Original Article

QTc prolongation in patients of cirrhosis and its relation with disease severity: An observational study from a rural teaching hospital

Abhinav Bhardwaj[1], Sandeep Joshi[1], Ruby Sharma[2], Sakshi Bhardwaj[3], Rishabh Agrawal[1], Nitin Gupta[1]

Departments of [1]Medicine and [2]Physiology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, [3]Department of Psychiatry, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India

Abstract

Introduction: Cirrhotic cardiomyopathy is characterised by increased baseline cardiac output, systolic and diastolic dysfunction, diminished cardiovascular response to stressful stimuli and electrophysiological abnormalities in patients of cirrhosis in the absence of any underlying cardiac disease. QTc prolongation has been described as a common electrocardiographic abnormality in cirrhosis patients. **Aims and Objectives:** This study was done to evaluate the prevalence of QTc changes in patients of cirrhosis coming to a rural tertiary care centre and to analyse its correlation with disease severity. **Materials and Methods:** The present study was conducted on 100 patients suffering from cirrhosis of liver presented to the department of medicine. Around 100 age and sex-matched individuals were recruited as controls. The Child-Pugh score was used to determine the disease severity in cirrhosis patients. Standard 12-lead ECG was recorded in all cases and controls. **Results:** Prolongation of QTc interval on ECG was observed in the majority (80%) of cirrhosis patients and it was significantly higher as compared to the healthy controls (P <0.01). The prolongation of QTc was significantly associated with the duration of disease (P <0.05) and disease severity as measured by the Child-Pugh score (P <0.01). **Conclusion:** QTc prolongation on ECG may be an early marker of cardiac involvement in patients of cirrhosis and is significantly associated with disease severity.

Keywords: Cardiomyopathy, Child-Pugh score, cirrhosis, QTc interval

Introduction

Cirrhosis represents a late stage of progressive hepatic fibrosis characterised by distortion of the hepatic architecture and the formation of regenerative nodules and occurs as a result of chronic injury to the liver parenchyma by aetiological factors such as alcohol and chronic viral hepatitis B/C.[1] In addition to its manifestations of portal hypertension and hepatocyte dysfunction, cirrhosis may have multisystem manifestations including involvement of major organs such as kidneys, central nervous system and cardiovascular system. Cardiovascular and circulatory alterations are frequently observed in the late stages of cirrhosis.[2]

Pathophysiologically, patients of cirrhosis exhibit a circulatory and cardiac dysfunction which is characterised by the presence of a hyperdynamic circulation and peripheral vasodilatation.[3] These circulatory and cardiac changes result in the development of cirrhotic cardiomyopathy which is defined as a group of phenomena including increased baseline cardiac output, decrease in systolic and diastolic function, blunted ventricular response to

Address for correspondence: Dr. Ruby Sharma, 78, Ekta Vihar, Ambala Cantt., Haryana - 133 001, India.
E-mail: drruby05@yahoo.co.in

Received: 04-03-2020 **Revised:** 27-03-2020
Accepted: 09-04-2020 **Published:** 30-06-2020

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_341_20

How to cite this article: Bhardwaj A, Joshi S, Sharma R, Bhardwaj S, Agrawal R, Gupta N. QTc prolongation in patients of cirrhosis and its relation with disease severity: An observational study from a rural teaching hospital. J Family Med Prim Care 2020;9:3020-4.

stimuli and electrophysiological abnormalities in patients of liver cirrhosis in the absence of any underlying cardiac disease.[4,5] The pathogenesis of cirrhotic cardiomyopathy may include multiple factors including impaired function of beta-receptors and excess release of factors having a cardio-depressant effect like nitric oxide, tumour necrosis factor α and endogenous cannabinoids.[6]

The QTc interval on electrocardiography signifies the length of ventricular systole. Prolongation of QTc (corrected for heart rate) is established as an important risk factor for the development of serious cardiac arrhythmias and sudden cardiac death.[7,8] Recent data suggest that QTc prolongation is one of the important electrophysiological abnormalities in patients of cirrhosis.[9] Early detection and management of cardiac involvement are important for reducing the overall morbidity and mortality, especially in rural and resource-limited settings. This study was conducted to evaluate the prevalence of QTc changes in patients of cirrhosis coming to a rural teaching hospital of north India and to analyse its correlation with disease severity as measured by the Child-Pugh scale.

Materials and Methods

The present study was a prospective observational study conducted at a rural tertiary care centre in north India. The study population included 100 patients of cirrhosis of liver presenting to the department of medicine at our hospital. Around 100 age and sex-matched individuals were recruited as controls. The study was done from November 2017 to May 2019 over a total duration of 1.5 years. Approval of the ethics committee of the institute was taken before commencing the study. All consecutive patients of liver cirrhosis presenting to a single unit of medicine department were considered for inclusion in the study. Subjects less than 18 years of age and those having known chronic illness including diabetes, hypertension, CKD or CAD were excluded from the study. Patients taking any drug known to have an effect on the QTc interval such as macrolides, chloroquine, antipsychotics, antidepressants, anti-arrhythmic, etc. were also excluded. Subjects who refused to give informed consent were also excluded from the study.

After fulfilling the inclusion and exclusion criteria, each participant in the study was explained about the aims and objectives of the study. Demographic details including age and gender were noted. Detailed clinical history (including present and past medical illness) and treatment history were noted, followed by a thorough physical examination. All patients underwent routine laboratory investigations including hemoglobin, RBS, liver function tests, renal function tests and ECG. The Child-Pugh score was used to determine disease severity.

Standard 12-lead ECG was recorded on the ECG machine of BPL company, model number Cardioline ECG200+. The same apparatus was used for all cases and controls. QTc interval was calculated using Bazett's formula i.e. QTc interval/sq. the root of the RR interval.[10] Any QTc interval of more than 430 ms in males and more than 450 ms in females were considered as abnormal. Any other ECG abnormalities were also noted.

Statistical analysis

The data collected were compiled on an excel sheet and was analysed statistically by using SPSS version 21.0 software. A Chi-square test was used for qualitative variables. Mean and the standard deviation was calculated for quantitative variables. Independent *t*-test and one-way ANOVA test was used to compare the means of quantitative variables. *P* value <0.05 was taken as significant.

Results and Observations

Table 1 shows a comparison between demographic and clinical parameters between the two groups. No statistically significant difference was observed between the two groups concerning age and gender (*P* >0.05). Liver function tests including S. bilirubin, serum transaminases and S. albumin were significantly deranged in cirrhotic patients as compared to the controls (*P* <0.01).

The clinical characteristics of the cirrhotic patients are tabulated in Table 2. The duration of illness in the majority of patients in our study was 2–5 years (53%) while 39% of patients had a duration of more than 5 years. The underlying aetiological factors included alcohol use, chronic hepatitis B/C and Non Alcoholic Fatty Liver Disease (NAFLD). The majority of our patients were in Child-Pugh Class C (61%), followed by Class B (35%) and Class A (4%). QTc prolongation was found in 80% of our study group. Other ECG abnormalities included an increased PR interval (11%) and a wide QRS segment (6%).

Table 3 compares the QTc interval between cases and controls. The statistical analysis shows that the QTc interval was significantly prolonged in cirrhotic patients as compared to

Table 1: Showing comparison of demographic and clinical parameters between cases and control groups

Parameter	Cases (100)	Controls (100)	*P*
Age (in years) (Mean±S.D.)	49.78±13.6	49.69±13.59	1.00
Gender			
Male	85%	82%	0.568
Female	15%	18%	
Systolic BP (mmHg) (Mean±S.D.)	113.3±9.69	117.22±8.37	0.009*
Diastolic BP (mmHg) (Mean±S.D.)	76.5±8.64	78.16±7	0.093
Hb (g/dL) (Mean±S.D.)	9.74±2.6	12.96±1.28	<0.001*
Total Bilirubin (mg/dL) (Mean±S.D.)	5.4±6.91	0.75±0.27	<0.001*
Direct Bilirubin (mg/dL) (Mean±S.D.)	3.12±4.74	0.22±0.22	<0.001*
SGOT (IU/mL) (Mean±S.D.)	116.87±160.11	17.41±8.76	<0.001*
SGPT (IU/mL) (Mean±S.D.)	79.01±99.81	16.84±9.71	<0.001*
Serum Albumin (Mean±S.D.)	2.59±0.91	3.85±0.68	0.018*
PT (s) (Mean±S.D.)	17.18±4.98	14.28±1.81	<0.001*
INR (Mean±S.D.)	1.77±1.06	1.46±0.3	0.005*

Table 2: Distribution of clinical characteristics of patients of liver cirrhosis

Parameter	*n* (%)
Duration of illness	
<2 years	8 (8%)
2-5 years	53 (53%)
>5 years	39 (39%)
Aetiological factor	
Alcohol	53 (53%)
Chronic Hepatitis B	8 (8%)
Chronic Hepatitis C	9 (9%)
Alcohol + Hepatitis B/C	8 (8%)
Others	12 (12%)
Use of beta-blocker therapy	36 (36%)
Child-Pugh Class	
A (CP Score 5-6)	4 (4%)
B (CP Score 7-9)	35 (35%)
C (CP Score 10-15)	61 (61%)
Clinical Features of Decompensation	
Ascitis	76 (76%)
Hepatic Encephalopathy	38 (38%)
Jaundice	16 (16%)
Coagulopathy	18 (18%)
ECG Abnormalities	
Increased QTc interval	80 (80%)
Wide QRS segment	6 (6%)
Low voltage QRS segment	9 (9%)
Increased PR	11 (11%)

Table 3: Comparison of QTc interval on ECG between cases and controls

QTc interval (in ms)	Cases	Controls	*P*
Total number of cases	100	100	
Mean±SD	458.5±26.95	424.35±27.73	<0.001**
Range	402-549	398-516	

controls (P <0.01).

A comparison of QTc interval in patients of cirrhosis subgrouped based on different clinical and demographic parameters as shown in Table 4. A significant difference in QTc interval was seen in association with the duration of disease ($P < 0.05$). Moreover, the prolongation of QTc interval was significantly affected as the disease progressed in severity from Child Pugh class A to C (P<0.01). No significant difference in QTc interval was seen with age, gender, ongoing beta-blocker therapy or aetiological factors ($P > 0.05$).

Discussion

Cirrhotic cardiomyopathy is a condition that is difficult to diagnose and its exact prevalence is still unknown. This is because it may remain asymptomatic for many years because of the near-normal cardiac function in the resting state. Clinical signs and symptoms appear under conditions of physical or pharmacological stress.[11] Electrocardiographic abnormalities like QTc prolongation may be the only initial findings of cardiac involvement in cirrhotic patients because the full spectrum of cirrhotic cardiomyopathy becomes manifested. This is also more relevant in the setting of liver transplantation.[12] This study was conducted to determine the frequency and factors associated with QTc abnormality in patients of cirrhosis presenting at a rural tertiary hospital.

In the present study, prolongation of QTc interval on ECG was observed in the majority (80%) of cirrhosis patients and it was significantly higher as compared to the healthy controls ($P < 0.01$). Similar studies done to evaluate QTc prolongation in cirrhosis patients have described a variable prevalence of abnormal QTc ranging from 30–84%.[13-16] This high variability is likely due to the differences in the clinical and demographic profile of patients in different populations studied. Puthumana *et al.* studied the relationship between prolonged QTc interval and autonomic cardiovascular reflexes in patients with cirrhosis. In their study, QTc prolongation was seen in 58 out of 130 patients (44.6%). They also observed that the QTc of 34 patients who died during follow-up was higher than the survivors.[14] In another study done by Bernardi *et al.*, the QTc prolongation was observed in 46.8% of patients.[15] In a retrospective analysis of ECG changes in pretransplant and transplant cohorts of cirrhosis patients, Bal *et al.* observed prolongation of QTc interval in 40% and 56% patients of the two groups, respectively.[16]

On subgroup analysis of data of cirrhosis patients based on disease severity, our findings showed that the mean QTc interval was highest in Child-Pugh Class C. There was a definite association between QTc prolongation and disease severity ($P < 0.01$). It was also significantly affected by the duration of the disease. Our results matched with other previous studies. In the study done by Bernardi *et al.*, QTc interval was found to be independently associated with the Child-Pugh score and plasma norepinephrine level.[15] In a Romanian study to look for factors associated with a prolonged QT interval in liver cirrhosis patients, Mozos *et al.* showed that liver disease severity measured by Child-Pugh score, alcoholic aetiology and serum uric acid level were significant factors associated with QTc prolongation.[17] Josefsson *et al.* conducted a retrospective analysis to study the prevalence and predictors of ECG changes in patients with cirrhosis undergoing liver transplantation and to define the risk of post-transplant cardiac events. The severity of cirrhosis, aetiology, older age and presence of systemic hypertension were associated with the presence of ECG abnormalities. They also suggested a significant relationship between prolonged QTc interval and post-transplant cardiac events ($P < 0.05$).[18]

Beta-blocker therapy is commonly used as a treatment of portal hypertension in patients of cirrhosis. In the present study, cirrhotic patients who were taking beta-blocker therapy had lower mean QTc interval as compared to those who were not taking beta-blockers, but the difference was not found to be statistically significant ($P > 0.05$). Previous research has suggested that the use of nonselective beta-blockers results in a reduction in QTc interval in cirrhosis patients.[19] The extent and clinical significance of this correction of QTc with beta-blocker use are uncertain. In

Table 4: Comparison of QTc interval in cirrhosis patients group for different clinical and demographic parameters

Parameter		No of patients '*n*'	QTc interval (in ms) Mean±S.D.	*P*
Age	≤40 years	28	463.61±34.02	0.482
	>40 years	72	458.58±25.09	
Gender	Males	85	459.34±26.41	0.511
	Females	15	453.73±30.40	
Duration of Disease	<2 years	8	451.44±22.34	0.031*
	2-5 years	53	460.98±28.07	
	>5 years	39	476.5±31.83	
Child-Pugh Class	A	4	413.25±11.41	0.001**
	B	35	439.17±16.68	
	C	61	472.56±21.88	
Beta-Blocker Therapy	Yes	36	456.13±20.83	0.659
	No	64	463.42±24.87	
Aetiological Factor	Alcohol	53	464.28±23.99	0.218
	Hepatitis B	8	469±42.76	
	Hepatitis C	9	454.75±19.22	
	Alcohol + Hepatitis B/C	8	457.83±21.22	
	Others	12	451.03±21.08	

a longitudinal study to evaluate the effect of chronic beta-blocker therapy on QT interval in 30 patients with cirrhosis, Zambruni *et al.* observed that shortening of QTc was seen only in patients who had prolonged value at baseline. They suggested that it is likely due to a direct effect on the heart.[20]

QTc prolongation is associated with ventricular arrhythmias as well as sudden cardiac death. Recent evidence also suggests that prolongation of QTc in cirrhotic patients may be associated with increased mortality.[21] Therefore, regular monitoring of these patients for any electrophysiological abnormalities is recommended for early detection of cardiac dysfunction.

Conclusion

QTc prolongation is a common electrophysiological abnormality found in patients of liver cirrhosis and may be used as an early indicator of potential cardiac involvement in these patients. Our findings showed that QTc prolongation correlates with the disease severity and duration of disease although no relation with aetiology.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383:1749-61.
2. Gatta A, Merkel C, Sacerdoti D, Angeli P. Cardiac involvement in liver cirrhosis. Ann Ital Med Int 1993;8:244-7.
3. Moller S, Henriksen JH. Cardiovascular complications of cirrhosis. Gut 2008;57:268-78.
4. Ruiz-del-Árbol L, Serradilla R. Cirrhotic cardiomyopathy. World J Gastroenterol 2015;21:11502-21.
5. Sezgin B, Cindoglu C, Uyanikoglu A, Yenice N. Association of Cirrhosis and Cardiomyopathy. Euroasian J Hepatogastroenterol 2019;9:23-6.
6. Karagiannakis DS, Papatheodoridis G, Vlachogiannakos J. Recent advances in cirrhotic cardiomyopathy. Dig Dis Sci 2015;60:1141-51.
7. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. Circulation 1991;84:1516-23.
8. Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The association between the length of the QT interval and mortality in the Cardiovascular Health Study. Am J Med 2003;115:689-94.
9. Karki N, KC S, Sharma D, Jaisi B, Khadka S. Cardiac dysfunction in patients with liver cirrhosis. J Nepal Health Res Counc 2019;17:357-61.
10. Bazett H. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353-67.
11. Carvalho MVH, Kroll PC, Kroll RTM, Carvalho VN. Cirrhotic cardiomyopathy: The liver affects the heart. Braz J Med Biol Res 2019;52:e7809.
12. Zardi EM, Zardi DM, Chin D, Sonnino C, Dobrina A, Abbate A. Cirrhotic cardiomyopathy in the pre- and post-liver transplantation phase. J Cardiol 2016;67:125-30.
13. Tsiompanidis E, Siakavellas SI, Tentolouris A, Eleftheriadou I, Chorepsima S, Manolakis A, *et al.* Liver cirrhosis-effect on QT interval and cardiac autonomic nervous system activity. World J Gastrointest Pathophysiol 2018;9:28-36.
14. Puthumana L, Chaudhry V, Thuluvath PJ. Prolonged QTc

interval and its relationship to autonomic cardiovascular reflexes in patients with cirrhosis. J Hepatol 2001;35:733-8.

15. 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;27:28-34.
16. Bal JS, Thuluvath PJ. Prolongation of QTc interval: Relationship with etiology and severity of liver disease, mortality and liver transplantation. Liver Int 2003;23:243-8.
17. Mozos I, Costea C, Serban C, Susan L. Factors associated with a prolonged QT interval in liver cirrhosis patients. J Electrocardiol 2011;44:105-8.
18. Josefsson A, Fu M, Björnsson E, Kalaitzakis E. Prevalence of pre-transplant electrocardiographic abnormalities and post-transplant cardiac events in patients with liver cirrhosis. BMC Gastroenterol 2014;14:65.
19. Henriksen JH, Bendtsen F, Hansen EF, Møller S. Acute non-selective beta-adrenergic blockade reduces prolonged frequency-adjusted Q-T interval (QTc) in patients with cirrhosis. J Hepatol 2004;40:239-46.
20. Zambruni A, Trevisani F, Di Micoli A, Savelli F, Berzigotti A, Bracci E, *et al.* Effect of chronic beta-blockade on QT interval in patients with liver cirrhosis. J Hepatol 2008;48:415-21.
21. Kim SM, George B, Alcivar-Franco D, Campbell CL, Charnigo R, Delisle B, *et al.* QT prolongation is associated with increased mortality in end stage liver disease. World J Cardiol 2017;9:347-54.