https://doi.org/10.37939/jrmc.v28i2.2419

Frequency Of Prolonged Qtc in Patients With Decompensated Chronic Liver Disease In A Rural Cohort Of Sindh

Adeel Ahmed[1], Bushra Rabbani[2], Muhammad Kamran[3], Ammarah Saeed[4], Jameel Ahmed[5]

Abstract

Objective: To determine the frequency of prolonged QTc (corrected QT) interval in patients. With decompensated chronic liver disease (DCLD) in a tertiary care hospital of Gadap town, Sindh.

Methods: This cross-sectional study was conducted from 1st January 2022 to 31 December 2022 at the Department Of Medicine, Baqai Medical University, Karachi. All partial and fully decompensated Cirrhotic patients aged 25 to 75 years regardless of sex, diagnosed based on history, physical Examination and ultrasonography findings, who were admitted to our medical ward, were included using a non-probability convenience sampling technique. Pregnant females, patients with other major co-morbid illnesses, electrolyte imbalances and those on medications affecting QTc interval were excluded. All patients meeting inclusion criteria were enrolled for a 12 lead ECG (three serial recordings each), from which QT, R-R interval, as well as QTc, were calculated. Data entry and analysis were performed using SPSS version 20. Categorical variables were described using frequency and percentages whereas continuous variables were summarized using mean and standard deviation.

Results: Out of 196 participants with decompensated liver disease included in the study, 59 (30.1%) participants were found to have prolonged QTc. Age, Child–Turcotte–Pugh (CTP) class and Bilirubin of the patients were significantly associated with QTc prolongation.

Conclusion: Prolonged QTc interval, a marker of cirrhotic cardiomyopathy, is a common occurrence in patients with decompensated chronic liver disease. The risk of developing prolonged QTc interval increases with advanced age and progressive liver disease.

Keywords: cirrhosis, liver, end stage liver disease.

[1] Senior Registrar, Baqai Medical University; [2] Assistant Professor, Baqai Medical University; [3] Assistant Professor, Fazaia RUTH, PFAU Medical Air University: KHI; [4] Assistant Professor, Fazaia Medical College, Islamabad; [5] Professor, Baqai Medical University.

Correspondence: Dr. Adeel Ahmed, Senior Registrar, Baqai Medical University. **Email:** adeeldr574@gmail.com

Cite this Article: Ahmed A, Rabbani B, Kamran M, Saeed A, Ahmed J. Frequency Of Prolonged Qtc in Patients With Decompensated Chronic Liver Disease In A Rural Cohort Of Sindh. JRMC. 2024 Jun. 29;28(2).242-246. https://doi.org/10.37939/jrmc.v28i2.2419.

Received October 11, 2023; accepted May 23, 2024; published online June 28, 2024

1. Introduction

Degeneration of liver parenchyma due to various continuous stimuli leads to liver Fibrosis called chronic liver disease or cirrhosis. This process takes a few months to years.[1] Chronic liver disease is common in Pakistan. The most common cause is chronic viral hepatitis. It is the 12th leading cause of death worldwide.[2] In patients with chronic liver disease, the presence of jaundice, ascites, variceal haemorrhage and hepatic encephalopathy define the onset of liver decompensation. It occurs in 11% of patients per year and is associated with high mortality (one-year mortality in compensated cirrhosis is 7% compared with 20% following liver decompensation).[3] Many of the complications of decompensated chronic liver disease (DCLD) like ascites, and variceal haemorrhage are well studied, however, more Understanding is required for other less researched complications like aortopulmonary hypertension and cirrhotic cardiomyopathy.

The term "cirrhotic cardiomyopathy"(CCM) was first used 25 years ago by 'Lee' to point out the cardiac dysfunction in cirrhosis. CCM has been used to describe chronic cardiac dysfunction in cirrhotic patients with no previous structural heart disease.[4] CCM is characterized by a hyperdynamic state, with both diastolic and systolic ventricular dysfunction, prolonged ventricular depolarization and an inappropriate chronotropic response to stress.[5] The left ventricular diastolic dysfunction (LVDD) was identified in echocardiography as the most common and the first sign of cardiac abnormality among cirrhosis patients.[6] ECG findings like QT interval (QTc) prolongation have been shown in patients with chronic liver disease and represent one of the most common ECG changes in cirrhotic cardiomyopathy. Recent data suggest that QTc prolongation is one of the important electrophysiological abnormalities in patients with cirrhosis.[7] Its prolongation provokes ventricular arrhythmias that can lead to sudden death. About

50% of liver cirrhosis patients are estimated to have an underlying cardiac dysfunction.[8]

The timely diagnosis & treatment can reduce the morbidity and mortality associated with this potential complication of DCLD.[9] Our study aims to observe the frequency of QTc interval prolongation in patients with DCLD patients by simple and cost-effective standard 12 lead electrocardiogram (ECG),[10] which will help to identify the magnitude of this problem. This, in turn, will translate into reduced mortality and morbidity in patients with DCLD, who can benefit from being routinely investigated for prolonged QTc.

2. Materials & Methods

This cross-sectional study was conducted from 1st January 2022 to 31 December 2022 at the Department of Medicine Baqai Medical University, Karachi, The ethical approval was taken from the Ethics Review Committee of Baqai Medical University (Ref: BMU-EC/06-2021). Keeping the percentage frequency of the study outcome at 50% for a most liberal estimate, with a 95% confidence level and 7% precision, the required sample size was calculated to be 196 participants using an online open epi calculator.[11] Against the calculated sample size, a total of 196 participants were included in the study using the non-probability convenience sampling technique. All partial and fully decompensated cirrhotic patients of age 25 to 75 years regardless of sex, were diagnosed based on history, physical examination and ultrasonographic findings (dilated portal vein, splenomegaly, shrunken liver with irregular margins, and presence of ascites) were included. All pregnant females and patients with hypertension, ischemic heart disease, bundle branch block, chronic obstructive pulmonary disease, renal failure and electrolyte imbalances (hypokalemia, hypocalcaemia, hypomagnesemia), those taking medications which prolong QT interval such as sotalol and disopyramide were excluded from the study. Keeping the percentage frequency of the study outcome at 50% for a most liberal estimate, with a 95% confidence level and 7% precision, the required sample size was calculated to be 196 participants using an online open epi calculator.11 Against the calculated sample size, a total of 196 participants were included in the study using the non-probability convenience sampling technique.

After taking informed and written consent, all patients meeting inclusion criteria Child-Turcot- pugh class B and C were enrolled for ECG i.e. 12 lead ECG. Three serial ECG recordings of each patient were obtained 5 minutes apart. QT and R-R interval were calculated from ECG. Corrected QT interval (QTc) was calculated by using Bazett's formula: QTc = QT÷R-R. A mean value of QTc was recorded. Data were collected on predesigned performed by the researcher to control the bias. In males, a QTc $\geq$ 470 ms was considered prolonged, whereas in females $\geq$ 480 ms was taken as prolonged.[12] Data entry and analysis were performed using SPSS version 20. Categorical variables (Age groups, Gender, Child-Pugh class, Meld Na category) were described using frequency and percentages whereas continuous (Age, Bilirubin, INR, Albumin, Meld Na score, QTc interval) variables were summarized using mean and standard deviation. For inferential analysis, binary logistic regression was applied to compute univariate odd ratios with a 95% confidence interval for determining the association of participant characteristics with Prolong QTc. Variables with $p<0.25$ and other important variables irrespective of $p<0.25$ in univariate analysis were used to build a multivariable regression model to compute adjusted odd ratios with a 95% confidence interval. A two-tailed p-value of ≤ 0.05 was considered statistically significant.

3. Results

A total of 196 participants with decompensated liver disease were included in the study. The mean age of participants was 51.1±12.36 years, the majority were aged up to 50 years (n=99, 50.5%), males (n=111, 56.6%), classified as Child Turcotte Pugh (CTP) class C (n=118, 60.2%) and had Meld Na score of 24 or less (n=145, 74.0%). Their mean QTc was calculated to be 0.45±0.11 seconds (table 1). Out of 196 participants, 59 (30.1%) were found to have prolonged QTc (figure 1). Multivariable logistic regression analysis of association between patients characteristics and prolong QTc revealed that after controlling for the potential confounding effects of other variables, age (AOR 4.86, 95%CI 1.98- 9.68, $p<0.001$), CTP class (AOR 5.24, 95%CI 1.96-13.96, $p = 0.001$), and bilirubin (AOR 0.51, 95%CI 0.28-0.91, $p=0.025$) of the patients were significantly associated with QTc prolongation.

Table 1: Participants Profile

Participant Characteristics (n=196)	Count (%)/Mean ± S.D.
Age (Years)	51.1±12.36
Age Group	
Up to 50 Years	99 (50.5)
51 years or above	97 (49.5)
Gender	
Male	111 (56.6)
Female	85 (43.4)
Child-Pugh Class	
Child-Pugh Class B	78 (39.8)
Child-Pugh Class C	118 (60.2)
Bilirubin	1.91 ± 0.66
INR	2.1 ± 0.60
Albumin	2.13 ± 0.62
MELD Na Score	20.65 ± 5.81
MELD Na Category	
Score up to 24	145 (74.0)
Score 25 and above	51 (26.0)
QTc (Seconds)	0.45 ± 0.11

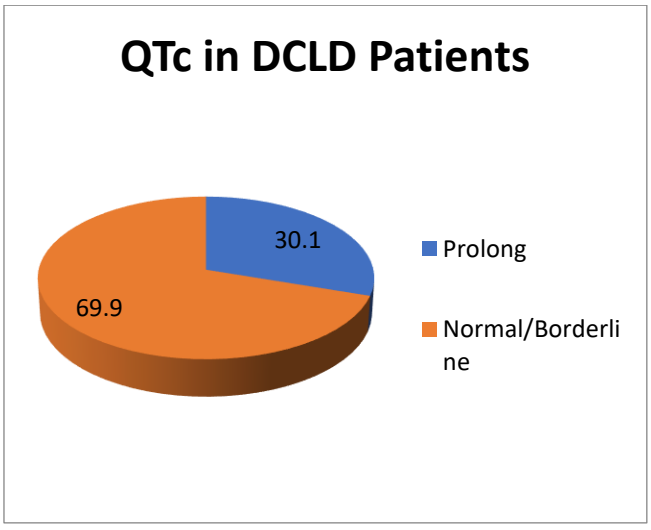

Figure 1: QTc in DCLD Patients

Patients who were aged 51 years or above and belonged to Child-Pugh class C had significantly higher odds of having QTc prolongation whereas those with higher bilirubin levels had lower odds of having QTc prolongation (table 2).

Table 2: Multivariable Analysis of the association between prolonged QTc and characteristics of decompensated liver disease patients

Patient Characteristics (n=196)	AOR	95% CI		P
		Lower	Upper	
Age Group				
51 years or above	4.38	1.98	9.68	<0.001
Up to 50 Years	**Ref**			
Gender				
Female	1.20	0.57	2.53	0.623
Male	**Ref**			
Child-Pugh Class				
Child-Pugh Class C	5.24	1.96	13.96	0.001
Child-Pugh Class B	**Ref**			
MELD Na				
Score 25 and above (High)	1.57	0.70	3.51	0.273
Score up to 24 (Low)	**Ref**			
Bilirubin	0.51	0.28	0.91	0.025
INR	2.00	0.97	4.11	0.057
Albumin	1.72	0.83	3.54	0.140

4. Discussion

Our study unfolded a unique aspect of decompensated chronic liver disease in a rural population of Sindh, by studying the frequency of QTc interval prolongation in such patients. Chronic liver disease is one of the leading causes of mortality and morbidity in the Asia-Pacific region, including Pakistan.[13] This is because chronic viral infections of the liver, namely hepatitis B and C (which lead to liver cirrhosis) are highly prevalent in this part of the world. One of the complications associated with chronic liver disease is cirrhotic cardiomyopathy, which is challenging to diagnose and its exact prevalence is still unclear. In this regard, aberrations in ECG findings such as prolonged QTc interval sometimes remain the only early sign of cardiac pathology before the full-blown manifestation of cirrhotic cardiomyopathy. This leads to increases in the risk of morbidity and sudden death in these individuals as well as intensifies the threat of developing further liver-related complications including variceal haemorrhage.[14] Our study involved only those patients who had chronic liver disease with decompensation (e.g. presence of ascites or a history of variceal haemorrhage).

It is a well-known fact that a long duration of time is needed from acquiring the hepatitis C infection to the development of decompensated chronic liver disease. Hence, most patients included in our study population were above 50 years of age and had advanced liver disease (CTP class B and C), with slight male preponderance. A study by Abbas et al. performed on 110 patients with chronic liver disease also recorded a mean age of 56 years.[15] We found that approximately one-third of patients with decompensated chronic liver disease had prolonged QTc interval (59 out of 196 subjects). A retrospective study conducted by Zhao et al. with a larger sample size showed a slightly higher percentage (38.1%).[16] However, Bhatti et al. reported a lower frequency of prolonged QTc interval in patients with chronic liver disease.[17-20] The difference in frequencies among various studies could be due to the variation in patient selection, since these studies recruited patients with liver cirrhosis regardless of decompensation. Other confounding factors include the use of drugs affecting QTc, electrolyte imbalances, and coexistent cardiac illnesses that may have been included in other studies but were excluded in our study. In our study, we noticed that the frequency of QTc prolongation was significantly higher in patients with CTP class C disease. This observation signifies a clear relationship between the severity of cirrhosis and the advancement of cirrhotic cardiomyopathy. To put it differently, patients with advanced liver cirrhosis have a higher probability of developing cirrhotic cardiomyopathy and related symptoms, a finding that has been appreciated in previous studies by Bhatti et al. and Genovesi et al.[9,15,21] Additionally, we noticed that advanced age and high serum bilirubin are also significantly associated with QTc prolongation in patients with chronic liver disease, again stressing the fact that such cardiac abnormalities become more frequent as liver disease progresses. QTc prolongation was not associated with gender difference, INR, serum albumin and MELD Na score. The major strength of our study was that we included patients from a rural community of Sindh, a population in which such studies had not been done in the past. Nevertheless, there were a few limitations of our cross-sectional analysis. Echocardiographic studies were not performed to confirm cardiac dysfunction and correlate with liver disease severity QTc prolongation in this cirrhotic population. However, these studies are not feasible and cost-effective to be conducted in the rural and under-privileged population of Gadap town, Sindh. Further prospective studies involving cardiac functional assessment are required to corroborate the diagnostic importance of prolonged QTc interval in recognizing cirrhotic cardiomyopathy. Another limitation was that we did not study the effect of the aetiology of liver disease on QTc interval prolongation.

5. Conclusion

We have shown in this study that a significant number of patients with decompensated chronic liver disease develop prolongation of the QTc interval, which may lead to cirrhotic cardiomyopathy later in life. Besides the known common complications of chronic liver disease, these patients are also at risk of adverse cardiac events like sudden death and cardiac arrhythmias secondary to cardiomyopathy. We also found a strong association of prolonged QTc interval with advanced cirrhosis. Therefore, we recommend that all patients with decompensated chronic liver disease should undergo a work-up for cardiomyopathy, regardless of the absence of a prior history of cardiovascular disease.

INSTITUTIONAL REVIEW BOARD

BMU-EC/06-2021 Dated 17-11-2021
Baqai Medical University, Karachi

CONFLICTS OF INTEREST- None

Financial support: None to report.
Potential competing interests: None to report

Contributions:

A.A, B.R - Conception of study
A.A, - Experimentation/Study Conduction
B.R - Analysis/Interpretation/Discussion
M.K - Manuscript Writing
A.A - Critical Review
J.A, A.S - Facilitation and Material analysis

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

References

1. Ginès P, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. The Lancet. 2021 Oct 9;398(10308):1359-76. doi:10.1016/S0140-6736(21)01374-X
2. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. The burden of liver diseases in the world. Journalofhepatology.2019 Jan 1;70(1):151-71.doi:10.1016/j.jhep.2018.09.014

3. D'Amico G, Bernardi M, Angeli P. Towards a new definition of decompensated cirrhosis. Journal of Hepatology. 2022 Jan 1;76(1):202-7. doi:10.1016/j.jhep.2021.06.018
4. Yoon KT, Liu H, Lee SS. Cirrhotic cardiomyopathy. Current gastroenterology reports. 2020 Sep;22:1-9. doi:10.1007/s11894-020-00783-1
5. Carvalho MV, Kroll PC, Kroll RT, Carvalho VN. Cirrhotic cardiomyopathy: the liver affects the heart. Brazilian Journal of Medical and Biological Research. 2019 Feb 14;52:e7809. doi:10.1590/1414-431X20187809.
6. Armstrong MJ, Gohar F, Dhaliwal A, Nightingale P, Baker G, Greaves D et al. Diastolic dysfunction on echocardiography does not predict survival after transjugular intrahepatic portosystemic stent-shunt in patients with cirrhosis. Alimentary Pharmacology & Therapeutics. 2019 Mar;49(6):797-806. doi:10.1111/apt.15164.
7. Karki N, Kc S, Sharma D, Jaisi B, Khadka S. Cardiac dysfunction in patients with liver cirrhosis. J Nepal Health Res Counc 2019;17:357-614(1):20. doi:20.500.14356/1413.
8. Toma L, Stanciu AM, Zgura A, Bacalbasa N, Diaconu C, Iliescu L. Electrocardiographic changes in liver cirrhosis—clues for cirrhotic cardiomyopathy.Medicina.2020Feb10;56(2):68. doi:10.3390/medicina56020068
9. Kumar A, Riaz SU, Kazmi SH, Kumar R, Ghauri MI. Prolongation of QT Interval in ECG: A Hidden Complication of Cirrhotic Liver Disease. Annals Of Abbasi Shaheed Hospital And Karachi Medical & Dental College.2019 Mar31;24(1):20-4. doi:10.58397/ashkmdc.v24i1.22.
10. Papadopoulos VP, Mimidis K. Corrected QT interval in cirrhosis: A systematic review and meta-analysis. World Journal of Hepatology. 2023 Sep 27;15(9):1060-85. doi: 10.4254/wjh.v15.i9.1060.
11. OpenEpi. Open Source Epidemiologic Statistics for Public Health. Available from: https://www.openepi.com/Menu/OE_Menu.htm [Accessed June, 2021].
12. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V and et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American College ofCardiologyFoundation.Circulation.2010Mar2;121(8):1047-60. doi:10.1161/CIRCULATIONAHA.109.192704
13. Sarin SK, Kumar M, Eslam M, George J, Al Mahtab M, Akbar SM,et al. Liver diseases in the Asia-Pacific region: a lancet gastroenterology & hepatology commission. The lancet Gastroenterology & hepatology. 2020 Feb 1;5(2):167-228. doi:10.1016/S2468-1253(19)30342-5.
14. Kim KS, Kwon HM, Jung KW, Sang BH, Moon YJ, Kim B,et al.Markedly prolonged QTc interval in end-stage liver disease and risk of 30-day cardiovascular event after liver transplant. Journal of Gastroenterology and Hepatology. 2021 Mar;36(3):758-66. Doi:10.1111/jgh.15179.
15. Abbas A, Khan F, Rehman S, Ahsan O, Afzal A. Comparison of QTC Interval Prolongation in Cirrhotic and Non-Cirrhotic Chronic Hepatitis C Patients. Ann. Pak. Inst. Med. Sci. 2018. 14 (2). doi: 10.48036/apims.v14i2.93
16. Zhao J, Qi X, Hou F, Ning Z, Zhang X, Deng H, et al.Prevalence, risk factors and in-hospital outcomes of QTc interval prolongation in liver cirrhosis. The American journal of the medical sciences. 2016 Sep 1;352(3):285-95. doi:10.1016/j.amjms.2016.06.012.
17. Ahmed N, Ahmad F, Soomro IA, Yusuf MA. Frequency of prolonged corrected qt interval in child pugh class in patients of cirrhosis of liver: child pugh class of cirrhosis of liver. Pafmj [internet]. 2018 oct. 30 [cited 2024 Feb. 11];68(3):475-78. Available from: https://pafmj.org/PAFMJ/article/view/261
18. Kanwal M, Hussain, W, Soomro A, Aijaz, R, Khalique S, Sadaf M. (2022). Prevalence of Prolonged QT Interval In Patients With Chronic Liver Disease: Prolonged Qt Interval in Patients with Chronic Liver Disease. Pakistan Journal of Health Sciences, 3(05), 162–166. doi:10.54393/pjhs.v3i05.258
19. Haider S, Tabassum S, Ansari N, Talpur MT. Frequency of Cardiomyopathy in Patients with Hepatic Cirrhosis. Journal of Liaquat University of Medical & Health Sciences. 2021;20(5):305-9. https://doi.org/10.22442/jlumhs.2021.00786
20. Hussain K, Singh D, Nizamani S. Comparison of Heart Rate and QTc Interval in Patients of Cirrhosis of Liver with Non Cirrhotic Controls. Annals of PIMS-Shaheed Zulfiqar Ali Bhutto Medical University. 2020 Apr 28;16(1):41-5. doi:10.48036/apims.v16i1.365
21. 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. Clinical science. 2009 Jun 1;116(12):851-9.doi:10.1042/CS20080325.