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ORIGINAL RESEARCH

Correlation Of QTC Interval With Direct, Indirect And Total Bilirubin

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Abstract

Background: Liver cirrhosis is associated with cardiac abnormalities, including QTc interval prolongation, which may predict cardiac involvement and poor outcomes.**Objective:** To analyze the correlation between QTc interval and liver function parameters (direct, indirect, and total bilirubin) in liver cirrhosis patients.**Methods:** This observational, cross-sectional study included 92 liver cirrhosis patients admitted to L.N. Medical College and Research Centre & J.K. Hospital, Bhopal. Patients with previous heart disease and those under 18 years old were excluded. Clinical, biochemical, and radiological evaluations were performed.**Results:** Significant increases in total bilirubin, direct bilirubin, and indirect bilirubin levels were observed with progressing disease severity (Child-Pugh scores A to C). Mean QTc interval values differed significantly among Child-Pugh score grades ($p < 0.01$). Higher bilirubin levels (total, direct, and indirect) were associated with QTc interval prolongation (>460 ms) ($p < 0.01$).**Conclusion:** This study demonstrates a significant correlation between QTc interval prolongation and liver dysfunction (reflected by elevated bilirubin levels) in liver cirrhosis patients. These findings support the utility of QTc interval as a potential marker for cardiac involvement in liver cirrhosis.

Keywords: Liver Cirrhosis; QTc Interval; Bilirubin; Child-Pugh Score; Cirrhotic Cardiomyopathy.

Introduction

QTc prolongation is an electrophysiological abnormality found in patients of liver cirrhosis and may be used as an early indicator of potential cardiac involvement in these patients. QTc prolongation correlates with the disease severity and duration of disease although no relation with aetiology and is associated with ventricular arrhythmias as well as sudden cardiac death.[1]Thus, it is important for both hepatologists and cardiologists to understand the relationship between the liver and the heart. Indeed, involvement of the cardiovascular system in end-stage liver disease is well recognized, and there are reports of cardiovascular symptoms in patients with liver cirrhosis, including chronotropic incompetence, cardiomyopathy, prolonged QT intervals, hyperdynamic circulation with an increased cardiac output and decreased peripheral vascular resistance, and impaired ventricular contractility in response to physiologic and pharmacologic stimuli.[2] Chronotropic incompetence (CI), broadly defined as the inability of the heart to increase its rate commensurate with increased activity or demand, is common in patients with cardiovascular disease, produces exercise intolerance which impairs quality-of-life, and is an independent predictor of major adverse.[3]The constellation of cardiac abnormalities is termed cirrhotic cardiomyopathy.[4] The cirrhotic cardiomyopathy which is defined as "cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress, diastolic dysfunction and electrophysiological abnormalities in the absence of known cardiac disease".[5]

The pathogenic mechanisms of cirrhotic cardiomyopathy are multifactorial and include cardiomyocyte plasma membrane physico-chemical changes, attenuated stimulatory pathways, and enhanced activity of inhibitory systems.[4]Although the presence of cardiomyopathy in cirrhotic patients has been described since 1960s, it had been speciously attributed to alcoholic cardiotoxicity.[6-8]It is merely in the last two decades, it is observed that cardiac dysfunction is also present in non-alcoholic cirrhosis.

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The term "cirrhotic cardiomyopathy" was introduced to describe impaired contractile responsiveness to stress, diastolic dysfunction and electrophysiological abnormalities in the absence of known cardiac disease.[5]However, Kowalski HJ et al[6] reported a prolonged QT interval in eight of the 22 cirrhotic patients in 1953. Unfortunately, it was only an incidental finding that was not further taken into account because the paper aimed to demonstrate other findings in cirrhosis and this phenomenon remained ignored till 1998 when a study by Bernardi M et al[9] reported QT prolongation in cirrhosis and found a significant correlation between the rate-corrected QT (QTc) interval and the Child-Pugh score, and that QTc prolongation may be associated with poor outcomes including mortality. Since then several studies of repolarization in cirrhosis have appeared. Despite these efforts, the underlying pathophysiology of QT prolongation in cirrhosis is poorly understood. Proposed mechanisms such as bile salt accumulation, altered autonomic tone, shifts in gonadal hormone balance and cirrhotic cardiomyopathy have been suggested.[30] Therefore, present study was needed and planned to evaluate cardiac function in cirrhosis patients. Thus, current study aims to analyse Qtc interval with direct, indirect and total bilirubin among patients with cirrhosis of liver.

Material and Method

The present observational, cross-sectional study was conducted among 92patients of liver cirrhosis admitted to the Department of General Medicine at L.N. Medical College and Research Centre & J.K. Hospital, Bhopal. Inclusion criteria comprised of all patients with cirrhosis of liver of age >18 years of either sex. Exclusion criteria comprised of patients with previous history of heart diseases with age group < 18 years.

Patients fulfilling the inclusion criteria were selected for study. Relevant clinical data was recorded. Patients asked for questionnaire-based on history of their present condition after their informed consent. General examination of the patient was carried that comprised of appearance, sensorium, temperature, pulse, blood pressure, respiratory rate, pallor, clubbing, cyanosis, jaundice, oedema, neck veins and lymph nodes. Systemic Examination consisted of assessment of abdomen, cardiovascular system and respiratory system.

Laboratory investigation included CBC (hemoglobin, TLC, DLC, platelet), Liver function test (total bilirubin, direct bilirubin, indirect bilirubin, SGOT, SGPT, ALP, albumin), renal function test, serum electrolyte (Na+, K+), random blood sugar (RBS) prothrombin time (PT), activated partial thromboplastin clotting time (aPTT) and INR (international normalized ratio).

Radiological examination consisted of electrocardiogram (ECG) ultrasonography (USG) whole abdomen, upper gastrointestinal endoscopy was done in all the patients.

Cirrhosis was labeled on the basis of:

- **Clinical** (reduced liver span <8 cm on clinical exam with ascites/or splenomegaly).
- **Biochemical** (prolonged prothrombin time>12 seconds and reduced level of serum albumin <3.5g/dl).
- **Radiological** (increased liver echo pattern, shrunken liver <8cm in mid-clavicle line, portal vein diameter >1.3 cm and spleen size >13 cm longitudinally).

The severity of liver cirrhosis was assessed and according to the child Pugh score, patients were grouped into group 1 that comprised patients of Liver cirrhosis withchild Pugh class-A (Score 5-6), group 2 that comprised patients of Liver cirrhosis withchild Pugh class-B (Score 7-9) and group 3 that comprised patients of Liver cirrhosis withchild- Pugh class-C (Score 10-15). Datawasanalysed statistically. Analysis was done in the form of percentages, proportions and represented as tables, charts, graphs wherever necessary.

Results

Table 1: Comparison of mean liver related parameters of study subjects classified according to Child Pugh score grades

Bilirubin	Child Pugh score grades	Mean	Std. Deviation	F value	p value
Total bilirubin	A	0.68	0.43	18.326	<0.01*
	B	1.84	2.79		
	C	10.51	10.29		
Direct bilirubin	A	0.33	0.14	20.688	<0.01*
	B	0.80	0.87		
	C	5.67	5.52		
Indirect bilirubin	A	0.35	0.33	8.865	<0.01*
	B	1.03	2.11		
	C	4.86	6.50		

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Table 1 shows a significant increase in total bilirubin, direct bilirubin, and indirect bilirubin levels as the disease severity progresses from grade A (mild) to grade C (severe). Specifically, the mean values for total bilirubin rise from 0.68 in grade A to 1.84 in grade B and 10.51 in grade C, while direct bilirubin increases from 0.33 to 0.80 and 5.67, and indirect bilirubin from 0.35 to 1.03 and 4.86, respectively.

These differences are statistically significant ($p < 0.01$), indicating a strong correlation between Child-Pugh scores and liver function. Additionally, the standard deviation increases with disease severity, suggesting greater variability in liver function parameters among patients with more severe disease. Overall, this data validates the Child-Pugh scoring system's effectiveness in assessing liver dysfunction and highlights its importance in clinical practice for stratifying patients by disease severity and guiding management decisions.

Table 2: Comparison of mean QTC of study subjects classified according to Child Pugh score grades

	Child Pugh score grades	Mean	Std. Deviation	F value	p value
QTC	A	446.44	67.12	10.409	<0.01*
	B	426.75	18.26		
	C	464.70	47.12		

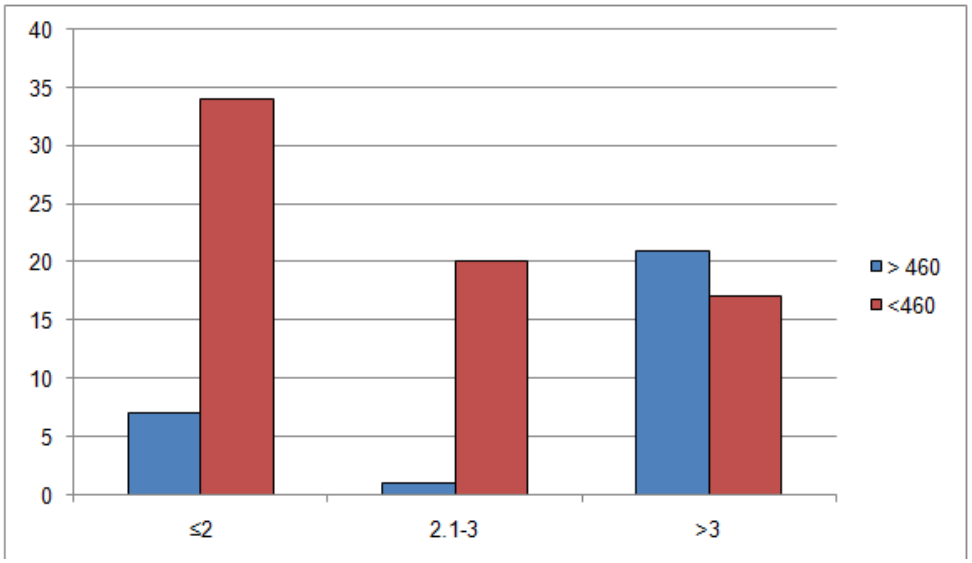
Table 2 shows comparison of mean QTC of study subjects classified according to Child Pugh score grades results revealed significant differences ($p < .01$).

Table 3: Bilirubin and QTC

	QTC			
	> 460		<460	
S.Billirubin	Frequency	Percent	Frequency	Percent
≤2	7	24.1	34	47.9
2.1-3	1	3.4	20	28.2
>3	21	72.4	17	23.9

P value- <0.01*

Table 3 shows bilirubin and QTC results revealed significant differences with higher bilirubin levels associated with QTC >460 ($p < .01$).



Graph1: Bilirubin and QTC

Table 4: Direct Bilirubin and QTC

Direct.Billirubin	QTC			
	> 460		<460	
	Frequency	Percent	Frequency	Percent
≤2	8	27.58	60	84.50

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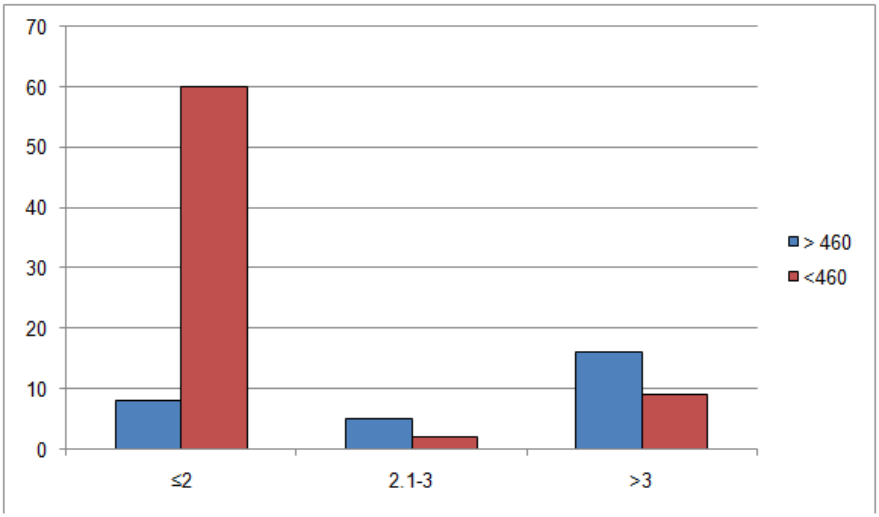
2.1-3	5	17.24	2	2.881
>3	16	55.17	9	12.67

P value- 2.046

Table 4 shows direct bilirubin and QTC results revealed significant differences with higher direct bilirubin levels associated with QTC >460



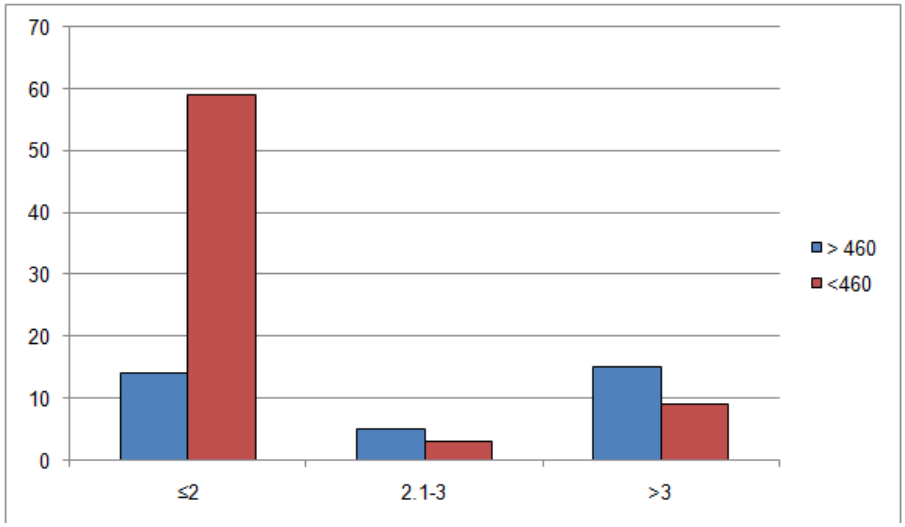
Graph 2: Direct Bilirubin and QTC

Table 5: Indirect Bilirubin and QTC

Indirect.Billirubin	QTC			
	> 460		<460	
	Frequency	Percent	Frequency	Percent
≤2	14	41.17	59	83.09
2.1-3	5	14.70	3	4.22
>3	15	44.11	9	12.67

P value- <0.01*

Table 5 shows indirect bilirubin and QTC results revealed significant differences with higher indirect bilirubin levels associated with QTC >460 ($p < .01$).



Graph 3: Indirect Bilirubin and QTC

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Discussion

Liver cirrhosis is characterized by a hyperkinetic circulatory state, marked by increased circulating blood volume and cardiac output, and decreased systemic vascular resistance.[10] The Child-Pugh score is a widely used clinical tool that assesses the severity of liver cirrhosis and aids in predicting patient prognosis. However, despite its established value in assessing hepatic function, the impact of liver cirrhosis on the cardiovascular system remains an area of ongoing investigation.[11]Hence, the present study was undertaken to find out correlation between cardiac function and hepatic dysfunction in liver cirrhosis patients as well as its correlation with Child Pugh score.

The present study was carried among 92 patients with liver cirrhosis. Patients underwent clinical evaluation, laboratory tests, and radiological examinations including ECG. The severity of liver cirrhosis was assessed using the Child Pugh score, and patients were grouped into three categories (A, B, and C) and echocardiographic findings revealed more cardiac abnormalities in subjects with higher Child-Pugh scores.

The Child-Pugh score comprises five key variables: bilirubin, albumin, prothrombin time, ascites, and hepatic encephalopathy. These factors were initially identified by experienced clinicians and later validated through numerous clinical studies. Each variable represents a distinct aspect of liver function: bilirubin levels indicate excretory function, albumin and prothrombin time reflect synthetic function, hepatic encephalopathy signals detoxification failure, and ascites development is a consequence of poor synthetic function and portal hypertension.[12]In the present study,the comparison of mean liver-related parameters of study subjects classified according to Child-Pugh score grades showed significant differences across the grades, particularly in bilirubin levels indicating worsening liver function with increasing Child-Pugh scores. The level of albumin and bilirubin can reflect liver function, and the change of albumin and bilirubin levels often means liver dysfunction and poor prognosis in patients with cirrhosis. The Child-Pugh score is widely used in the clinic since it was proposed 50 years ago, and it is determined by calculating serum bilirubin and albumin, prothrombin time, hepatic encephalopathy, and ascites.[13]

In the present study, the assessment of the relationship between different forms of bilirubin (total, direct, indirect) and the QTc interval revealed that higher bilirubin levels (especially above 2) are associated with a prolonged QTc interval, which could suggest an association between liver dysfunction and cardiac abnormalities. In a comparable study by **Bernardi M et al[1],** patients with cirrhosis exhibited significantly longer Q-Tc intervals compared to controls, the Q-Tc length was unaffected by the underlying cause of cirrhosis but correlated strongly with the Child-Pugh score ($P < 0.001$), as well as with liver function tests, including prothrombin activity, albumin, bilirubin and plasma bile salts.

In the present study, the comparison of mean QTc of study subjects classified according to Child-Pugh Score Grades reported a significant difference suggesting cardiac function, as reflected by the QTc interval, is affected by the severity of liver disease. A comparative study by **Baik SK et al[14]** reported that 30-60% of cirrhotic patients exhibited a prolonged QT interval. Similarly, **Abd-El-Aziz TA**et al[15] reported the QT interval was prolonged among 40% cirrhotic patients. In another alike study by **Al Atroush HH et al[16]**, QTc interval was significantly prolonged in patients compared to controls and Child-Pugh classification was the only predictor of mortality, with Child C patients having worse survival. **Salve C et al[17]** found QTc interval was prolonged in cirrhotic patients (431.6±62.84 ms) as compared to controls (382.9±47.34 ms). Another alike study by **Chandey M etal[18]**foundQTc interval and diastolic dysfunction were found to increase linearly with the severity of liver cirrhosis, as per Child-Pugh score. Systolic function was normal in all patients and study concluded that diastolic dysfunction and QTc interval prolongation are related to the severity of liver cirrhosis and are major criteria of cirrhotic cardiomyopathy. Correspondingly, **Karki N et al[19]** found that cirrhotic cardiomyopathy was present in 51.4% of patients, with QTc prolongation (>0.44 seconds) noted in 79%, mainly in Child-Pugh C patients and reported QTc prolongation may be an early indicator of cardiac dysfunction. The observed prolongation of the QT interval may be attributed to changes in ion channel activity within the plasma membranes of cardiomyocytes.[20]

This study has several limitations. Firstly, study is limited by cross-sectional assessment in a single tertiary care hospital which may not provide the exact representation of patients who are seen in community settings.

It is highly recommended to conduct further research and gather data using a substantial sample size.

Conclusion

In conclusion, this study demonstrates associations between lower albumin levels and higher Child-Pugh scores, as well as between higher bilirubin levels and a prolonged QTc interval, suggesting a link between liver dysfunction and cardiac abnormalities. ECG findings also revealed more cardiac abnormalities in subjects with higher Child-Pugh scores.

Overall, this study highlights the significant correlation between cardiac function and hepatic dysfunction in liver cirrhosis patients, emphasizing the need for

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comprehensive management of both liver and cardiac diseases in this population.

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