
Mild QTc prolongation vs none	1.67	0.045	1.01-2.76
Moderate QTc prolongation vs none	2.11	0.013	1.17-3.81
Severe QTc prolongation vs 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^[12-19,40].

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^[41,42]. 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^[14,19,24,25,28,36]. 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.*^[27] and Adigun *et al.*^[30]. 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^[41,42]. 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.*^[29] and Day *et al.*^[35].

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.*^[39], to account for gender differences in QT prolongation that are typically longer for females^[7,38,39,43]. 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.*^[30] 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^[32-34]. In addition, partial or full reversal of QT prolongation following liver transplantation has also been noted^[14,26-31]. 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

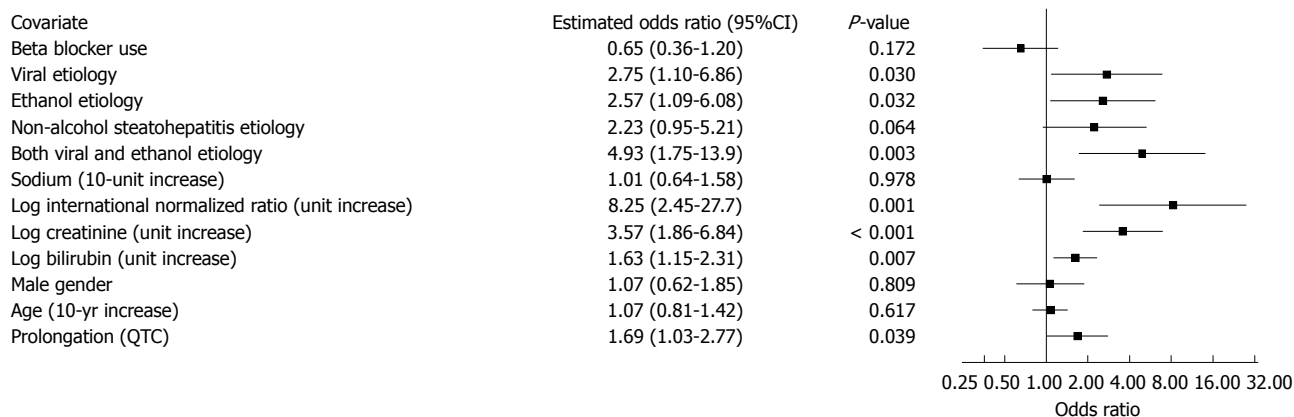


Figure 1 Association of mortality with Model for End-Stage Liver Disease components and clinical variables.

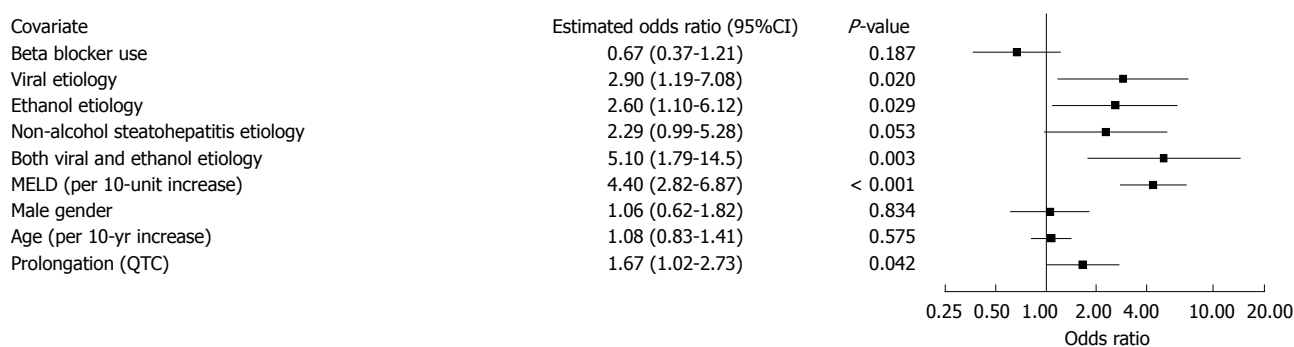


Figure 2 Association of mortality with total Model for End-Stage Liver Disease score and clinical variables.

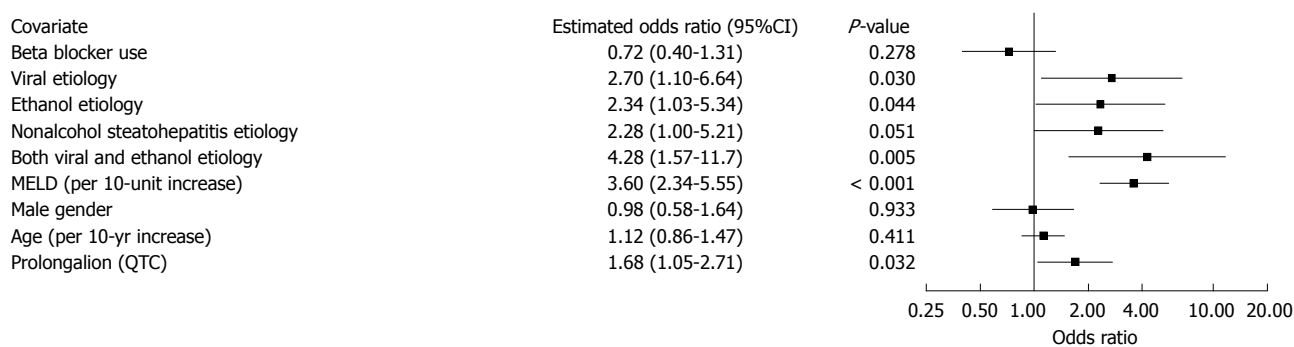


Figure 3 Association of mortality with total Model for End-Stage Liver Disease with incorporation of serum sodium score and clinical variables.

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^[44]. 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 QT_c prolongation was evident, a greater degree of QT_c prolongation did not clearly portend worse outcomes. Finally, while QT_c 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 (QT_c) for each patient, with prolongation defined as QT_c > 450 ms for males and QT_c > 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 QT_c interval was seen after liver transplantation.

Applications

QT_c 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; QT_c: 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.

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