

Alterations in Corrected QT Interval Following Liver Transplant in Patients With End-Stage Liver Disease

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ABSTRACT

Background: Studies have demonstrated that patients with end-stage liver disease (ESLD) often have a prolonged corrected QT interval (QTc) with variable changes in the QTc post-transplant. We sought to characterize the prevalence and degree of QTc prolongation in ESLD patients, identify risk factors for QTc prolongation, and assess changes in QTc following transplant.

Hypothesis: QTc interval is prolonged in ESLD patients pre-transplant due to a variety of risk factors and shortens following liver transplantation.

Methods: We conducted a retrospective, multicenter study utilizing 2 large liver-transplant databases. QTc intervals were calculated utilizing Bazett's formula. The cutoff used for prolonged QTc was 440 milliseconds for men and 460 milliseconds for women.

Results: There were 269 patients (169 men, 100 women) included in the final analysis. The mean pre-transplant QTc was prolonged (449.0 ms), whereas the mean post-transplant QTc shortened and was within normal limits (416.7 ms) ($P < 0.0001$). QTc shortened after transplant in 87% of patients. QTc normalized in 70% of patients. Age and Model for End-Stage Liver Disease (MELD) score were not predictive of prolonged QTc at baseline.

Conclusions: ESLD patients often have a prolonged QTc, which frequently shortens or normalizes after transplant. Screening for prolonged QTc is warranted if medications known to prolong the QTc interval are used in ESLD patients pre-transplant. MELD score, age, and sex were not predictive of prolonged QTc at baseline.

Introduction

The QT interval, measured from the onset of the QRS complex to the end of the T wave on a standard 12-lead electrocardiogram (ECG), measures ventricular electrical repolarization and is typically corrected for heart rate (QTc). Prolongation of the QTc interval is associated with ventricular arrhythmias, namely torsade de pointes, and increased mortality.¹⁻⁴ Acquired QT prolongation

is known to occur with several classes of medication, including antiarrhythmics, certain antibiotics, and some antidepressants. The QTc is also known to be prolonged in the setting of various medical conditions, such as coronary ischemia, electrolyte abnormalities, inherited genetic mutations causing various ion-channel disorders, and end-stage liver disease (ESLD).

More specifically, QTc-interval prolongation has been found in association with both alcoholic and nonalcoholic liver disease.⁵⁻⁷ Previous studies have reported that in patients with ESLD the degree of QTc prolongation correlates with the severity of autonomic dysfunction.⁸ Autonomic dysfunction is common among patients with liver disease, with a similar frequency among patients with

Ms. Lorenze is a student at the University of Wisconsin whose involvement on this project included, but was not limited to, data collection and analysis and manuscript editing. The authors have no funding, financial relationships, or conflicts of interest to disclose.

alcoholic and nonalcoholic liver disease.^{9,10} The presence of autonomic dysfunction is a poor prognostic indicator among those with ESLD, leading to a 25% increase in mortality in 15 to 48 months.^{7,11} No clear etiology has been found to account for the development of autonomic dysfunction among these patients, but several mechanisms have been suggested, including an electrolyte imbalance, elevated serum bile acids, increased sympathetic activity, toxic metabolites, and impaired concentrations of circulating neurotransmitters.¹⁰

Several prior studies have evaluated the effect of liver transplant on QTc interval; however, most were small and with mixed results.^{6,12–15} One study by Bal and Thuluvath from Johns Hopkins University found that a prolonged QTc interval was common in patients with cirrhosis, with a prevalence of up to 56%. They concluded that age, an alcoholic etiology of cirrhosis, and Child-Pugh scores were independent predictors of a prolonged QTc.¹³ Carey and Douglas from the Mayo Clinic in Arizona similarly reported that 54% of their 46 patients with ESLD had a prolonged QTc prior to liver transplant. However, in contrast they found no correlation between QTc prolongation and clinical factors such as Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, diabetes mellitus, age, or etiology of liver disease.¹⁴ Both studies did find that most patients with ESLD and a prolonged QTc often had a significant improvement in QTc after transplant. Another European study of 94 cirrhotic patients also found that QTc was prolonged in these patients, with a mean QTc of 440 milliseconds. Interestingly, QTc only correlated to Child-Pugh score and no other clinical factors.⁷

Based on these reports with somewhat mixed results, we sought to further validate these findings and characterize the QTc interval in a large, multicenter cohort of patients with ESLD who subsequently underwent liver transplant. Thus, the purpose of this study was to determine both the prevalence and degree of QTc prolongation among patients with ESLD and to determine interval QTc changes following liver transplant.

Methods

Study Design and Patients

After institutional review board approval was obtained, we performed a retrospective study evaluating the difference in QTc interval before and after liver transplant at 2 academic institutions. At the University of North Carolina, Chapel Hill, data were collected on 701 consecutive primary liver transplant recipients from 1990 to 2006. At the University of Wisconsin Hospital and Clinics, data were collected on 410 consecutive primary liver transplant recipients from 2002 to 2006. Subjects were identified and data were obtained through a prospectively constructed database with subsequent review of individual electronic and paper medical records. Of the 1111 transplant recipients identified, 269 subjects met the inclusion criteria for the study

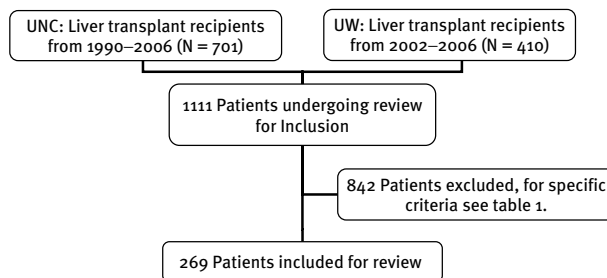


Figure 1. Flow diagram of patient selection.

(Figure 1). Patients included in the final data analysis included men and women with ESLD, age 18–70 years, who were undergoing liver transplant for any indication (Table 1). Patients were excluded if they did not have an interpretable ECG pre-transplant and/or post-transplant. The most common reasons for exclusion were absence of a pre-transplant or post-transplant ECG, multiple organ transplant, and age <18 years.

QTc Interval Calculation

The QT interval was measured from the beginning of the QRS complex to the termination of the T wave (defined as the return to the isoelectric line). QTc was calculated manually using Bazett's formula: $QTc = QT \text{ interval (sec)} /$

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	
ESLD (EtOH and non-EtOH)	
Pre-transplant 12-lead ECG at most 1 mo prior to transplant	
Post-transplant 12-lead ECG 1–12 mo following transplant	
Age 18–70 y	
Exclusion Criteria	
History of cardiorespiratory disease	
Clinically significant valvular heart disease or septal defects	
Known ischemic cardiomyopathy	
AF	
IVCD	
Evidence of pre-excitation	
BBB	
Paced rhythm	
Multiple liver transplants	
Simultaneous multiorgan transplantation	
Abbreviations: AF, atrial fibrillation; BBB, bundle branch block; ECG, electrocardiogram; EtOH, alcohol; ESLD, end-stage liver disease; IVCD, interventricular conduction delay.	

(R-R interval^{1/2}) (sec). Bazett's formula was chosen because the QTc interval calculated this way has been shown to be a predictor of cardiovascular mortality. Lead II was the first choice for calculating the QTc; however, if lead II could not be used due to poor T-wave visualization, the lead with the clearest T wave was utilized. A dramatic QTc decrease was defined as a reduction ≥ 60 ms. A prolonged QTc interval was defined as a QTc >440 ms for men and >460 ms for women.¹⁶ Different QTc cutoff values were used based on sex, because women are known to have longer QTc values than men and sex-specific QTc cutoff values frequently are used when looking at QTc prolongation.^{17,18} We wanted to be able to account for baseline QT differences due to gender irrespective of liver disease and other risk factors for QT prolongation.

Variables

To evaluate potential clinical risk factors for prolonged QTc, various patient variables were analyzed: patient characteristics (age at transplant, gender, race, baseline heart rate), liver transplant indication and type of liver transplant performed, serum potassium, MELD score, and medication use (β -blockers, fluoroquinolones, antifungal agents such as azoles, quinine, and any antiarrhythmic medications) (Table 2). In addition, the change in the QTc interval before and after transplant was calculated to determine the effect of transplant on the QTc interval. Survival status was determined at the end of the follow-up period. Death was confirmed by searching the Social Security Death Index on November 15, 2007 (<http://ssdi.rootsweb.com>).

Statistical Methods

The difference in QTc interval before and after liver transplant and the effect of gender and MELD score on QTc were assessed using *t* tests. Age, gender, potassium level, use of quinolones, MELD, and donor type were considered as possible predictor variables. Their effects on the difference between the pre-transplant QTc and post-transplant QTc interval were assessed using multiple linear regression. The effect of the predictor variables on the response variables of prolonged preoperative QTc interval, normal preoperative QTc interval, postoperative normalized QTc interval, and whether the patient survived the surgery was assessed using multiple logistic regression. We used *t* tests for 2 sample comparisons of continuous variables.

Results

Patient Characteristics

There were 1111 primary liver transplants performed at the participating institutions between 1990 and 2006. Of those, 269 met inclusion criteria for data analysis. The baseline pre-transplant characteristics of the 269 patients are summarized in Table 2. The mean age at the time

Table 2. Baseline Patient Characteristics

Patient Characteristics (N = 269)	Cases
Age at transplant (mean y)	50.9
Gender (% M/F)	62/38
Race (% Caucasian)	85.5
Donor type (% orthotopic)	94
Post-transplant mortality at end of follow-up (%)	22.7
Etiology of liver disease	
EtOH alone %	26
EtOH involvement %	34.8
Non-EtOH %	65.2
MELD score (median)	19
Pre-transplant medications (n)	
β -Blockers	98
Fluoroquinolones	52
Antifungals (azoles)	5
Quinine	15
Antiarrhythmics	7
Abbreviations: EtOH, alcohol; F, female; M, male; MELD, Model for End-Stage-Liver Disease; n, number of patients.	

of transplant was 51 years. The majority of subjects were Caucasian and male (169 men, 100 women; 230 Caucasian, 26 African American, 13 Hispanic). Most patients received an orthotopic transplant (94%). Alcohol alone was the most common sole etiology of liver disease and was identified in 26% of the transplant recipients, whereas alcohol involvement was identified 35% of the time. The mean MELD score of all patients at the time of transplant was 20.7 (median 19). For spontaneous bacterial peritonitis prophylaxis 19% of patients were on a fluoroquinolone, a medication class known to prolong the QTc interval.

Pre-Transplant QTc Data Analysis

The overall mean baseline QTc interval was 449 milliseconds (range, 320–554 ms). There was no difference in baseline QTc between men and women. Of the 269 included subjects, 50% (n = 135) had a prolonged QTc interval pre-transplant. Of the clinical predictors of prolonged QTc that we considered, only sex was found to be a possible predictor; men were more likely than women to have a prolonged QTc interval pre-transplant (31% vs 19%; odds ratio: 2.3, *P* = 0.001). However, this was using the longer QTc of 460 milliseconds as the definition of prolonged QTc for women; men were more likely to have a QTc >440 milliseconds than women were to have a QTc >460 milliseconds.

Post-Transplant QTc Data Analysis

The overall mean QTc interval normalized post-transplant, with a decrease in QTc interval from 449 milliseconds to 417 milliseconds ($P < 0.001$). Both men and women had a significant reduction in mean QTc interval post-transplant compared with baseline ($P < 0.001$). However, women did have a longer post-transplant mean QTc than men (421 ms vs 414 ms), which corresponds to a gender difference that is typically seen in healthy noncirrhotic adults.

Of the 135 patients (84 men, 51 women) with baseline prolonged QTc, 87% shortened, but not necessarily normalized, their QTc interval post-transplant. Of the 135 subjects with initial prolongation of their QTc, 70% ($n = 95$; 67 men, 28 women) had corrected their prolongation and were now in normal range, while 30% ($n = 40$; 17 men, 23 women) continued to have a prolonged QTc post-transplant, as based on our prespecified definition (Table 3). Of those who did shorten their QTc interval, 23% experienced a dramatic decrease (ie, >60 ms). These large decreases were fairly similar for both sexes (25% of men and 19% of women).

As of 2006, 80% of men and 73% of women were still alive and being actively followed in transplant clinics. There was no difference in baseline QTc between those who died and those who were still alive at the end of the study.

Analysis of Predictors and Comparative Data

Clinical variables including age, gender, serum potassium, quinine use, etiology of liver disease, MELD score, medications, and donor-liver type were collected and evaluated for being potential predictors of prolonged QTc interval in cirrhotic patients awaiting transplant (Table 2). Of these predictors, only gender was significantly related to prolonged QTc interval; however, this depended on the definition of prolonged QTc in women that was used. When 440 milliseconds was used as a cutoff value for both sexes, the difference in QTc at baseline was not significantly different and male gender was no longer a predictor of QT prolongation.

Discussion

QTc interval prolongation has been documented previously in patients with chronic liver disease. However, most of these reports were small, single-center studies. Our study represents a large, multicenter cohort consisting of 269 patients undergoing liver transplant. Overall, our results showing a 50% prevalence of prolonged QTc in patients with severe liver disease are consistent with and further validate prior studies. Most studies reviewed found a prevalence of prolonged QTc in ESLD patients ranging from 36% to 60%.^{7,13–15,19} However, 1 study conducted in Madrid, Spain with 37 subjects did not have any enrollees with a QTc >440 milliseconds, and conversely, the prevalence of prolonged QTc (>440 ms) in a study from Birmingham, England was

Table 3. QTc Interval Data for Overall Cohort, Men and Women, Both Pre-Transplant and Post-transplant

QTc Analysis (N = Overall 269, M 169, F 100)		P Value
Overall QTc pre-transplant (mean ms)	449	
M	449	
F	449	
Overall QTc post-transplant (mean ms)	417	<0.001
M	414	<0.001
F	421	<0.001
Overall QTc difference pre-transplant vs post-transplant (mean ms)	32	<0.001
Prolonged QTc pre-transplant ($n = 135$)/ post-transplant ($n = 40$) (% all patients)	50/15	<0.001
Prolonged QTc pre-transplant ($n = 135$)/ post-transplant ($n = 40$); (% M/F)	62/38; 43/57	
Normalized post-transplant QTc (overall/M/F)	95/67/28	
Dramatic decrease in QTc (% M/F)	22/20	
Abbreviations: F, female; M, male; n, number of patients. Additionally, number of patients with prolonged pre-transplant QTc and number of patients with normalized QTc following transplantation are included.		

87%.^{6,12} Our data showing that the QTc interval significantly shortens post-liver transplant also correlates with these prior studies that showed QT shortening anywhere from 55% to 95% of the time following liver transplant.

Gender Differences

We were surprised to find that men and women with ESLD have a similar mean QTc interval pre-transplant as well as post-transplant. Women tend to have longer QTc intervals than men in healthy cohorts. Gender differences in the incidence of ventricular arrhythmias have been reported, and torsades de pointes associated with prolonged QTc is more common in women than in men.^{20,21} To our knowledge, there are only 2 other studies in the literature that looked at the interaction of gender and QTc in ESLD subjects. They found, as we did, essentially equal QTc values between men and women.^{7,19} Adigun and colleagues showed that there was no statistically significant difference between females and males both before and after transplant.²² Bernardi et al in Italy also showed that there was no gender difference following liver transplantation; however, unfortunately, they only looked at gender-related QTc differences post-transplant.⁷ One possible explanation for the loss of gender difference regarding the QTc may be due to the hormonal abnormalities present in cirrhotic

patients. Adigun and colleagues demonstrated that cirrhotic men have profoundly diminished levels of testosterone, whereas cirrhotic women have normal levels.²² Although they felt that this should translate into men having a QTc greater than females, it may very well be the reason why the males with ESLD “catch up” to the women in terms of QTc duration, rather than continue to have shorter QTc intervals as seen in healthy populations.

QTc and MELD Score

The lack of association between pre-transplant QTc interval and various clinical variables has previously been shown in other retrospective studies. However, these studies had fewer patients and could possibly have been underpowered to detect this association.^{6,7,14,15} An association between Child-Pugh or MELD score and the QTc interval has been reported in some prior studies, but the majority did not show any correlation. Our study confirms the lack of association between MELD score and the QTc interval. Perhaps this is explained by a lack of association between these various clinical variables and autonomic function.

QTc and Mortality

In our study, there did not appear to be a difference in post-transplant mortality based on baseline QTc prolongation. However, autonomic dysfunction is known to worsen overall prognosis and increase mortality in patients with chronic conditions such as heart failure and diabetes. In addition, increased mortality, predominantly from cardiovascular causes, in chronic alcohol abusers with vagal neuropathy has been reported.²³ There is also 1 study in liver disease patients where autonomic dysfunction does portend an increased mortality¹¹; however, this dataset was in less-sick patients who were stable clinically and therefore not listed for transplant. A few studies have looked at the baseline pre-transplant QT prolongation and autonomic neuropathy and its potential influence on post-transplant mortality. They did not see any relationship between QTc and autonomic neuropathy on mortality.^{6,13} Since the QTc prolongation and the autonomic neuropathy reverse in the majority of patients after transplant, we believe that the liver transplant and subsequent reverse remodeling of autonomic tone reverse the increased mortality risk that is present pre-transplant. We hypothesize that a lack of reversal in QTc and autonomic tone post-transplant would have a worse prognosis, but longer-term data may be needed to assess this adequately. Finally, since cause of death was not a specific variable included in this study, it is also difficult to know for certain whether patients died due to a cardiac or noncardiac cause.

QTc After Liver Transplant

A large majority of patients had reductions and even normalization in their QTc interval following transplant. Chronic liver disease is known to impair cardiovascular

autonomic reflexes.¹⁷ It has been hypothesized by other authors that alterations in autonomic function play an important role in reversing this impairment. We believe that one of the major mechanisms of QTc normalization is the reversal of autonomic dysfunction. There are reports in the literature that severity of autonomic dysfunction increases with worsening liver dysfunction. There are also data that hepatic dysfunction severity correlates to QTc prolongation severity, although our dataset did not show this. It is not understood how liver failure causes autonomic neuropathy, but it may be related to abnormal lipid metabolism or abnormal immunoglobulin deposition, both of which would return to normal post-transplant. However, since not all patients normalized their QTc post-transplant, there is probably a multifactorial cause of the QTc interval, with the absence of liver disease being the major component.

In addition to, and possibly synergistic with, autonomic dysfunction, alteration of the sympathetic nervous and renin-angiotensin-aldosterone systems can prolong the action potential duration, which can affect the QT interval. The degree of action potential increase may be different from patient to patient. Michael et al discuss a phenomenon known as repolarization reserve, in which certain ion channels can increase function or compensate when other ion channels have reduced functionality. This is affected by cardiac disease states such as heart failure and atrial fibrillation, and we wonder whether the cardiac sequelae of liver disease can include altered functioning of various ion channels. Genetic susceptibility to ion-channel dysfunction may affect the improvement in QT post-transplant, where some patients with reduced reserve do not normalize their QT as most patients can.²⁴ Additionally, an entity known as cirrhotic cardiomyopathy has been previously described, albeit mostly in the gastroenterology literature. This condition consists of 4 common features: (1) baseline increased cardiac output, (2) attenuated systolic contraction and diastolic relaxation, (3) electrophysiologic abnormalities including repolarization change, and (4) reduced response of the heart to direct β -stimulation (β -incompetence).²⁵ While patients may exhibit some or all of these features, it is not well understood how these features reverse after liver transplant and why some patients would reverse less than others, or never normalize.

Use of QTc-Prolonging Drugs

Several medications are known to increase QTc interval, including quinine and certain antibiotics that are frequently used in ESLD patients. Use of these medications needs to be carefully considered, because they will likely cause further QTc interval prolongation in addition to that from the underlying liver disease. Interestingly, our model did not find that use of β -blockers, fluoroquinolones, antifungals (azoles), or quinine was statistically associated with an increased probability of QTc interval prolongation prior to

liver transplant. However, their utilization should still be considered carefully in this at-risk population, and at a minimum the ECG should be monitored for changes in QTc interval.

Study Limitations

Our study has several limitations. We recognize that our preoperative ECGs were obtained during an arbitrarily defined time period. Given the significant electrolyte alterations typically encountered in the ESLD patient population, it is difficult to account for this possible confounding factor. Furthermore, postoperative ECGs were arbitrarily obtained 1 to 12 months following liver transplant. This extended time interval certainly permitted a larger cohort for evaluation purposes; however, because there was no prespecified a priori time frame for obtaining postoperative ECG evaluations, we realize this permits sampling bias. In addition, it is possible, although not really known, that 1 month is insufficient time to allow the QT to reach its new baseline following liver transplant.

Conclusion

We believe that cautious medication administration in this patient population is warranted, particularly in those patients with QTc intervals markedly >440 milliseconds. Baseline and serial ECG monitoring seems warranted perioperatively, and even potentially up to 1 year postoperatively, to evaluate for QTc interval change. We also feel that more research needs to be done to further elucidate the underlying etiology of QTc interval prolongation in this patient population, as well as the long-term effects of prolonged QTc in these patients. A prospective trial with pre-transplant and post-transplant testing of autonomic function might help to further elucidate the mechanism of QTc interval prolongation in these patients and assess for any relationship between QTc prolongation and post-transplant mortality, particularly sudden cardiac death.

In summary, our data show that the QTc interval is often prolonged in ESLD patients awaiting transplant and that it shortens significantly following liver transplant in most patients. The degree of QTc prolongation is independent of age, severity of liver disease as determined by MELD score, or etiology of liver failure. Approximately 50% of patients receiving liver transplant will have a prolonged QTc interval while waiting on the transplant list, potentially putting them at increased risk of ventricular arrhythmias. Medications known to prolong QTc interval should be used with caution in this select subset of patients, and baseline as well as serial ECGs should be obtained to evaluate for this irregularity.

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