INTRODUCTION

Cirrhosis is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules. The progression of liver injury to cirrhosis may occur over weeks to years. According to the World Health Organization, deaths from cirrhosis have been estimated to increase, making it the 11th leading cause of death in 2020. Fibrosis describes the encapsulation or replacement of injured tissue by a collagenous scar. Liver fibrosis is a pathological condition that results from an ongoing wound-healing response and abnormal production and deposition of connective tissue, also known as fibrogenesis. Variables such as the fundamental cause of liver disease, environmental factors, and host variables can influence the course of fibrosis. As liver fibrosis advances, its tissue becomes progressively scarred, resulting in a decline in its efficiency and, eventually, the development of cirrhosis. The severity and progression rate of fibrosis can differ significantly between individuals and be affected by various causes.

QTc prolongation and diastolic dysfunction in cirrhosis patients with higher Child-Pugh score

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ABSTRACT

Background: Cirrhosis is associated with numerous cardiac abnormalities, which include increased cardiac output, left ventricular diastolic dysfunction, increased wall thickness of cardiac chambers, and pulmonary arterial hypertension. Without further identified cardiac disorders, cirrhotic cardiomyopathy (CCM) is a chronic cardiac dysfunction with an impaired contractile reaction to stress stimuli, impeded diastolic relaxation, and electrophysiological anomalies with a prolonged QT interval. In chronic hepatic disease, echocardiography is a non-invasive method for detecting CCM.

Aims and Objectives: The focus was to examine the link between cardiac dysfunction and conduction disturbances in cirrhosis individuals and the extent of the disorder.

Materials and Methods: A case–control investigation was conducted at a Medical College. The research involved a cohort of 50 patients and an equal number of 50 healthy controls. The Child-Pugh (CP) Score was utilized to evaluate the degree of liver cirrhosis severity. Bazett’s formula was utilized to compute the QTc interval. The 2D echocardiography revealed the presence of diastolic dysfunction, as evidenced by the E/A ratio.

Results: Of 50 patients, 37 (74%) were male, 13 (26%) were female, and the mean age of the patients was 51.76±9.89 years. The E/A ratio in the control group had a mean value of 1.10±0.19, whereas in the cases, it had a mean value of 0.94±0.20. A statistically significant relationship was observed between the control and cases, with a P-value of less than 0.0001. The QTc interval between control with a mean value of 382.9±47.34 ms and cases with a mean value of 431.6±62.84 ms was found statistically significant with P<0.0001.

Conclusion: QTc prolongation and transmitral flow abnormality are markers of severe cardiac abnormality in patients with higher CP score in cirrhosis. Hence, recognition of such abnormalities in cirrhotic patients may prevent arrhythmogenic cardiovascular deaths in such patients.

Key words: Child–Pugh score; Cirrhosis; Cirrhotic cardiomyopathy; Diastolic dysfunction; QTc interval
Cirrhosis represents an advanced phase of liver fibrosis accompanied by vasculature distortion. It causes the portal and arterial blood supply to be diverted directly into the hepatic outflow (central veins), compromising the circulation across hepatic sinusoids, and surrounding liver parenchyma, that is, hepatocytes. Impaired hepatocyte (liver) function, and greater intrahepatic resistance (portal hypertension), alongside the occurrence of hepatocellular carcinoma (HCC), are the main medical implications of cirrhosis (HCC).5

Portal hypertension is a significant complicating feature of decompensated cirrhosis. It is responsible for developing ascites and bleeding from esophageal and gastric varices, two complications that signify decompensated cirrhosis. Loss of hepatocellular function results in jaundice, coagulation disorders, and hypoalbuminemia and contributes to the causes of portosystemic encephalopathy.4,5

Patients with cirrhosis develop a progressive impairment in their circulatory and cardiac function during their illness. A systemic circulatory disorder in liver cirrhosis was described more than 60 years ago.

In cirrhosis, cardiac function anomalies are not clinically evident, most likely due to the reduced SVR exhibited by the individuals, thereby decreasing the cardiac afterload. Initially, the diminished functioning of the left ventricle (LV) in patients with cirrhotic conditions was attributed to the direct deleterious effect of alcohol.6

The findings support the notion of a distinct cardiac ailment known as “cirrhotic cardiomyopathy” (CCM).5 Thus, it can be inferred that CCM exhibits distinct clinical and pathophysiological characteristics compared to alcoholic cardiomyopathy.

As per the proceedings of the 2005 World Congress of Gastroenterology, CCM denotes a persistent cardiac malfunction that is typified by compromised contractile reactivity toward stress-inducing stimuli,7,8 and/or hindered diastolic relaxation,9,10 and anomalous electrophysiology that manifests as prolonged QT interval,11 in the nonexistence of any other discernible cardiac ailment. In contrast, individuals afflicted with cirrhosis exhibit predominantly left ventricular diastolic dysfunction (LVDD) while maintaining normal systolic function during rest periods.

Diastolic dysfunction is present in most patients with CCM, and that simple echocardiographic indices such as the E/A ratio may detect diastolic dysfunction even at rest. This represents the best available screening test to diagnose cardiac dysfunction.12 The grading of left ventricular diastolic dysfunction was performed using the 2009 American Society of Echocardiography guidelines Grade 0 or normal is defined as “E/A >1”, left ventricular ejection fraction >50% without LVDD. Grade I or mild diastolic dysfunction is characterized by E/A ratio <0.8, DT >200 ms, and E/Ea<8.” Grade II or moderate diastolic dysfunction is defined as “E/A ratio 0.8–1.5, DT 160–200 ms, and E<7 cm/s. Finally, Grade III or severe diastolic dysfunction is characterized by E/A ratio >2, DT <160 ms, E/Ea>15, and E<7 cm/s.”13

LVDD was defined as E/A; “the velocity of the diastolic early filling wave (E) divided by the velocity of the late or atrial filling wave (A). DT: Deceleration time; Ea: Early filling wave.”

Aims and objectives
To determine the prevalence of diastolic transmitral flow abnormalities (E/A ratio) on echocardiography and assess the prevalence of QTc interval prolongation on electrocardiogram (ECG) in patients diagnosed with liver cirrhosis.

Objectives
To examine the correlation between the severity of liver cirrhosis, as determined by the Child score, and the severity of diastolic transmitral flow abnormalities on echocardiography.

To investigate the correlation between the severity of liver cirrhosis, as determined by the Child score, and the prevalence of QTc interval prolongation on electrocardiogram (ECG).

To explore the combined effect of QTc prolongation and diastolic transmitral flow abnormalities and their correlation with the severity of liver cirrhosis.

MATERIALS AND METHODS
This study was conducted at a Medical College, with 50 patients and 50 healthy controls in this cross-sectional case–control study after ethical approval. The study was conducted from August 01, 2019, to July 31, 2020, for a period of 1 year. All admitted patients diagnosed during this period with liver cirrhosis were included in the study. Patients are subjected to a detailed history, general and systemic examination, relevant investigation, ultrasonography (USG), electrocardiography, and echocardiography. The Child-Pugh (CP) score was utilized to assess the severity of cirrhosis.

Inclusion criteria
Fifty patients with liver cirrhosis with or without ascites were diagnosed based on ultrasonographic features.
consistent with cirrhosis and 50 healthy controls were included in the study.

Exclusion criteria
Patients with a history or clinical evidence of cardiovascular disease, major lung disease, diabetes mellitus, severe anemia, renal failure, or major arrhythmias were excluded from the study.

Procedure
Using a machine, a 12-lead surface EGG was obtained from all subjects in the supine position immediately before echocardiography. The ECG was recorded at a paper speed of 25 mm/s and studied for prolonged QT intervals (rate corrected). The present investigation employed a 3.5 MW Mechanical Probe USG apparatus to evaluate the presence of cirrhosis of the liver and ascites, with particular emphasis on the caudate lobe, portal vein, and spleen. The 2D Echocardiography machine employed an Adult Cardiac Probe Electronics Phased Array probe featuring 512 independent electronic channels and 2D and M mode capabilities. To evaluate the cardiac structure with particular emphasis on the left ventricular end-diastolic diameter, interventricular septal thickness, left ventricular posterior wall thickness, and M mode to assess E/A ratio, which is E velocity, is early maximal ventricular filling velocity, and A velocity is late diastolic or atrial velocity. The severity of the cirrhosis was evaluated by CP criteria and divided into three groups: A (mild), B (moderate), and C (severe).

Statistical methods
All data were entered on MS Excel sheet and statistical analysis was done using statistical software primer and graphed. Results on continuous measurements are presented on mMean and SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Analysis of variance has been used to find the significance of study parameters between three or more groups of patients. Student t-test (two-tailed, independent) has been used to find the significance of study parameters on continuous scale between two or more groups.

RESULTS
Fifty cases with liver cirrhosis and 50 healthy controls were studied. Patients were included, irrespective of age and sex, who were admitted to the Department of Medicine of a Medical College.
In our study, out of 50 patients, 37 (74%) were male, 13 (26%) were female, and the mean age of the patient was 51.76±9.89 years. Based on the etiology of cirrhosis, 17 (34%) patients were hepatitis B positive, where seven were males, and ten females and 3 (6%) patients were hepatitis C positive, of which one was male and two females. The remaining 30 (60%) patients were negative for both hepatitis B and C.

Distribution of study variables based on CP score and age group

All liver cirrhosis patients were classified based on the CP score. Six patients belong to Class A, eight to Class B, and 36 to Class C. The gender-wise distribution of different CP Class was done where, Six patients belong to Class A, 8 to Class B, and 36 to Class C. After applying the Fisher exact test, P=0.6791, which concluded that there was a statistically insignificant association between gender and CP classification.

In Table 1, we showed different laboratory parameters of the case and control study subjects. There was a statistically significant association concerning total S. bilirubin, S. albumin, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), HB, white blood cell, platelet, creatinine, NA+ level, CL- level, prothrombin time (PT), and international normalized ratio (INR) between the case and control.

In 50 patients, LVDD was present in 36, and the remaining did not have LVDD. LVDD was measured in terms of the E/A ratio. The occurrence of diastolic transmitral flow abnormality, as indicated by the E/A ratio, was 72% among individuals diagnosed with liver cirrhosis. An aggregate of 50 patients was observed, out of which 19 patients with LVDD and six patients without LVDD exhibited ECG QTc prolongation. Therefore, 25 patients demonstrated QTc prolongation. In individuals who developed liver cirrhosis, the incidence of prolongation of QTc interval in ECG was 50%. We found that ECG QTc interval distribution among study subjects based on gender, 25 patients had QTc prolongation (>440), out of which 18 (72%) were male, and 7 (28%) were female.

In Table 2, we found that the QTc interval between control with a mean value of 382.9±47.34 ms and cases with a mean value of 431.6±62.84 ms was found statistically significant with P<0.0001. The E/A ratio in the control group showed a mean value of 1.10±0.19, while in the cases group, it had a mean value of 0.94±0.20. The study also found a statistically significant relationship between the control and cases groups, with a p-value of <0.0001.

In Table 3, we found the distribution of LVDD based on the E/A ratio, 12 patients had grade I diastolic dysfunction, and 24 patients had grade II diastolic dysfunction out of 50 patients. A statistically significant association existed between the E/A ratio and diastolic dysfunction with P=0.0118 by the Fisher exact test.

In Graph 2, out of 50 patients, 36 patients had diastolic dysfunction. According to CP classification of LVDD, 2 (5.6%) patients belong to Class A, 8 (22.2%) patients belong to Class B, and 26 (72.2%) patients belong to Class C. The result shows P<0.05.

In Table 4, the distribution of QTc prolongation among different CP classes was analyzed. After applying the Fisher exact test, a statistically significant correlation with
increasing severity of liver disease (by CP scoring system) was observed, with a p-value of 0.0339 (P<0.05).

Our study found a correlation between combined diastolic dysfunction and QTc prolongation with increased severity of liver cirrhosis based on the CP score. Class A had no patients; Class B had seven, and Class C had 14 patients, which showed QTc+LVDD. After applying Fisher exact test, P=0.0424 showed a statistically significant correlation.

**DISCUSSION**

CCM is a condition that is difficult to diagnose, and its exact prevalence is still unknown. It may remain asymptomatic for many years due to the near-normal cardiac function in the resting state. Clinical signs and symptoms appear under conditions of physical or pharmacological stress. The manifestation of CCM may be limited to electrocardiographic abnormalities such as QTc prolongation in the initial stages of cardiac involvement among individuals with cirrhosis. This is due to the complete range of CCM symptoms not being apparent at this stage.

The present investigation was undertaken to ascertain the incidence and variables linked to QTc anomaly in individuals diagnosed with cirrhosis. The present study comprised patients with liver cirrhosis of diverse etiologies, including alcohol, hepatitis B, and hepatitis C. The study participants underwent standard laboratory assessments, including a complete blood count, renal function test, liver function test, PT/INR, USG abdomen, color Doppler, endoscopy, electrocardiography, and 2D echocardiography. Laboratory investigations revealed significant differences between cases and controls in various parameters. Diastolic dysfunction (LVDD) and QTc prolongation were prevalent among liver cirrhosis patients, with 72% exhibiting LVDD and 50% showing QTc prolongation. Correlations were found between the severity of liver cirrhosis and both the E/A ratio (diastolic dysfunction) and QTc prolongation. These findings contribute to our understanding of liver cirrhosis and its associated cardiovascular abnormalities, suggesting the importance of laboratory markers and highlighting the need for further research.

According to Table 1 and Figure 1, the present investigation enrolled a cohort of 50 patients with a mean age of 51.76±9.89 years. Among them, 37 (74%) were male, and 13 (26%) were female. Most patients resided within the age range of 40–49 years, while the lowest number of patients was 20–29.

In the Study by Sidmal et al., the mean age of patients was 53±12 years, including 42 male and 18 female patients. In another study by Patil et al., among 60 patients, the mean age of patients was 55.82±7.44 years, which included 41 males and 19 females.

The etiology of cirrhosis was assessed, and it was found that hepatitis B was the leading cause (34%), followed by hepatitis C (6%) and others (60%) (Table 2).

Further analysis was conducted based on the CP scoring system, which categorizes patients into three classes (A, B, and C) based on the severity of liver disease. It was observed that a higher proportion of patients belonged to Class C (72%) compared to Class B (16%) and Class A (12%), as shown in Table 3.

Table 4 shows the distribution of study variables based on gender and age group. Among the age groups, the proportions of male and female patients varied: 20–29 years
(one male, 0 female), 30–39 years (one male, one female), 40–49 years (14 males, five females), 50–59 years (12 males, three females), and above 60 years (nine males, four females). However, the (P=0.8361) indicated a non-significant relationship.

According to results shown in Table 5 among 50 cases and 50 controls, it was found that serum bilirubin, serum albumin, SGOT, SGPT, ALP, Hemoglobin, total leukocyte count, platelet, S. creatinine, serum sodium level, and serum chloride level, PT/INR had a statistically significant correlation between cases and controls.

In Table 6, we found that the QTc interval between control with a mean value of 382.9±47.34 ms and cases with a mean value of 431.6±62.84 ms was found statistically significant with P<0.0001. The E/A ratio in the control group showed a mean value of 1.10±0.19, while in the cases group, it had a mean value of 0.94±0.20(Figure 2). A statistically significant relationship was found between the control and cases groups, with a p-value of less than 0.0001 (P<0.0001). The study revealed that 50% of patients who developed liver cirrhosis exhibited QTc prolongation. Compared to Patil et al.,16 our study revealed that 38.32% of individuals with liver cirrhosis exhibited a prolonged QTc interval and found that the QTc interval was significantly higher in cirrhotic patients than in non-cirrhotic controls.17

In Table 7, we found the distribution of LVDD based on the E/A ratio, 12 patients had grade I diastolic dysfunction, and 24 patients had grade II diastolic dysfunction out of 50 patients (Figure 3). A statistically significant association existed between the E/A ratio and diastolic dysfunction with P=0.0118 by the Fisher exact test similar to Dadhicha et al.,18 study, 28 patients had LVDD out of 40 cases of cirrhotic patients studied, another study by Sidmal,15 showed that LVDD was diagnosed in 91.6% of cirrhotic patients,19 patients had mild LVDD. In contrast, 36 patients had moderate to severe LVDD.

In Table 8, the distribution of QTc prolongation among different C.P classes was analyzed. The Fisher exact test was applied, revealing a statistically significant correlation with the increasing severity of liver disease (as determined by the CP scoring system) with a p-value of 0.0339 (P<0.05).

Our study found a correlation between combined diastolic dysfunction and QTc prolongation with increased severity of liver cirrhosis based on the C.P Score (Table 9). Class A had no patients; Class B had seven, and Class C
had 14 patients, which showed QTC+LVDD. After applying Fisher exact test, P=0.0424 showed a statistically significant correlation similar to Chandey et al., study. In an independent study conducted by Pourafkari et al., it was observed that there existed a significant correlation (P=0.048) between the extent of cirrhosis and diastolic dysfunction. The progression of cirrhosis from Child A to Child C was correlated with a decline in typical diastolic function and a rise in diastolic dysfunction.20

Our findings are similar to Pourafkari et al.,20 which showed more QTC prolongation with a higher child score. QTC interval increased linearly with the severity of liver cirrhosis. The mean values of QTC in CP Class A, CP Class B, and CP Class C were 425.00 (±20.97), 437.35 (±42.60), and 479.71 (±29.48) respectively. The statistical analysis revealed a p-value of 0.04, indicating a significant difference among the CP classes.

Limitations of the study

Sample size

The study involved a relatively small sample size of 50 patients and 50 healthy controls. A larger sample size would provide more statistical power and enhance the generalizability of the findings.

Selection bias

The participants in the study were recruited from a single medical college, which may not represent the overall population of cirrhosis patients. This could introduce selection bias and limit the generalizability of the results to other settings or populations.

CONCLUSION

Prolongation of QTC and abnormality in transmural flow indicate significant cardiac dysfunction among individuals with elevated CP score in cirrhosis. Therefore, identifying such anomalies in individuals with cirrhosis could be a preventive measure against arrhythmogenic cardiovascular fatalities in such a group. Furthermore, the aforementioned cardiac anomalies indicate notable advancement in cirrhosis, necessitating prompt and suitable medical interventions to impede the expeditious progression of cirrhosis.

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REFERENCES


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CS- Conceptualization and design of the study, execution of the study protocol, data collection and analysis, and initial manuscript drafting; JK- Definition of intellectual content, literature review, manuscript preparation, and revision; DSM- Oversight of the entire study, responsible for the statistical analysis and interpretation of data, manuscript review, and final editing.

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