Author/s:
Koshy, AN;Ko, J;Farouque, O;Cooray, SD;Han, HC;Cailes, B;Gow, PJ;Weinberg, L;Testro, A;Lim, HS;Teh, AW

Title:
Effect of QT interval prolongation on cardiac arrest following liver transplantation and derivation of a risk index

Date:
2021-02-01

Citation:
Koshy, A. N., Ko, J., Farouque, O., Cooray, S. D., Han, H. C., Cailes, B., Gow, P. J., Weinberg, L., Testro, A., Lim, H. S. & Teh, A. W. (2021). Effect of QT interval prolongation on cardiac arrest following liver transplantation and derivation of a risk index. American Journal of Transplantation, 21 (2), pp.593-603. https://doi.org/10.1111/ajt.16145.

Persistent Link:
https://hdl.handle.net/11343/275981

DR ANOOP N KOSHY (Orcid ID : 0000-0002-8741-8631)

Article type : O - Original Article

Effect of QT Interval Prolongation on Cardiac Arrest following Liver Transplantation and Derivation of a Risk Index

Anoop N. Koshy MBBS[1,2]; Jefferson Ko MBBS[1]; Omar Farouque MBBS, PhD[1,2]; Shamil D. Cooray MBBS[3]; Hui-Chen Han MBBS[1,2]; Benjamin Cailes MBBS[1]; Paul J. Gow MBBS, MD[2,4]; Laurence Weinberg MD[2,5]; Adam Testro MBBS, PhD[2,4]; Han S. Lim MBBS, PhD[1,2]; Andrew W. Teh MBBS, PhD[1,2]

Author Affiliations

[1] Department of Cardiology, Austin Health, Melbourne, Victoria, Australia

[2] The University of Melbourne, Parkville, Victoria, Australia

[3] Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

[4] Victorian Liver Transplant Unit, Austin Hospital, Melbourne, Victoria, Australia

[5] Department of Anaesthesia, Austin Health, Melbourne, Victoria, Australia

[6] Eastern Health Clinical School, Cardiology Department, Monash University, Melbourne, Victoria, Australia

Corresponding author:

A/Prof. Andrew W Teh

Email: andrew.teh@austin.org.au

Abbreviations

CA/VA: cardiac arrest/ventricular arrhythmias

LT: liver transplantation

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/AJT.16145

QTc: QT-interval

CARI: cardiac arrest risk inde

MELD: model for end-stage liver disease

CAD: coronary artery disease

ECG: electrocardiogram

LoA: limits of agreement

OR: odds ratio

ROC: receiver operator characteristic

Abstract

Liver transplantation(LT) has a four-fold higher risk of periprocedural cardiac arrest and ventricular arrhythmias(CA/VA) compared with other noncardiac surgeries. Prolongation of the corrected QT interval(QTc) is common in patients with liver cirrhosis. Whether it is associated with an increased risk of CA/VA following LT is unclear. Rates of 30-day CA/VA post-LT was assessed in consecutive adults undergoing LT between 2010-2017. Pre-transplant QTc was measured by a cardiologist blinded to clinical outcomes. Among 408 patients included, CA/VA occurred in 26(6.4%) patients. QTc was significantly longer in CA/VA patients(475±34 vs 450±34 milliseconds, p<0.001). Optimal QTc cut-off for prediction of CA/VA was ≥480ms. After adjustment, QTc≥480ms remained the

strongest predictor for the occurrence of CA/VA(Odds ratio[OR] 5.2 95%CI 2.2-12.6). A point-based cardiac arrest risk index(CARI) was derived with the bootstrap method for yielding optimism-corrected coefficients(2-points:QTc ≥480, 1-point:MELD≥30, 1-point:age≥65 and 1-point:male). CARI score≥3 demonstrated moderate discrimination(c-statistic 0.79, optimism-corrected c-statistic 0.77) with appropriate calibration. *Conclusion:* QTc≥480ms was associated with a five-fold increase in the risk of CA/VA. The CARI score may identify patients at higher risk of these events. Whether heightened perioperative cardiac surveillance, avoidance of QT prolonging medications or beta-blockers could mitigate the risk of CA/VA in this population merits further study.

Introduction

Liver transplantation (LT) is a life-saving intervention for individuals with end-stage liver disease. Despite improvements in anesthetic management and surgical techniques, patients undergoing LT are at a substantial risk of perioperative cardiovascular complications.(1-3) Rates of cardiac arrest and ventricular arrhythmias (CA/VA) are over four-fold greater in LT in comparison with other noncardiac surgeries.(4, 5) This has been attributed to electrophysiological conduction abnormalities from reduced density and sensitivity of beta-adrenoreceptors, defects in calcium channel transport function, post-receptor signal defects, and excitation-contraction coupling.(6-8) However, there remains a paucity of data examining predictors of cardiac arrest in patients undergoing LT.

The QT interval is an indirect measure of cardiac ventricular repolarization.(9) QT prolongation is an electrophysiological hallmark of cirrhotic cardiomyopathy, evident in up to half the patients with liver cirrhosis.(10-15) A prolonged QT interval identifies patients at increased risk of sudden cardiac death in a variety of congenital and acquired cardiac pathologies.(9, 16, 17) Evidence suggests that it not only predicts sudden cardiac death but also be involved in its pathogenesis.(18) Studies in patients undergoing LT have evaluated the association of QT-interval prolongation and cardiovascular events with mixed results.(14, 15, 19-21) However, none have evaluated whether QT prolongation is associated with CA/VA after LT.(22, 23) This

is important to ascertain as hemodynamic stress, electrolyte shifts, elevated bile acids, hypothermia and anesthetic agents can contribute to lengthening of the QT interval in cirrhotic patients who may already have a diminished repolarization reserve.(10, 12, 24-26) The primary aim of this study was to examine whether QT prolongation predicted the development of CA/VA in a cohort of consecutive patients undergoing LT. We also aimed to develop a risk prediction score to guide risk stratification of patients at risk of CA/VA following LT.

Methods

Study Population

A retrospective cohort study of consecutive adult patients (age ≥18 years) undergoing liver transplantation between 2010-2017 at the state-wide liver transplant centre in Melbourne, Australia were included. Patients were excluded if they were undergoing re-transplantation, multi-organ transplantation, had significant unrevascularized coronary artery disease, cardiomyopathy, valvular heart disease or if patients were transplanted for haemochromatosis/amyloidosis. The project received approval from the Human Research Ethics Committee at Austin Health (LNR/18/Austin/177).

Clinical Data

Patient demographics, medical history, medications, etiology and severity of liver disease (based of the model for end-stage liver disease [MELD] score and Child-Pugh Score) were obtained from the prospectively collected institutional liver transplant database and supplemented by case history review as required. The primary indication for transplantation was classified by the treating transplant team. At transplant evaluation, all patients were evaluated for ascites using ultrasonography, varices by esophagogastroduodenoscopy, and encephalopathy by a transplant hepatologist. All patients were abstinent from alcohol for six months prior to transplant listing.

Cardiovascular risk factor data including a history of diabetes mellitus, arterial hypertension, dyslipidemia and smoking were collected. At our transplant centre, patients aged ≥50 years with one other cardiovascular risk factor or any clinical symptoms of coronary artery disease, underwent further testing with dobutamine

stress echocardiography or coronary angiography as appropriate. A patient was classified as having CAD if they had previously been diagnosed with myocardial infarction, heart failure due to ischemia, angina pectoris or in the context of a positive test for CAD, such as computed tomographic coronary angiography or invasive coronary angiography. Blood samples were taken for measurement of liver function, urea, creatinine, serum electrolytes including serum calcium, magnesium and phosphate prior to LT. Patient's medications at transplantation were also reviewed to identify drugs that prolong QT-interval.(27, 28)

ECG Analysis

Baseline 12-lead electrocardiograms (ECGs) were obtained pre-operatively on the day of LT surgery on all patients. All ECGs were recorded at 25mm/second. These were reviewed independently by a cardiologist (ANK) blinded to clinical details. Ischemic changes assessed on ECG included the presence of Q waves, ST segment depression and/or a pathologic T wave.(29) The Q-T interval was manually assessed using the average of three consecutive QT intervals and measured in leads free of noise and ectopic beats. QT intervals were assessed from the onset of the QRS complex to the end of the T wave, defined as the return to the T-P segment baseline. If a U wave was present, the Q-T interval was measured from the onset of QRS complex to the nadir of the curve between the T and U waves.(13)

QT interval was corrected (QTc) according to the Bazett formula (QTc=QT inteval/√RR interval).(30) The Bazett's formula was used in this study as it is the most commonly used formula for QT interval correction in clinical practice. Sex-specific cut-offs were not used given the loss of physiological differences in QT length between genders in liver disease.(13, 31, 32) Additional sensitivity analyses assessing the QT interval by Fridericia's formula were also performed (QTc= QT interval/RR interval^0.33).(33) Interobserver variability was assessed by quantification of QTc on 50 randomly selected ECGs by an independent cardiologist (HCH), blinded to initial measurements and clinical details. Intraobserver variability was also assessed on a sample of 50 random ECGs which were reassessed by the initial reviewer (ANK) three months after initial QT-interval measurement.

Clinical Outcome Assessment

The primary outcome was to assess the relationship between the corrected QT-interval and the occurrence of CA/VA within 30-days. A 30-day time period was chosen for quantifying early outcomes in accordance with current reporting of perioperative outcomes in non-cardiac surgery.(34) Cardiac arrest was defined as profound hemodynamic derangement necessitating external or direct cardiac massage or cardioversion.(35) Ventricular arrhythmias included ventricular tachycardia, defined as an ectopic ventricular rhythm ≥3 beats with a QRS complex rate >120/min or ventricular fibrillation.(36) The secondary aims were to identify determinants of QTc prolongation and their correlation with cirrhosis severity, assess 30-day and long-term mortality, and develop a risk index for CA/VA.

Cases of CA/VA were identified, and independently reviewed by an anesthesiologist (LW) and two cardiologists (ANK, HCH) to further characterize the underlying arrhythmia and precipitant for the event. Intra-operative outcomes were obtained from a prospectively collected anesthetic database. This included data from the time of induction of general anesthesia in the operating room to admission to an intensive care unit. Retrospective chart review by 2 physician researchers using detailed case-report forms was used to determine 30-day outcomes. The database recorded details including the intraoperative complications, cardiac arrhythmias and occurrence of any surgical complications during transplantation.

Electrocardiographic Assessment & Interrater Agreement

Interobserver and intraobserver variability was assessed by the Bland Altman comparison with 95% limits of agreement (LoA) (37) and intraclass correlation (ICC) coefficient. Assessment of interobserver variability of QTc indicated strong agreement among both cardiologists (mean bias 4.7 ms, LoA -22 to 31 ms; ICC=0.87, 95%CI 0.73-0.93, p<0.001). Intraobserver variability also demonstrated strong agreement and correlation (mean bias -3.7 msec LoA -27 to 20 ms, ICC 0.90, 95%CI 0.79-0.95, p<0.001). (Supplementary Figure S1, S2)

Statistical Analysis

Results are expressed as mean ± standard deviation or median with interquartile range (IQR) for non-normally distributed data. Comparisons between groups were

performed with the chi-square test or Fisher's exact test for categorical data and the Student t-test or Mann-Whitney U test as appropriate for continuous data. To identify independent predictors for the development of CA/VA stepwise multivariable logistic regression was performed.(38) Outcomes are presented as odds ratio (OR) with 95% confidence intervals (CIs). Discrimination of the final model was estimated using area under the receiver operating curve (ROC) with estimation of the c-statistic. Optimal cut-off levels were established using the point on the ROC curves where the Youden index was maximal.(39) Given low event rates, we prespecified inclusion of only three variables in addition to the QTc to minimize model overfitting. Variables yielding $p<0.1$ were considered for inclusion in the model. A risk index for CA/VA after LT was developed by assigning each risk factor one or two points according to the logistic regression model. This was based on the coefficient value derived from logistic regression divided by the smallest coefficient in the model. Apparent model performance was evaluated in terms of discrimination using the c-statistic and calibration using the Hosmer-Lemeshow goodness-of-fit test.(38) Internal validation was performed with bootstrap re-sampling (1000 resamples with replacement) with bias-corrected 95% confidence intervals to adjust for over-optimism in the estimation of model performance. A Fagan's nomogram was used to graphically depict how the risk score would affect the probability of CA/VA.(40) This is a Bayesian graphical tool that estimates how the result of a diagnostic test changes the probability of a patient having a condition. A line drawn from the pre-test probability through the likelihood ratio of interest intercepts the new post-test probability for the patient. Long-term mortality risk was assessed using time-to-event analysis and Cox-regression. All reported p values are two-tailed, with $p< 0.05$ considered significant. Statistical analysis was performed using Stata 13/MP (Statacorp, College Station, TX, USA).

Results

A total of 408 patients with pre-transplant ECGs meeting the study inclusion criteria were included in the final analysis. Mean age was 57 ±12 years and the majority (67.7%) were male. The most common etiology of cirrhosis was hepatitis B or C (32.7%) and the mean MELD score was 19 ±8. Baseline characteristics including complications of end-stage liver disease, cardiovascular risk factors and echocardiographic indices are summarized in Table 1.

QT interval and Pre-Transplant Indices

Electrocardiographic parameters in the groups are summarized in Table 2. The average QTc was 452 ±31 ms. To identify determinants of QTc prolongation, correlation with markers of liver function or cirrhosis severity (serum albumin, Child-Pugh and MELD score), hemodynamic and biochemical markers (mean arterial blood pressure, heart rate, creatinine, sodium) and factors that may affect QTc length (serum potassium, magnesium, calcium, phosphate) were assessed. A weak positive linear correlation was noted between QTc, MELD (r=0.15, p=0.003) and Child-Pugh (r=0.12, p=0.02) scores, indicating a higher QT-interval with increasing severity of liver disease (Figure 1). An inverse linear correlation was also noted between QTc and pre-transplant potassium levels (r= -0.12, p=0.04).

Occurrence of Cardiac Arrest/Ventricular Arrhythmias

Overall, 26 (6.4%) patients experienced CA/VA event. A majority (65.4%) of events were ventricular tachycardia/ventricular fibrillation with the remainder being asystolic or pulse electrical activity (PEA) arrests. Most (53.8%) events occurred intraoperatively on reperfusion of the donor liver. Patient characteristics, timing and precipitants for these events are summarized in Supplementary Table S1. CA/VA rhythms were also stratified by whether they occurred in the context of reperfusion vs in a post-operative setting. This demonstrated that reperfusion events tended to be predominantly asystolic arrests while post-operative arrhythmias tended to be ventricular fibrillation or tachycardia (Table S1).

Patients that experienced CA/VA were older with higher MELD scores, demonstrated a trend towards being male with non-alcoholic steatohepatitis as the etiology of liver disease (Table 1). These patients also received more blood products although cumulative doses of vasopressors were similar across the groups. No significant differences in cardiovascular risk factors, serum electrolytes, donor characteristics or rates of postoperative surgical complications were observed between groups. Further, the proportion of patients on beta-blockers or QT prolonging drugs at the time of transplantation were similar in both groups (Table 1).

QT-Interval and Risk of Cardiac Arrest/Ventricular Arrhythmias

Patients that experienced CA/VA had significantly higher preoperative corrected QT interval (475 ±34 vs 450 ±34 ms, p<0.001) regardless of QT correction method (Table 1, Figure 2). No differences in the rates of atrial fibrillation, bundle branch block or resting ischemic ECG abnormalities were observed between groups.

The optimal QTc cut-off value to predict occurrence of CA/VA in this patient cohort was ≥480ms. The risk of CA/VA was substantially higher in those with a QTc ≥480 ms (13 [18.8%] vs 13 [3.8%]; OR 5.8, 95% CI 2.6-13.2; p<0.001). On multivariate logistic regression after adjusting for significant demographic and clinical variables including age, gender and MELD score, QTc ≥480 ms remained the strongest predictor for the occurrence of CA/VA (OR 5.2 95%CI 2.2-12.6, p<0.001). Addition of serum potassium levels or NASH as etiology of cirrhosis in the final model did not improve final model fit (Table 3). A trend to a stepwise increase in risk of CA/VA was observed with 20 ms increments in QTc over 440 ms (Figure S3). Sensitivity analyses using Fridericia's correction, excluding patients in AF and on QT prolonging drugs and excluding patients with potential triggers for CA/VA were undertaken (Supplement Table S2). Consistent with prior analyses, a prolonged QTc remained the strongest independent predictor of CA/VA.

Assessment of 30-Day and Long-Term Mortality following CA/VA

Seven (1.7%) patients died within 30-days following LT. Those with CA/VA had a significantly higher rate of early mortality (11.5% vs 1.0%, p=0.007). Over a median follow-up of 4.8 (IQR 2.6-6.9) years, 46 (11.3%) patients died. Rate of death in patients that experienced perioperative CA/VA was significantly higher (26.9% vs 10.2%, p=0.009; Hazard ratio 2.67, 95% CI 1.1-6.3).

Development of a Risk Index for CA/VA: Cardiac Arrest Risk Index (CARI)

Optimal cut-off points for age (≥65 years), MELD score (≥30) and QTc (≥480 ms) were estimated using ROC curves. Gender was also included in the final model. For estimation of the risk index, each risk predictor was assigned one or two points according to the logistic regression model (two points for QTc ≥480 ms, one point for age ≥65, one point for MELD score ≥30 and one point for male). The bootstrap model yielded bias corrected 95% confidence intervals for the regression coefficients. The final model demonstrated moderate discrimination (C statistic 0.79,

bias corrected C statistic 0.77) with appropriate calibration (Hosmer-Lomeshow p=0.30). The Cardiac Arrest Risk Index (CARI) was established by the sum of all risk points for each patient. Based on the observed occurrence of CA/VA, a CARI score of ≥3 was deemed to identify high-risk individuals. A CARI score ≥3 was associated with a high-risk for CA/VA (OR 8.9 95%CI 3.9-20.6, p<0.001).

The clinical utility of CARI was further evaluated using a Fagan's nomogram- a Bayesian risk assessment tool. In a hypothetical patient undergoing LT with a pre-test probability of CA/VA of 6.5% (based on our study population), a CARI score <3 would result in a post-test probability of 3%. However, a CARI score ≥3 would increase the probability of CA/VA to 25% (Figure 3).

Discussion

The clinical significance of QT-interval prolongation and whether it increases risk of CA/VA following LT is unclear.(41) This large study of consecutive patients undergoing LT demonstrated the following key findings:

a) Incidence of CA/VA after LT was 6.4% and conferred significant risk for early and late mortality
b) Patients that experienced CA/VA had significantly prolonged QT-intervals and a QTc ≥480ms was the strongest predictor for these events with a five-fold higher risk after risk adjustment
c) Derivation of a novel points-based score (CARI) incorporating key risk variables demonstrated good discrimination for the occurrence of CA/VA

Cardiovascular mortality is the leading cause of early death following LT.(1) Cause-specific analysis of mortality from the Organ Procurement and Transplantation Network (OPTN) of 54,697 patients implicates CA/VA as the cause of early cardiovascular death in 47.8% of cases.(4) This was comparable to our study population where approximately half the early deaths were due to CA/VA. Potential triggers for perioperative CA/VA are multifactorial, including, but not limited to, postreperfusion syndrome, acute coronary syndrome, severe metabolic derangements and uncontrolled bleeding.(22, 42) The heterogeneity in events that precipitate CA/VA coupled with low event rates in small single-centre studies have

limited prior efforts to ascertain robust clinical predictors for these events. Notwithstanding, a higher perioperative and long-term mortality conferred by CA/VA in this study highlight the importance of these events in dictating post-transplant survival.

In patients with liver cirrhosis, prevalence of QT prolongation ranges from 47-83%.(12, 13, 31) The exact mechanism for this observation is unclear. However, upregulation of sympathetic nervous system activity, impaired potassium/calcium handling and portosystemic shunting of inflammasomes are all thought to contribute to the observed abnormalities in ventricular repolarization.(6, 43, 44) Further, QT interval prolongation is also considered a supporting criteria for the diagnosis of cirrhotic cardiomyopathy.(8) Despite the relationship between QTc and CA/VA, no differences in structural cardiac abnormalities including diastolic indices were observed in this study. This may indicate that structural and electrical components of cirrhotic cardiomyopathy may have distinct underlying pathophysiology. QTc in our cohort correlated with the severity of liver disease and was independent of the etiology of cirrhosis. This is consistent with prior studies in both patients with compensated and end-stage liver disease awaiting transplantation.(12, 13, 15, 21) The inverse correlation with serum potassium levels, however, is a novel finding in this population. Increase in extracellular potassium may decrease the driving force for potassium ion movement across cardiac cellular membrane which can lead to shortening of the action potential. This has clinical implications as potassium supplementation has been demonstrated to reduce QT intervals.(45)

A prolonged QT interval identifies patients at increased risk of sudden cardiac death and ventricular arrhythmias. This is the case in both healthy individuals and in patients with a variety of congenital and acquired conditions such as the congenital long QT syndrome, diabetes and coronary artery disease.(16-18) Recent studies with intraprocedural electrocardiograms during liver transplantation indicate lengthening of QTc to above 500 ms in more than half the patients during the anhepatic phase of surgery.(23) For reference, less than 5% of patients undergoing general noncardiac surgery have intraprocedural QT-intervals that exceed this threshold.(46) An already diminished baseline ventricular repolarization reserve coupled with QT-interval lengthening during transplant surgery highlights the

importance of ascertaining whether QT-prolongation predisposes to CA/VA following the physiological stress of LT.

In this study, QTc was significantly higher in patients that experienced CA/VA following LT. There was an incremental rise in the risk of CA/VA with an increase in the QT-interval (Figure S3) with a QTc ≥480ms conferring highest risk. After adjusting for important clinical covariates including MELD score, QTc ≥480 ms was associated with over a 5-fold increased risk of CA/VA. This is a clinically important finding that warrants attention. With the exception of case reports(47-49), only one previous study by Day et al has investigated whether QT-prolongation confers risk of CA/VA in patients with liver cirrhosis.(50) However, this was only limited to a small cohort of patients with alcoholic cirrhosis with low event rates (number of events= 6) and did not evaluate this risk in patients undergoing LT. As such, our findings are novel and suggest a potential mechanistic link between ventricular repolarization abnormalities and the observed high rates of CA/VA in patients undergoing LT.

Assessment of cause-specific mortality from our centre evaluating over 4,000 adult LT performed in Australia and New Zealand between 1985-2017 implicated CA/VA as the leading mode of cardiovascular death following LT.(1) While prior studies have evaluated risk scores for prediction of all-cause cardiovascular events following LT, none have addressed specific risk predictors for CA/VA.(42, 51) This is important given the heterogeneity of post-transplant cardiovascular events that range from congestive heart failure to cerebrovascular events. The derivation of the CARI in this study integrates key demographic and clinical risk predictors including age, gender, MELD score and corrected QT-interval which demonstrated appropriate calibration with internal validation. Calculation of this simple points-based score, may aid transplant physicians and anesthesiologists in risk-stratifying patients that may be at risk of malignant ventricular arrhythmias or perioperative cardiac arrest. The mean MELD score in our study population is also lower than what has been reported from other centres.(51) The strong observed relationship between QTc and cardiac arrest/ventricular arrhythmias in this lower MELD cohort has important implications to the broader liver transplant population, whereby it predicted events in a cohort with less pronounced physiological derangements. It would be of interest to study the

relationship between MELD scores, QTc and risk of CA/VA from transplant centres with a higher baseline MELD score as well as the predictive accuracy of the CARI.

There are several clinical implications of our findings. First, this study challenges the current notion of QT prolongation in cirrhosis as a 'benign' entity.(41) The adjusted hazard for CA/VA conferred by a QTc ≥480 ms is substantial and warrants validation in larger, prospective trials. Second, the majority of CA/VA occurred intraoperatively. Assessment of the QT interval by anesthesiologists preoperatively with avoidance of QT prolonging drugs when feasible may be beneficial, especially among those with an elevated baseline QTc. Given the inverse correlation between QTc and serum potassium levels, studies are needed to assess whether judicious potassium replacement could lead to cardiac membrane stabilization and QT interval reduction. However, this should be done cautiously and under close monitoring as hyperkalemia during reperfusion can also precipitate cardiac arrhythmias. Third, prior studies have demonstrated the favourable effect of beta-blockade on QT derangement due to the pharmacological counteraction of chronic adrenergic hyperactivity frequently present in cirrhotic patients.(52) Whether targeted use of beta-blockers in patients with a prolonged QT interval can mitigate the high rates of CA/VA warrant further study.

We acknowledge certain limitations of this study. First, the retrospective study design limits our ability to establish temporality and causality of the observations. Although QT prolongation was associated with CA/VA, the causes for these events are usually multifactorial. QTc could also represent unmeasured confounding factors including donor specific factors that may not be captured in this dataset. Further, how this risk score compares to other established risk scores such as the CAROLT score in the prediction of cardiovascular events is unclear. Second, as CA/VA was not frequently encountered following LT, the results are based on a modest number of clinical events. However, all recorded events in this study were adjudicated by a multidisciplinary panel which increases external validity of our results. Third, we implemented the widely used Bazett's formula for QTc estimation, which may lead to QTc overcorrection in patients with cirrhosis.(10) However, Bazett's correction remains the most widely used in clinical practice. Further, sensitivity analyses using the alternative Fridericia's correction also demonstrated an increased risk of QTc

with CA/VA. Fourth, while QT prolongation has mechanistic links to ventricular arrhythmia, the exact mechanism of precipitating other cardiac arrest rhythms such as asystole and PEA is unknown. Episodes of low voltage ventricular arrhythmia not appreciable on intraoperative ECG monitoring is a possibility. Further, the sympathetic stimulation, hemodynamic and electrolyte shifts during liver reperfusion can also lead to early-afterdepolarization mediated arrhythmias that are both ventricular and non-ventricular in origin.(53) Fifth, although we used the bootstrap method for internal validation of our CARI risk prediction score, external validation to demonstrate generalizability to new populations is a prerequisite for translation into clinical care. Lastly, this study focused on the perioperative risk of QT prolongation in a cohort of patients with end-stage liver disease undergoing LT. Whether a similar proarrhythmic risk is may be observed in an all-comer population with liver cirrhosis is unclear.

Conclusion

Despite advances in surgical technique and perioperative management, CA/VA is a significant risk after LT affecting over 1 in 20 patients and is associated with excess long-term mortality. QTc ≥480ms was associated with a five-fold increase in the risk of CA/VA and the CARI score may identify patients at a high risk of these events. Whether heightened perioperative cardiac surveillance, avoidance of QT prolonging drugs or beta-blocker use in high-risk individuals is able to lower the risk of malignant arrhythmias in this population merits further study.

Acknowledgements

Dr Anoop N Koshy a recipient of the National Health and Medical Research Council of Australia/National Heart Foundation Post-Graduate Scholarship and Royal Australasian College of Physicians Blackburn Scholarship (1150874)

Disclosure

The authors of this manuscript have no conflicts to disclose as described by the *American Journal of Transplantation.*

Data Availability Statement

Data not available due to privacy/ethical restrictions as part of ethics approval.

Table 1: Baseline Characteristics

	Overall (n=408)	Cardiac arrest/Ventricular arrhythmias (n=26)	No Cardiac arrest/Ventricular arrhythmias (n=382)	p value
Age (years)	57.1 ±12	60.7 ±12	56.9 ±12	0.02
% Male	275 (67.4)	22 (84.2)	253 (66.2)	0.053
MELD score	19 ±9	23 ±11	19 ±8	0.03
Child-Pugh Score	9 ±3	10 ±2	9 ±2	0.66
Encephalopathy (≥Grade 1)	44%	52.40%	43.50%	0.42
Refractory ascites	45.60%	60	44.4	0.17
Hepatorenal syndrome	79 (19.4)	8 (30.8)	71 (18.6)	0.12
Etiology of Liver Disease				
Hepatitis B/C	133 (32.6)	5 (19.2)	128 (33.5)	0.13
Non-alcoholic steatohepatitis	52 (12.7)	6 (23.1)	46 (12.0)	0.09
Alcoholic	38 (9.3)	2 (7.7)	36 (9.4)	0.77
Hepatocellular carcinoma	36 (8.8)	3 (11.5)	33 (8.6)	0.61
Other	149 (36.5)	10 (38.4)	139 (36.4)	0.83
Serum creatinine (umol/L)	92 (71-127)	105 (84-128)	90 (70-127)	0.57
Serum sodium (mEq/L)	135 ±6	136 ±5	135 ±6	0.91
Serum albumin (g/L)	29 ±7	31 ±8	29 ±7	0.14
Serum potassium (mmol/L)	4.1 ±0.6	3.9 ±0.6	4.1 ±0.5	0.1
Adjusted serum calcium (mmol/L)	2.4 ±0.1	2.4 ±0.2	2.4 ±0.1	0.59

Serum phosphate (mmol/L)	1.10 ±0.3	1.12 ±0.3	1.10 ±0.3	0.76
Serum magnesium (mmol/L)	0.82 ±0.1	0.84 ±0.1	0.82 ±0.1	0.54
Cardiovascular risk factors				
Hypertension	39.80%	34.6	40.2	0.57
Coronary artery disease	9.40%	12	9.3	0.65
Diabetes	30.8	30.8	30.8	0.99
Smoking history	253 (62.1)	17 (65.4)	236 (61.8)	0.71
Dyslipidemia	24.40%	21.7	24.6	0.76
Non-selective beta blocker use	20.30%	16	20.6	0.58
QT prolonging medication use	48 (11.8)	0 (0)	48 (12.6)	0.054
Echocardiographic Indices*				
Left atrial area (cm^2)	23.7 ±6	23.8 ±6	23.6 ±5	0.94
Peak E velocity (m/sec)	0.92 ±0.2	0.88 ±0.29	0.92 ±0.25	0.59
Peak A velocity (m/sec)	0.77 ±0.2	0.71 ±0.2	0.77 ±0.3	0.42
E/a ratio	1.3 ±0.7	1.4 ±0.9	1.3 ±0.7	0.72
Left ventricular diastolic dimension (cm)	4.9 ±0.6	4.9 ±0.7	4.9 ±0.6	0.82
Left ventricular systolic dimension (cm)	3.0 ±0.6	2.9 ±0.5	3.0 ±0.6	0.86
Right ventricular systolic pressure (mmHg)	29 ±7	28 ±7	29 ±7	0.98
Cardiac output (L/min) **	7.2 ±2	7.0 ±1	7.2 ±2	0.79
Donor and operative parameters				
Cold ischemia time (mins)	367 (308-440)	384 (310-404)	365 (308-441)	0.48
Warm ischemia time (mins)	44 (39-50)	44 (39-52)	44 (39-50)	0.5

Anhepatic time (hours)	1.0 ±0.26	1.0 ±0.30	0.99 ±0.26	0.6
Packed red blood cells (units)	3.5 (0-6)	4 (2.0-7.5)	2 (0-5)	0.02
Fresh frozen plasma (units)	1 (0-3)	4 (0-4)	1 (0-3)	0.003
Cryoprecipitate (units)	3.8 ±2.2	4.5 ±2	3.7 ±3	0.12
Platelets (units)	1.0 ±1	1.2 ±1	1.0 ±1	0.4
Cumulative norepinephrine dose (mcg)	2400 (1350-4200)	3600 (1800-5880)	2400 (1260-4050)	0.17
Requiring ≥1 vasopressor	46.9%	52.9%	46.5%	0.85
Postoperative surgical complication	123 (30.2)	9 (36)	114 (29.8)	0.52

Values presented as mean ± standard deviation or median (interquartile range) or number (proportion)

* Echocardiographic data available in 279 patients

** Cardiac output assessed on echocardiographic Doppler measurements

Table 2: Electrocardiographic Parameters

	Overall	**Cardiac arrest/Ventricular arrhythmias**	**No Cardiac arrest/Ventricular arrhythmias**	**p value**

	(n=408)	(n=26)	(n=382)	
Atrial fibrillation	27 (6.6)	1 (3.7)	26 (6.8)	0.55
Heart rate (bpm)	80 ±15	80 ±17	80 ±15	0.95
Mean arterial pressure	80 ±14	78 ±9	80 ±14	0.75
R-R interval	773 ±158	779 ±169	772 ±157	0.84
Right bundle branch block	22 (5.4)	3 (11.5)	19 (5.0)	0.16
Left bundle branch block	2 (0.50)	1 (3.8)	1 (0.30)	0.12
Ischemic changes at baseline*	26 (6.4)	1 (3.8)	25 (6.6)	0.49
QT interval	395 ±39	414 ±45	393 ±39	0.008
Corrected QT interval (Bazett's)	451 ±31	475 ±34	450 ±30	<0.001
Corrected QT interval (Fridericia)	431 ±29	455 ±32	430 ±28	<0.001

Values presented as mean ± standard deviation or number (proportion)

Table 3: Predictors for the occurrence of cardiac arrest and ventricular arrhythmias following liver transplantation

	Unadjusted OR (95% CI)	Unadjusted p value	Adjusted OR (95% CI)	Adjusted p value
Model 1				
Age	1.04 (0.99-1.10)	0.1	1.03 (0.98-1.10)	0.22
Male gender	2.80 (0.95-8.3)	0.06	2.70 (0.87-8.38)	0.08
MELD score	1.05 (1.00-1.10)	0.02	1.03 (0.99-1.08)	0.1
Corrected QT interval ≥480 ms*	5.80 (2.56-13.21)	<0.001	5.24 (2.18-12.58)	<0.001
Model 2				
Age	1.04 (0.99-1.10)	0.1	1.01 (0.96-1.06)	0.6
Male gender	2.80 (0.95-8.3)	0.06	2.92 (0.79-10.75)	0.1
MELD score	1.05 (1.00-1.10)	0.02	1.03 (0.98-1.09)	0.24
Corrected QT interval ≥480 ms*	5.80 (2.56-13.21)	<0.001	3.70 (1.33-10.26)	0.012
NASH cirrhosis	2.19 (0.84-5.73)	0.1	1.98 (0.62-6.33)	0.25
Pre-transplant serum potassium	0.55 (0.24-1.30)	0.17	0.64 (0.26-1.55)	0.32
Model 3				
Age	1.04 (0.99-1.10)	0.1	1.02 (0.97-1.07)	0.33
Male gender	2.80 (0.95-8.3)	0.06	3.84 (1.06-14.2)	0.04
MELD score	1.05 (1.00-1.10)	0.02	1.03 (0.98-1.09)	0.19
Corrected QT interval ≥480 ms*	5.80 (2.56-13.21)	<0.001	5.81 (2.35-14.35)	<0.001

Any packed red blood cell use intraoperatively	1.79 (0.65-4.85)	0.20	1.60 (0.52-4.89)	0.41

MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis, QT correction by Bazett's formula

*QT ≥480 ms based on receiver operating characteristic curve

References

1. Koshy AN, Gow PJ, Han HC, Teh AW, Jones R, Testro A et al. Cardiovascular Mortality following Liver Transplantation: Predictors and Temporal Trends over 30 years. Eur Heart J Qual Care Clin Outcomes 2020.
2. Konerman MA, Fritze D, Weinberg RL, Sonnenday CJ, Sharma P. Incidence of and Risk Assessment for Adverse Cardiovascular Outcomes After Liver Transplantation: A Systematic Review. Transplantation 2017;101(7):1645-1657.
3. Koshy AN, Farouque O, Cailes B, Ko J, Han HC, Weinberg L et al. Prediction of Perioperative Cardiovascular Events in Liver Transplantation. Transplantation 2020.
4. VanWagner LB, Lapin B, Levitsky J, Wilkins JT, Abecassis MM, Skaro AI et al. High early cardiovascular mortality after liver transplantation. Liver Transpl 2014;20(11):1306-1316.
5. Sanaiha Y, Juo YY, Aguayo E, Seo YJ, Dobaria V, Ziaeian B et al. Incidence and trends of cardiac complications in major abdominal surgery. Surgery 2018;164(3):539-545.
6. Wiese S, Hove JD, Bendtsen F, Moller S. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. Nat Rev Gastroenterol Hepatol 2014;11(3):177-186.
7. Gaskari SA, Honar H, Lee SS. Therapy insight: Cirrhotic cardiomyopathy. Nat Clin Pract Gastroenterol Hepatol 2006;3(6):329-337.
8. Izzy M, VanWagner LB, Lin G, Altieri M, Findlay JY, Oh JK et al. Redefining Cirrhotic Cardiomyopathy for the Modern Era. Hepatology 2019.
9. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ Arrhythm Electrophysiol 2012;5(4):868-877.
10. 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(1):77-82.
11. Wong F. Cirrhotic cardiomyopathy. Hepatol Int 2009;3(1):294-304.
12. 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(5):1128-1134.
13. Bernardi M, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G et al. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. Hepatology 1998;27(1):28-34.
14. Sonny A, Ibrahim A, Schuster A, Jaber WA, Cywinski JB. Impact and persistence of cirrhotic cardiomyopathy after liver transplantation. Clin Transplant 2016;30(9):986-993.

15. Flaherty D, Kim S, Zerillo J, Park C, Joseph T, Hill B et al. Preoperative QTc Interval is Not Associated With Intraoperative Cardiac Events or Mortality in Liver Transplantation Patients. J Cardiothorac Vasc Anesth 2019;33(4):961-966.
16. Beinart R, Zhang Y, Lima JA, Bluemke DA, Soliman EZ, Heckbert SR et al. The QT interval is associated with incident cardiovascular events: the MESA study. J Am Coll Cardiol 2014;64(20):2111-2119.
17. Sauer AJ, Moss AJ, McNitt S, Peterson DR, Zareba W, Robinson JL et al. Long QT syndrome in adults. J Am Coll Cardiol 2007;49(3):329-337.
18. Tomaselli GF, Beuckelmann DJ, Calkins HG, Berger RD, Kessler PD, Lawrence JH et al. Sudden cardiac death in heart failure. The role of abnormal repolarization. Circulation 1994;90(5):2534-2539.
19. Lee SH, Park M, Park KM, Gwag HB, Park J, Kim J et al. Corrected QT interval on the electrocardiogram after liver transplantation: Surrogate marker of poor clinical outcomes? PLoS One 2018;13(10):e0206463.
20. Glowczynska R, Galas M, Oldakowska-Jedynak U, Peller M, Tomaniak M, Raszeja-Wyszomirska J et al. Pretransplant QT Interval: The Relationship with Severity and Etiology of Liver Disease and Prognostic Value After Liver Transplantation. Ann Transplant 2018;23:622-630.
21. Bal JS, Thuluvath PJ. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. Liver Int 2003;23(4):243-248.
22. Matsusaki T, Hilmi IA, Planinsic RM, Humar A, Sakai T. Cardiac arrest during adult liver transplantation: a single institution's experience with 1238 deceased donor transplants. Liver Transpl 2013;19(11):1262-1271.
23. Shin WJ, Kim YK, Song JG, Kim SH, Choi SS, Song JH et al. Alterations in QT interval in patients undergoing living donor liver transplantation. Transplant Proc 2011;43(1):170-173.
24. Kies SJ, Pabelick CM, Hurley HA, White RD, Ackerman MJ. Anesthesia for patients with congenital long QT syndrome. Anesthesiology 2005;102(1):204-210.
25. Koshy AN, Farouque O, Cailes B, Testro A, Ramchand J, Sajeev JK et al. Impaired Cardiac Reserve on Dobutamine Stress Echocardiography Predicts the Development of Hepatorenal Syndrome. Am J Gastroenterol 2020;115(3):388-397.
26. Koshy AN, Farouque O, Calafiore P, Gow PJ. Letter to the Editor: Diagnosis of Cirrhotic Cardiomyopathy: The Role of an Impaired Cardiac Reserve. Hepatology 2020;71(5):1883.
27. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018;72(14):1677-1749.

28. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA 2003;289(16):2120-2127.
29. Auer R, Bauer DC, Marques-Vidal P, Butler J, Min LJ, Cornuz J et al. Association of major and minor ECG abnormalities with coronary heart disease events. JAMA 2012;307(14):1497-1505.
30. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353.
31. Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. J Hepatol 2006;44(5):994-1002.
32. Adigun AQ, Pinto AG, Flockhart DA, Gorski JC, Li L, Hall SD et al. Effect of cirrhosis and liver transplantation on the gender difference in QT interval. Am J Cardiol 2005;95(5):691-694.
33. Fridericia LS. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. 1920. Ann Noninvasive Electrocardiol 2003;8(4):343-351.
34. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014;64(22):e77-137.
35. Sprung J, Warner ME, Contreras MG, Schroeder DR, Beighley CM, Wilson GA et al. Predictors of survival following cardiac arrest in patients undergoing noncardiac surgery: a study of 518,294 patients at a tertiary referral center. Anesthesiology 2003;99(2):259-269.
36. Katritsis DG, Zareba W, Camm AJ. Nonsustained ventricular tachycardia. J Am Coll Cardiol 2012;60(20):1993-2004.
37. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307-310.
38. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med 2008;3:17.
39. Youden WJ. Index for rating diagnostic tests. Cancer 1950;3(1):32-35.
40. Fagan TJ. Letter: Nomogram for Bayes theorem. N Engl J Med 1975;293(5):257.
41. Bernardi M, Maggioli C, Dibra V, Zaccherini G. QT interval prolongation in liver cirrhosis: innocent bystander or serious threat? Expert Rev Gastroenterol Hepatol 2012;6(1):57-66.
42. VanWagner LB, Serper M, Kang R, Levitsky J, Hohmann S, Abecassis M et al. Factors Associated With Major Adverse Cardiovascular Events After Liver Transplantation Among a National Sample. Am J Transplant 2016;16(9):2684-2694.
43. Trevisani F, Merli M, Savelli F, Valeriano V, Zambruni A, Riggio O et al. QT interval in patients with non-cirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic porto-systemic shunt. J Hepatol 2003;38(4):461-467.

44. Genovesi S, Prata Pizzala DM, Pozzi M, Ratti L, Milanese M, Pieruzzi F et al. QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium. Clin Sci (Lond) 2009;116(12):851-859.
45. Etheridge SP, Compton SJ, Tristani-Firouzi M, Mason JW. A new oral therapy for long QT syndrome: long-term oral potassium improves repolarization in patients with HERG mutations. J Am Coll Cardiol 2003;42(10):1777-1782.
46. Nagele P, Pal S, Brown F, Blood J, Miller JP, Johnston J. Postoperative QT interval prolongation in patients undergoing noncardiac surgery under general anesthesia. Anesthesiology 2012;117(2):321-328.
47. Faigel DO, Metz DC, Kochman ML. Torsade de pointes complicating the treatment of bleeding esophageal varices: association with neuroleptics, vasopressin, and electrolyte imbalance. Am J Gastroenterol 1995;90(5):822-824.
48. Di Micoli A, Zambruni A, Bracci E, Benazzi B, Zappoli P, Berzigotti A et al. "Torsade de pointes" during amiodarone infusion in a cirrhotic woman with a prolonged QT interval. Dig Liver Dis 2009;41(7):535-538.
49. Chin JH, Park JY, Kim YK, Kim SH, Kong YG, Park PH et al. Torsades de pointes triggered by severe diastolic hypotension with low hematocrit in the neohepatic stage of liver transplantation: a case report. Transplant Proc 2010;42(5):1959-1962.
50. Day CP, James OF, Butler TJ, Campbell RW. QT prolongation and sudden cardiac death in patients with alcoholic liver disease. Lancet 1993;341(8858):1423-1428.
51. VanWagner LB, Ning H, Whitsett M, Levitsky J, Uttal S, Wilkins JT et al. A point-based prediction model for cardiovascular risk in orthotopic liver transplantation: The CAR-OLT score. Hepatology 2017;66(6):1968-1979.
52. Henriksen JH, Bendtsen F, Hansen EF, Moller S. Acute non-selective beta-adrenergic blockade reduces prolonged frequency-adjusted Q-T interval (QTc) in patients with cirrhosis. J Hepatol 2004;40(2):239-246.
53. Weiss JN, Qu Z, Shivkumar K. Electrophysiology of Hypokalemia and Hyperkalemia. Circ Arrhythm Electrophysiol 2017;10(3).

Figure 1

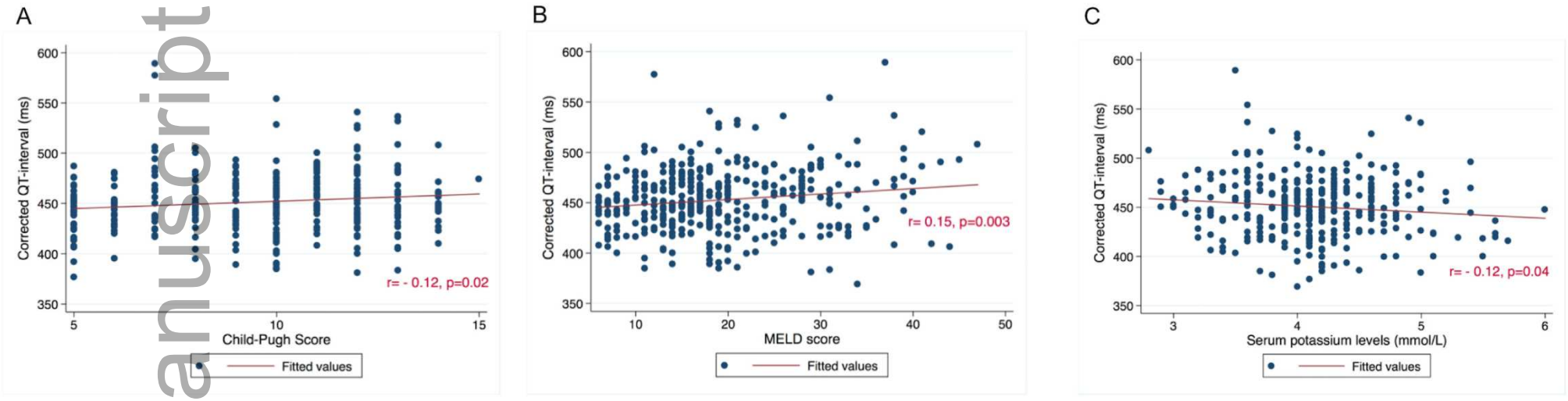

Figure 2

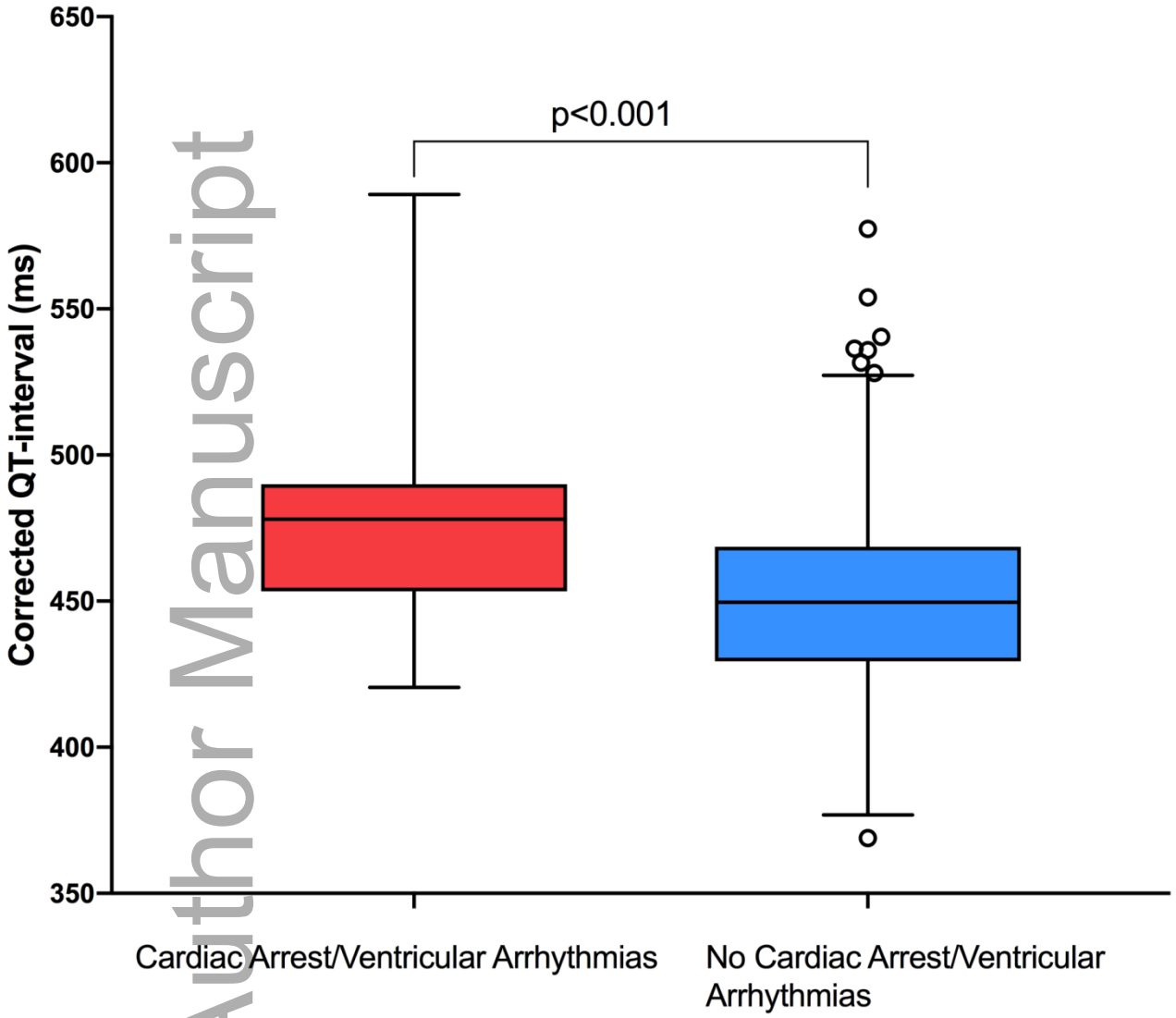

Figure 3