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Original research article

Evaluating diastolic dysfunction as an indicator of cirrhotic cardiomyopathy in decompensated chronic liver disease

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Abstract

Background and objective: Cirrhotic cardiomyopathy (CCM) is a common occurrence in people with decompensated chronic liver disease (DCLD), even in the absence of any previous episodes. The diminished life expectancy in such circumstances was the primary factor that motivated us to undertake this investigation. The objective of this study was to examine the frequency of diastolic dysfunction in people with chronic liver disease, to comprehend the diagnostic criteria for left ventricular diastolic dysfunction (LVDD) in individuals with cirrhosis, and to assess its incidence as an early predictor of cardiac cirrhotic cardiomyopathy (CCM).

Method: A cross-sectional study was conducted on 135 patients admitted to the Department of General Medicine, Raja Rajeshwari Medical College, Kambipura, Karnataka, India from February 2011 to January 2012. These patients were selected based on our criteria for inclusion and exclusion. The individuals were diagnosed with chronic liver disease based on clinical and radiological assessments. Regression analysis was conducted to assess the impact of various variables on the prediction of diastolic dysfunction (DD) outcomes.

Result: Among the 135 patients, 115 fell into the age range of 31-60 years, indicating that age is a key determinant in the development of LVDD. Out of the total number of participants, 55 had blood bilirubin levels higher than 2mg/dL. We observed a significant link between serum bilirubin levels and LVDD, as indicated by a p-value of less than 0.0001. The Child-Turcotte-Pugh score class (p-value=0.0196) and QTc (p-value <0.0001) both show a strong link with the development of LVDD. This correlation is further supported by their area under the curve (AUC) values of 0.64 in the receiver operating characteristic (ROC) curve.

Conclusion: Our study determines that LVDD serves as an initial marker for evaluating the extent of liver cirrhosis in DCLD. The association between DCLD and extended QTc may make patients with DCLD more susceptible to ventricular arrhythmias. Therefore, it is advisable for these patients to regularly undertake serum bilirubin testing and electrocardiographic monitoring in order to detect any potential issues early on and improve their chances of survival.

Keywords: Child turcottepugh score, diastolic dysfunction (DD), left ventricular diastolic dysfunction (LVDD), decompensated chronic liver disease (DCLD), cirrhotic cardiomyopathy (CCM), cirrhosis

Introduction

Cirrhosis, a term coined by French physician René Laënnec in 1819, is characterized by histological alterations in the regenerating clusters of liver cells, which exhibit nodules and extensive fibrous septae. It is a significant contributor to global health burdens that can be prevented but is not fully recognized. According to estimates from the World Health Organization (WHO), cirrhosis is responsible for 2.4% of global deaths, and this percentage may increase in the future. Cirrhotic cardiomyopathy (CCM) is one of the potential outcomes of cirrhosis or decompensated liver disease. It is a myocardial condition characterized by impaired cardiac pumping function and often accompanied by arrhythmia. Cardiomyopathy, as defined by the American Heart Association, refers to a wide range of abnormalities in the heart muscle. These abnormalities typically involve mechanical or electrical issues, resulting in either excessive enlargement or thickening of the ventricles. The causes of cardiomyopathy are varied and can be attributed to multiple factors. The primary pathophysiological abnormalities detected include

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cardiac electrical anomalies, structural and functional ventricular anomalies, and reactions associated with pharmacological, physiological, or surgical stress. Cardiomyopathies often lead to the development of heart failure-related impairments and cardiovascular mortality [1-3].

Cryptogenic cirrhotic nodules (CCM) occur spontaneously in individuals with cirrhosis, without any identifiable cause. Research suggests that CCM is present in nearly 50% of patients with cirrhosis. CCM greatly diminishes life expectancy [4]. In 2019, the Cirrhotic Cardiomyopathy Consortium and the World Congress of Gastroenterology included echocardiographic examination, specifically focusing on diastolic function, as a criterion for Cirrhotic Cardiomyopathy (CCM). Cardiac contractility is impaired as a result of systolic and diastolic dysfunction (DD) caused by electrophysiological abnormalities. Left ventricular diastolic dysfunction (LVDD) is defined by the American Society of Echocardiography as the presence of specific indicators, including mitral inflow patterns, left atrial (LA) volume index ≥34 mL/m2, septal e' velocity of 8cm/sec, and lateral e' velocity of less than 10cm/sec. Therefore, tissue Doppler imaging studies are better suited to detect left ventricular diastolic dysfunction (LVDD). Hemodynamic stress-inducing factors such as exercise, some drugs, liver transplantation (LTx), and transjugular intrahepatic portosystemic shunt (TIPS) implantation might adversely affect heart function [5].

Portal hypertension, a consequence of cirrhosis, leads to an increase in the overall amount of blood and blood flow in the abdominal organs, while simultaneously decreasing the amount of blood circulating throughout the body. As a result, there is an increase in total peripheral resistance, an elevation in cardiac output, and a reduction in arterial pressure. Although the baseline cardiac output is higher, these individuals show reduced systolic and diastolic function as a result of physiological, pharmacological, and surgical stressors, as well as cardiac electrical abnormalities such as QTc prolongation. The imminent chaos is worsened by the assault of pro-inflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumor necrosis factor-α (TNFα), as well as vasoactive peptides that harm the cardiac myocytes. The molecular routes of left ventricular diastolic dysfunction (LVDD) include aberrations in collagen composition, titin phosphorylation, and cardiomyocyte sarcolemma membrane fluidity. These pathways have also been observed in rat cirrhotic models.

The cardiac processes, both in terms of structure and function, undergo alterations as cirrhosis progresses and its consequence unfolds. Therefore, our objective was to investigate the frequency of DD in individuals with cirrhosis by analyzing demographic, etiological, clinical, and biochemical factors, and to determine if it can serve as an early marker for CCM [6].

Material and Method

This cross-sectional investigation was conducted in a hospital setting. A cohort of 135 liver cirrhosis patients, who voluntarily participated in the study, were included in the sample size. Patients were identified with liver cirrhosis based on clinical and radiological assessments and were then admitted to the Department of General Medicine, Raja Rajeshwari Medical College, Kambipura, Karnataka, India from February 2011 to January 2012.

The study was conducted on patients with liver cirrhosis who met all the specified criteria for inclusion and exclusion. The aim was to examine the frequency of cerebral cavernous malformations (CCM) in individuals with decompensated chronic liver disease (DCLD) and to identify any connections or patterns between demographic, etiological, clinical, and biochemical factors, as well as left ventricular diastolic dysfunction (LVDD). In addition, our goal was to determine a relationship between the severity of liver illness using the Child-Turcotte-Pugh (CTP) scoring system and left ventricular diastolic dysfunction (LVDD), in order to establish LVDD as an early predictor of chronic cholestatic liver disease (CCM). ECG and conventional echocardiography were used to examine QTc prolongation and LVDD in all 135 individuals as part of the CCM screening.

Result

Table 1: LVDD distribution categorized by serum bilirubin levels

Echocardiography	Bilirubin(mg/dL)				Total
	<2	2.1-4	4.1-10	>10	
No.	8	17	9	4	38
Grade1LVDD					
%	21.05	44.7	23.68	10.52	100
No.	0	3	6	9	18
Grade2LVDD					
%	0	16.66	33.33	50	100
No.	9	18	17	15	59
Total					
%	15.25	30.50	28.81	25.42	115

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Table 2: Left ventricular diastolic dysfunction (LVDD) distribution based on the Child-Turcotte-Pugh grade

Echocardiography		Child-Pugh Scoring System		Total
		B	C	
Grade 1 LVDD	No.	18	20	38
	%	47.36	52.63	100
Grade 2 LVDD	No.	2	16	18
	%	11.11	88.88	100
Total	No.	22	37	59
	%	37.28	62.71	115

Table 3: Data showing the presence of QTc interval in left ventricular diastolic dysfunction (LVDD) patients for Grade 1 and Grade 2 conditions

QTcinterval	Grade 1 LVDD	Grade 2 LVDD	Total
<400msec	85	15	100
>400msec	20	15	35
Total	105	30	135

Discussion

Cirrhosis is characterized by many cardiovascular problems. This study was conducted in patients with decompensated chronic liver disease (DCLD) to determine the frequency of cerebral cavernous malformations (CCM) in this population and to establish left ventricular diastolic dysfunction (LVDD) as a reliable biomarker of CCM. The study also sought to establish a correlation between demographic, etiological, biochemical, and clinical factors with DD in patients with DCLD and comprehend their distribution pattern in CCM.

Out of the 63 patients with CCM, 30 patients (47.61%) were between the ages of 46 and 60. This indicates that CCM is most frequently observed in the adult population within this age range. Our analysis revealed a significant correlation between age and a higher occurrence of CCM, with a p-value of 0.0439. Multiple studies have confirmed that age is a risk factor in these patients. However, a research conducted by Uyanikoglu *et al*. found no significant link between age and CCM [7].

Out of the 63 individuals diagnosed with CCM, 60 instances (37.97%) were found in male patients, while the remaining three cases were found in female patients. Given that the majority of the participants in our study were male, it follows that most of the individuals with cirrhosis and cardiomyopathy were adult males. The majority of conducted research do not demonstrate a noteworthy association between sex and LVDD, while Belay *et al*. identified female gender as one of the factors contributing to a higher prevalence.

The significance of circulatory alterations in liver cirrhosis became apparent in the early 1990s with the identification of systemic hemodynamic changes in patients with cirrhosis. During the 1950s, researchers found that individuals with alcohol-dependent liver illness exhibited hyperdynamic circulation, characterized by low arterial blood pressure, low peripheral resistance, and increased cardiac output. This phenomenon was attributed to the influence of alcohol. Chronic alcohol consumption is a primary cause of chronic liver disorders, with viruses and a smaller portion of cases being attributed to autoimmune and cryptogenic causes. The findings of our investigation indicate that there is no statistically significant relationship between alcohol use and cardiomyopathy (p-value=0.34) among the patients included in our study. Therefore, alcohol usage is unlikely to have a significant influence on LVDD in our population. Four patients with HBV infection and one patient with HCV infection, all of whom had cirrhosis, developed CCM in this study. HCV infection is the primary cause of cirrhosis-related deaths worldwide, with alcohol-related causes being the second most common. However, the burden from alcohol-related causes is increasing steadily, perhaps due to changes in lifestyle [8].

The increasing coverage of HBV vaccination and the greater availability of effective anti-HBV antiviral medications have had a key role in decreasing global mortality rates. The majority of individuals with HCV infection experience persistent inflammation of the heart muscle, leading to the development of dilated cardiomyopathy, necrosis, and ultimately, the death of heart muscle cells. The velocity of the local pulse wave increases in individuals with HCV-related liver cirrhosis and is associated with a lower survival rate in patients with decompensated liver function. The study found that the rates of alcohol intake, association with HBV and relationship with HCV were 3.16%, 2.5%, and 0.63% correspondingly. Our study does not relate the development of LVDD to either alcohol use or viral connection. Neither alcohol use nor hepatic encephalopathy could be determined as causative factors for left ventricular diastolic dysfunction (LVDD) in this case [8].

Due to the disproportionate representation of males compared to females in the study population, we were unable to determine the impact of sex on the evaluation. Several studies have shown that CCM is more prevalent in adult males who are over 50 years old and have cirrhosis as a result of alcohol misuse. Nazar *et al*. ascribed the genesis of cirrhosis to alcohol in 45% of the patients and to HCV in 40%. In our investigation, there was no significant correlation (p-value=0.35) found between CCM and other

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potential causes such as autoimmune, cryptogenic, and metabolic illnesses.

Serum albumin alleviates hepatic encephalopathy. The levels of serum albumin decline significantly as liver disease progresses. However, in our study of 158 patients, we did not detect any statistical significance between the serum albumin level and LVDD (p-value=0.7719), showing that there is no association between serum albumin level and the advancement of liver disease [9].

Grade I LVDD refers to an anomaly in the early relaxation of the left ventricle, whereas Grade II implies an increase in the pressure of filling in the atrium. A strong association was seen between serum bilirubin levels and LVDD, with a p-value of 0.0001. Approximately 39.8% of the patients exhibited elevated blood bilirubin levels ranging from over 2.1 to over 10 mg/dL. Approximately, 49.2% and 34.9% of patients with serum bilirubin levels greater than 2.1 mg/dL exhibited Grade I and Grade II LVDD correspondingly, resulting in a combined total of 84.1%. Therefore, the level of bilirubin serves as a biomarker of left ventricular diastolic dysfunction (LVDD).

The impact of hepatic illness on the outcome is more significant than that of cardiac dysfunction. The correlation between cardiac dysfunction and the severity of hepatic disease can be demonstrated biochemically by elevated levels of bilirubin in the blood serum. The advancement of liver disease is accompanied by a rise in serum bilirubin and creatinine levels from Child A to Child C grades. The study conducted by Khurana *et al*. found that among the 41 patients with high bilirubin levels, 13 had Grade I LVDD (left ventricular diastolic dysfunction), while among the 22 patients with elevated bilirubin levels, 21 had Grade II DD (diastolic dysfunction). Additionally, there was a strong association between the severity of cardiomyopathy and the presence of higher bilirubin levels. The results of our experiment indicate a strong association between elevated levels of bilirubin in the blood and left ventricular diastolic dysfunction (LVDD) [10].

In this investigation, we observed a statistically significant association between the echocardiographic pattern and serum bilirubin levels in the detection of CCM. The results of our study indicate that 146 patients had portal hypertension and 23 patients had hepatic encephalopathy with chronic decompensated liver disease. This suggests a potential association between the severity of liver disease and the occurrence of hepatic encephalopathy. However, it is important to note that Scarpati *et al*. did not find a direct link between hepatic encephalopathy and chronic decompensated liver disease. Kapoor *et al*. reported that the incidence of complications associated with cirrhosis, such as hepatic encephalopathy, is higher in the CCM group.

The grading system developed by CTP is a valuable indicator of the extent of liver damage. The scores of Class A, Class B, and Class C: 5-6, 7-9, and 10-15 accordingly represent liver disease severity levels ranging from least severe to moderately severe and most severe. The study findings indicated that out of the 158 patients, 63 (39.8%) were diagnosed with CCM. Among these patients, 24 (38%) were classified as CTP Class B, while 39 (62%) were classified as CTP Class C. The prevalence of LVDD, as categorized by CTP grade, revealed that 41 patients (25.9%) had Grade I LVDD, while 22 patients (13.9%) experienced Grade II LVDD. Out of the twenty patients with Child-Pugh B, twenty had Grade I left ventricular diastolic dysfunction (LVDD) and four had Grade II diastolic dysfunction (DD) [22, 23]. Out of the total of 21 patients with Child-Pugh C, 18 of them experienced Grade II DD, while the remaining 3 had Grade I LVDD. The strong connection between LVDD and CTP grades (p-value = 0.0180) and an AUC value of 0.646 in the multiple regression ROC curve from our study indicates the severity of LVDD in line with liver cirrhosis. ROC analysis is a methodical methodology used to measure the effect of variability in decision thresholds among individuals. Research conducted by Sankar *et al*. has shown that a majority of patients with CCM exhibit diastolic dysfunction (DD), either on its own or in conjunction with other characteristics such as systolic dysfunction and QTc prolongation. These findings are statistically significant. Higher Child-Pugh scores in Class B and C indicate significant cardiovascular abnormalities in cirrhosis [10].

Typically, the ECG detects QTc prolongation as the primary indicator of CCM. Compensated cirrhotic individuals have exhibited a noteworthy elevation of QTc, which remains within the range of normal limits, as compared to the control group. A robust link exists between QTc and elevated serum bilirubin levels, leading to cardiac arrhythmia. Individuals exhibiting elevated levels of bilirubin in their bloodstream experience a notable lengthening of the QTc interval, necessitating hospitalization in specialized care facilities. Echocardiographic parameters, namely QTc intervals, show similarity only in patients with CTP B and CTP C grades. However, no significant link was established between echocardiographic parameters, QTc interval, and hepatic disease. Out of the 158 individuals being investigated, 130 of them have a QTc interval that is less than 400 milliseconds, whereas 28 patients have a QTc interval that is greater than 400 milliseconds. There are 136 patients with Grade I LVDD and 22 patients with Grade II LVDD. Our research revealed a strong link between the QTc interval and the development of LVDD. This correlation was statistically significant, with a p-value of less than 0.0001. Additionally, when using multiple linear regression to analyze the ROC curve, the area under the curve (AUC) was determined to be 0.648. The computed average QTc interval was 0.63 msec. Class B Child-Pugh had an average QT of 0.57 msec, whereas Class C Child-Pugh had 0.66 msec. Both left ventricular diastolic dysfunction (LVDD) and lengthening of the QTc interval are associated with severe liver

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cirrhosis and are also considered important criteria for the diagnosis of cardiac cirrhosis (CCM). Patients diagnosed with Child-Pugh C exhibit an extended QTc interval, with the majority of them displaying Grade II DD. LVDD is a condition that occurs when there is a delay in the filling of the left ventricle of the heart [11].

This delay can be caused by ventricular hypertrophy (enlargement of the heart muscle), disturbance of collagen structure (the protein that provides support to the heart), or subendocardial oedema (swelling in the inner lining of the heart). Individuals with an extended QTc interval typically experience reduced survival rates compared to those with a normal QTc interval. Prolongation of the Corrected QTc interval is associated with both severe cirrhosis and problems of the liver, such as hepatic encephalopathy and hepatorenal syndrome. There is a statistical correlation between the Child-Pugh score and the duration of QTc. We assert that CCM is a serious consequence of cirrhosis, and its severity is directly related to the stages of liver fibrosis as determined by the Child-Pugh criteria.

The scope of our study is constrained by the prevalence of males compared to females in the study population, which hinders our ability to determine the impact of gender on the evaluation. Assessing left ventricular diastolic dysfunction (LVDD) using the E/A ratio by traditional echocardiography has limitations due to its reliance on preload and the need for age adjustment. Therefore, pulsed tissue Doppler imaging is the most suitable method for evaluating left ventricular diastolic dysfunction (LVDD). It is not influenced by the volume status or left atrial pressure. Our study strategy was unable to expose the patients to further physiological, pharmacological, surgical, or stress-related challenges. As a result of insufficient clinical follow-up, it was not possible to evaluate the impact of CCM on mortality in the individuals.

This study suggests that the severity of liver disease can be determined using the CTP scoring system. Our study indicates that the following factors can be used as supportive markers for early diagnosis of CCM: patient age over 46 years, serum bilirubin levels greater than 2.1 mg/dL, CTP grades B and C, and irregular QTc intervals [11-13].

Conclusion

Cerebral cavernous malformation (CCM) is a disorder that is clearly different in terms of clinical presentation and underlying physiological mechanisms. It is found in 40% of individuals with cirrhosis who have a normal resting systolic function. There is a strong association between the severity of LVDD and higher levels of bilirubin in the blood. There is a clear correlation between the rising severity of liver cirrhosis, specifically from Child-Pugh Classes A to C, and the increasing degree of left ventricular diastolic dysfunction (LVDD). QTc prolongation and LVDD characteristics can be helpful in diagnosing CCM in patients with liver cirrhosis. The LVDD may be implicated in the initiation and advancement of liver disease in DCLD. Therefore, it is recommended that individuals with liver cirrhosis undergo regular electrocardiographic and echocardiographic evaluations to promptly identify any signs of left ventricular diastolic dysfunction (LVDD). This intervention has the potential to be advantageous in patients who are at risk, as it may enhance overall rates of survival.

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Conflict of Interest: Nil.

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