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Cardiac Dysfunction and Its Relation to Degree of Esophageal Varices in Cirrhotic Patients

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Running head: Cardiac dysfunction and esophageal varices

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Abstract

Background and study aim.

Esophageal varices can cause upper gastrointestinal bleeding. Due to vascular alterations and other factors, cardiac dysfunction can develop in cirrhotic individuals. It is strongly correlated with the

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severity of liver disorders. Therefore, this study examined the relationship between the degree of esophageal varices and cardiac dysfunction in cirrhotic patients.

Patients and methods

This cross-sectional study was carried out on 60 cirrhotic patients. They were divided into three groups: group I included 20 cirrhotic patients with no esophageal varices; Group II included 20 cirrhotic patients with small varices; and Group III included 20 cirrhotic patients with large varices. Laboratory investigations, ultrasonography, echocardiography, and electrocardiography were done for all patients.

Results

A highly statistically significant difference was found between group III and the other two groups regarding having a history of upper GIT bleeding (p-value <0.001) and the corrected QT interval (QTc) (p-value <0.001). A statistically significant difference was found regarding the relation between the Child score of the patients and cardiomyopathy (p = 0.001). A strong positive correlation was found between the Child score and QTc (p<0.001). Also, a strong positive correlation was found between the degree of varices and QTc (p = 0.001). Other parameters evaluated by echocardiography showed no statistically significant difference between the studied groups (p> 0.5).

Conclusion.

Only a prolonged QT interval strongly relates to large varices regarding cardiac alterations and their linkage with the degree of esophageal varices. In our study, echocardiographic parameters had no relation to esophageal varices.

Keywords: Cirrhotic cardiomyopathy, corrected QT interval, esophageal varices.

Introduction

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Worldwide, cirrhosis is a significant factor in the morbidity and death of patients with chronic liver disease. Cirrhosis was associated with 2.4% of fatalities worldwide in 2019 [1].

Cirrhotic cardiomyopathy (CCM) was initially suggested by specialists at the 2005 Global Congress of Gastroenterological Surgery and is defined as persistent heart insufficiency, systolic and diastolic dysfunction, and electrical abnormalities, such as prolongation of the QT interval [2].

The Cirrhotic Cardiomyopathy Group was established in 2019 by a multidisciplinary team of cardiologists, hepatologists, and anesthesiologists. The organization has proposed new criteria for CCM [3].

A comparison of the criteria for the diagnosis of CCM is shown in Table (1). [4]

Regarding the pathophysiology of CCM, it has been suggested that a hyperdynamic circulation initially compensates for the significant splanchnic arterial vasodilatation seen in liver cirrhosis; subsequently, liver disease progression and portal hypertension leads to additional splanchnic vasodilatation and a reduced effective arterial blood volume, which triggers the sympathetic nervous system and the renin-angiotensin-aldosterone system. Overexposure to sympathetic effector molecules results in downregulation, internalization, and cardiac damage, which impairs the function of β -adrenergic receptors [5]. Another theory for the increased synthesis of endogenous cardio-depressant mediators includes nitric oxide, carbon monoxide, endogenous cannabinoids, and inflammatory cytokines [6].

QT interval prolongation occurs in 30–70% of patients with liver cirrhosis [7]. Previous research has demonstrated that the length of the QT interval caused by cirrhosis strongly correlates with the severity of the condition, indicating the severity of the disease [8].

Although the pathophysiological process of QT interval prolongation in cirrhosis is still not fully known, it may involve genetic susceptibility, cirrhotic heart failure, metabolic, autonomic, or hormonal abnormalities. Other exogenous risk factors for QTc prolonging include bradycardia, electrolyte imbalances, underlying cardiomyopathy, acute sickness, and drugs [8]. The QT interval's extension increases cardiac output and reduces myocardial contraction. The decline in

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the ventricle's transmission raises the possibility of arrhythmia of the ventricles, exceptionally polymorphic ventricular fibrillation, and tachycardia, which can cause unexpected death [9, 10].

Unfortunately, these abnormalities are rarely identified because of their subclinical course. Until patients are exposed to stress, the condition remains typically asymptomatic with nearly normal cardiac function. Liver transplantation may result in circulatory system decompensation, which raises perioperative mortality from cardiovascular causes [11].

One of the symptoms of decompensated cirrhosis is portal hypertension, which frequently causes upper gastrointestinal bleeding (UGIB). Patients with liver cirrhosis often experience UGIB, a potentially fatal consequence [12].

In addition to causing myocardial ischemia, the bleeding also results in anemia, hypotension, and tachycardia. For this reason, individuals with CCM and extended QT have an even worse clinical state [13]. So, this study aimed to study cardiac changes in cirrhotic patients about the degree of esophageal varices.

Patients and methods

Study design: This is a cross-sectional study.

Study setting: This study was conducted on 60 patients presenting to the Department of Tropical Medicine and Infectious Diseases at Tanta University Hospital between February 2023 and August 2023.

Study patients and sample size:

Our studied sample (60 cirrhotic patients) was divided into three groups: Group I included 20 cirrhotic patients without esophageal varices, Group II included 20 cirrhotic patients with small esophageal varices (grade I – II), and Group III included 20 Cirrhotic patients, with large esophageal varices (grade III–IV). The varices grades were classified according to the Baveno IV classification [14].

Inclusion criteria:

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All adult patients (>18 years) were diagnosed with liver cirrhosis based on clinical, biochemical, and radiological features.

Exclusion criteria:

They included patients with alcoholic liver cirrhosis, thyroid disease, hypertension, dyslipidemia, and renal disease, as well as patients with congenital heart disease, rheumatic heart disease, dilated cardiomyopathy, and other coexisting cardiac diseases. Antiviral medications, such as beta blockers used for non-cardiac reasons, were also excluded, as individuals were on drugs that may impact the heart, and these were stopped at least seven days before evaluation.

Patients' assessment:

Sixty patients who met the inclusion criteria were enrolled in our study and were subjected to complete history, a full clinical examination, and routine laboratory investigation, including complete blood count (red blood cell count, hemoglobin percent, platelet count, white blood cell count and differentiation), liver function tests (albumin, bilirubin alanine aminotransferase, aspartate aminotransferase), international normalized ratio, and renal function tests (blood urea and serum creatinine).

All patients underwent abdominal ultrasonography, upper endoscopy, electrocardiography, and echocardiographic examination. Patients were defined according to the modified Child-Turcotte-Pugh classification [15].

1. Upper endoscopy

After overnight fasting, the entire esophagus, stomach, and proximal duodenum were examined wherever possible.

2. Abdominal Ultrasonography

It was performed in the Tropical Medicine Department, where an expert specialist assisted with the hepatic condition, portal vein diameter, and maximum spleen bipolar diameter.

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3. Transthoracic echocardiography TTE:

Conventional Doppler echocardiography, Tissue Doppler imaging (TDI) in the lateral decubitus position, and 2D, M-mode measurement were all performed on each patient during a standard transthoracic echocardiographic examination (TTE).

a. Two-dimensional guided M-mode echocardiographic tracings recorded at mid-chordal level in the parasternal long axis view were used to evaluate the left ventricle's internal dimensions and wall thickness. The Teichholz formula was used to determine the percentage of fractional shortening (FS) and the ejection fraction (EF) [16].

b. Pulse-wave Doppler obtained mitral inflow velocities in the apical 4-chamber view with the sample volume placed at the tips of the mitral valve leaflets. The peak early and late diastolic mitral inflow velocities were measured and averaged over five cardiac cycles during normal respiration. The early diastolic to late diastolic mitral inflow velocities (E/A) ratio was calculated. A ratio of 0.75-1.5 indicates normal diastolic function [17].

c. Tricuspid annular systolic plane excursion (TAPSE):

The longitudinal plane is where right-ventricular contraction mostly happens. TAPSE is one of the methods recommended by the American Society of Echocardiography for evaluating RV function. RV systolic function is diminished when the TAPSE value is less than 16 mm. To measure it, the RV apical four-chamber image aligned an M-mode cursor parallel to the RV free wall where it meets the tricuspid annulus [18].

d. Pulmonary artery systolic pressure (PASP): The right atrium and right ventricle pressure differences were measured using the tricuspid regurgitation (TR) trace's continuous wave (CW) Doppler. This pressure difference is found using peak TR velocity and the simplified Bernoulli equation ($P = 4 [TR \text{ max}]^2$). This is the RV systolic pressure, and by adding RA pressure. Usually, $PASP < 30$ mmHg is considered normal [19].

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Tissue Doppler imaging (TDI) uses Doppler principles to measure the velocity of myocardial motion. Color tissue Doppler imaging was performed from the apical 4-chamber view using a 2.5-MHz transducer and frame rates of $> 80/\text{second}$, and the images were digitized. Derivation and analysis of tissue Doppler velocity profiles were performed offline using commercially available computer software (Echopac, GE-Vingmed).

e. The heart's velocity was determined by positioning a 6-mm sample volume at the intersection of the mitral annulus and septal myocardial wall, and the septal mitral annulus profiles were acquired. The early diastolic (E'), late diastolic (A'), and peak mitral septal systolic (S') velocities were recorded from two consecutive cardiac cycles and averaged. Additionally, the ratio (E/E') of the peak early diastolic mitral annulus velocity by tissue Doppler imaging and the peak early diastolic mitral inflow velocity by pulse-wave Doppler was calculated. Longitudinal systolic function was measured by systolic myocardial velocity (S') at the septal mitral annulus; a measurement $>7.5 \text{ cm/s}$ is thought to be sensitive and specific in predicting normal global left ventricular systolic function [20].

The ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/E' ratio) is used to evaluate LV filling pressure, and it has been used as a marker to diagnose diastolic HF. An average $E/E' > 15$ was deemed specific for elevated LV filling pressure, and <8 indicated low/normal filling pressures [21].

f. Cirrhotic cardiomyopathy was diagnosed according to the revised CCM criteria [22].

4. Electrocardiography

For all patients, a baseline 12-lead standard electrocardiogram (ECG) was conducted in a supine posture at a rate of 25 mm/s with a calibration of $1 \text{ mV/cm} = 10 \text{ mm}$. Throughout the analysis, all the patients had sinus rhythms. At least ten leads could be analyzed in every ECG, and three consecutive beats were utilized for analysis.

Where necessary, the heart rate was measured and adjusted. The $QTC = QT/\sqrt{RR}$ formula was used to calculate the Qt interval, and a QT interval greater than 0.44 was considered prolonged [23].

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Statistical analyses of data

Data was uploaded onto the computer and analyzed using IBM SPSS software version 20.0. (New York, Armonk, IBM Corp.). For categorical data, percentage and numerical representations were utilized. Any correlations between the category variables were examined using a chi-square test. Suppose the expected count was less than five in more than 20% of the cells; an alternative test known as the Monte Carlo correlation test was employed. To verify that continuous data were average, the Shapiro-Wilk test was employed. Quantitative data were described using mean, standard deviation, median, and range (minimum and maximum). The student t-test was employed to compare two sets of quantitative data that were regularly distributed. For non-normally distributed quantitative variables, the Kruskal-Wallis test was used to compare groups, and for pairwise comparisons, Dunn's multiple comparisons test and the Post Hoc test were utilized. The results were deemed significant at the 5% level.

Results

The study population consisted of 60 cirrhotic patients. Twenty did not have EVs and served as the control group. The other 40 patients were diagnosed to have EVs, 20 of whom had small EVs (grades I and II), and the other 20 had large EVs (grades II and III). There were no significant differences in age between the three groups. The sex distribution was similar in the three groups, with no significant differences. Regarding the history of having previous episodes of upper GIT bleeding, there was a high statistically significant difference between the three groups (p-value <0.001).

Tab 1. Comparison of criteria of CCM in 2005 and 2019.

CCM Diagnostic Criteria	
I. Systolic Dysfunction	
2005 criteria:(any of the following)	2019 proposed criteria:(any of the following)
LV ejection fraction < 55%	LV ejection fraction ≤ 50%
Blunted contractile response on stress testing	Absolute 1 GLS < 18%

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AND/OR

II. Diastolic dysfunction

2005 criteria:

(any of the following)

Deceleration time > 200 ms

Isovolumetric relaxation time > 80 ms

E/A < 1

IIIa. Supportive criteria

(Not diagnostic!)

2005 criteria:

Electrophysiological abnormalities

Abnormal chronotropic response

Electromechanical uncoupling

Prolonged QTc interval

Enlarged left atrium.

Increased cardiac mass.

Elevated BNP

Elevated proBNP

Increased troponin I

2019 proposed criteria:

(≥3 of the following)

Septal e' velocity < 7 cm/s

E/e' ratio ≥ 15

LAVI > 34 mL/m²

TR velocity 2 > 2.8 m/second

IIIb. Areas for further research (Validation required)

2019 proposed criteria:

Abnormal chronotropic or inotropic response 3

Electrocardiographic changes

Electromechanical uncoupling

Myocardial mass change

Serum biomarkers

Chamber enlargement.

Cardiac MRI 4

GLS; global longitudinal strain; LV; left ventricle; E; early diastolic transmitral filling; A; late diastolic transmitral filling; e'; early diastolic mitral annular velocity; LAVI; left atrium volume index; TR; tricuspid regurgitation; QTc; corrected QT interval; BNP; brain natriuretic peptide; MRI; magnetic resonance imaging.

There was no significant difference between the studied groups regarding diabetes mellitus or their fasting blood glucose levels. According to the Child-Pugh classification, 5 (25%) of the patients in the control group were Child A, 12 (60%) patients were Child B, and 3 (15%) were Child C. Besides that, 5 (25%) of the patients in the group with a tiny EV were child A, 11 (55%) were child B, and 4 (20%) were child C. In the group of patients with large EVs, 1 (5%) patient was child A, 9 (45%) patients were child B, and 10 (50%) were child C. These details are shown in Table (2).

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Tab 2. Comparison between the studied groups according to different parameters.

	Control (n = 20)	Cases S (n = 20)	Cases I (n = 20)	p
Sex				
Male	15 (75%)	13 (65%)	12 (60%)	0.592
Female	5 (25%)	7 (35%)	8 (40%)	
Age (Mean ± SD)	58.3 ± 6.6	62.7 ± 6	60.6 ± 6.6	0.109
History of bleeding	0 (0%)	16 (80%)	20 (100%)	<0.001*
Diabetic				MC _p =1.000
Diabetic	3 (15%)	3 (15%)	3 (15%)	
Not diabetic	17 (85%)	17 (85%)	17 (85%)	
Fasting blood glucose				0.841
Mean ± SD.	98.5 ± 13.6	99.3 ± 15.9	101.8 ± 24.2	
Child-Pugh classification				0.088
A	5 (25%)	5 (25%)	1 (5%)	
B	12 (60%)	11 (55%)	9 (45%)	
C	3 (15%)	4 (20%)	10 (50%)	

SD: Standard deviation, p: p-value for comparing the three studied groups, *: Statistically significant at $p \leq 0.05$.

Both groups were compared for blood biochemical and radiological parameters, which show there were statistically significant differences for platelet count, albumin, bilirubin, portal vein diameter, spleen diameter, and grade of ascites ($p < 0.05$), but there were no significant differences for red blood cell count, hemoglobin percent, international normalized ratio, alanine aminotransferase, or aspartate aminotransferase. This data is demonstrated in Tab (3).

Tab 3. Comparison between the studied groups according to biochemical and radiological findings.

	Control (n = 20)	Cases S (n = 20)	Cases I (n = 20)	p
RBCS /mcl				0.562
Mean ± SD.	3.6 ± 0.6	3.7 ± 0.7	3.5 ± 0.6	
Hemoglobin (g/dl)				0.666
Mean ± SD.	10 ± 1.6	10.1 ± 1.8	9.7 ± 1.5	
Platelets x10³				0.001*
Mean ± SD.	122 ± 37.3	85.2 ± 29.1	90.9 ± 26.4	
Sig. bet. Groups.		p ₁ =0.001*, p ₂ =0.007*, p ₃ =0.833		
Albumin (g/dl)				0.007*
Mean ± SD.	3 ± 0.5	2.9 ± 0.5	2.6 ± 0.4	
Sig. bet. Groups.		p ₁ =0.718, p ₂ =0.007*, p ₃ =0.054		
Bilirubin (mg/dl)				

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Median (Min. – Max.)	1.7 (0.5 – 4.9)	1.5 (0.5 – 8)	2.8 (0.9 – 8.4)	0.036*
Sig. bet. Groups.	p ₁ =0.849, p ₂ =0.033*, p ₃ =0.020*			
INR				
Mean ± SD.	1.6 ± 0.4	1.5 ± 0.2	1.7 ± 0.4	0.091
AST (IU/ml)				
Median (Min. – Max.)	56 (16 – 115)	53.5 (25 – 135)	63.5 (42 – 123)	0.255
ALT (IU/ml)				
Median (Min. – Max.)	36 (10 – 67)	32 (12 – 84)	40.5(13 – 85)	0.201
PV diameter (mm)				
Mean ± SD.	13.5 ± 2	13.8 ± 2.1	15.6 ± 1.9	0.003*
Sig. bet. Groups.	p ₁ =0.875, p ₂ =0.005*, p ₃ =0.018*			
Spleen diameter (cm)				
Mean ± SD.	16 ± 2.7	17 ± 3	19.1 ± 2.9	0.003*
Sig. bet. Groups.	p ₁ =0.505, p ₂ =0.003*, p ₃ =0.057			
Ascites				
Median (Min. – Max.)	1 (0 – 3)	1 (0 – 3)	2 (0 – 3)	0.034*
Sig. bet. Groups.	p ₁ =0.473, p ₂ =0.012*, p ₃ =0.069			

p₁: p-value for comparing between Control and Cases S p₂: p-value for comparing between Control and Cases I p₃: p-value for comparing between Cases S and Cases I ALT: alanine aminotransferase, AST: aspartate aminotransferase, PV: portal vein, INR: international normalized ratio.

The three studied groups were compared regarding their cardiac condition as evaluated by ECG and measuring the corrected QT interval, showing a highly statistically significant difference between the three groups (p<0.001). The echocardiographic parameters showed no significant difference between the studied groups (p > 0.5). These studied parameters included septal velocity, the ratio of early diastolic to late diastolic mitral inflow velocity (E/A) ratio, tricuspid annular systolic plane excursion (TAPSE), systolic pulmonary artery pressure (SPAP), the ratio of peak early diastolic mitral inflow and peak early diastolic annular velocity (E/E') ratio, and tricuspid regurgitation velocity (TR).

Upon studying the number and percent of patients with cirrhotic cardiomyopathy (CCM) within each group, it was found that in group I, 5 (25%) patients had CCM; in group II, 6 (30%) patients

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had CCM, and in group III, 7 (35%) patients had CCM, with no significant difference between the three groups. The previously mentioned data is demonstrated in Table (4).

A highly statistically significant difference was found upon studying the relation between the child score of the patients in the total studied sample and cardiomyopathy ($p = 0.001$), where only one patient (9.1%) with child score A had CCM. In contrast, 6 (18.8%) patients with child score B had CCM, and 11 (64.7%) had CCM patients with child score C, as shown in tab (5).

Also, a highly statistically significant difference was found upon studying the relation between the child score of the patients and the corrected QT interval ($p < 0.001$) (tab 4).

Tab 4. Comparison between the three studied groups according to cardiological assessment parameters

	Control (n = 20)	Cases S (n = 20)	Cases I (n = 20)	p
QTC (ms)				
Mean \pm SD.	379.8 \pm 44.1	387.8 \pm 38.9	439.3 \pm 57.6	<0.001*
Sig. bet. grps.		$p_1=0.856, p_2=0.001^*, p_3=0.003^*$		
S' (cm/sec)				
Mean \pm SD.	9.7 \pm 2.5	9.9 \pm 2.7	8.9 \pm 2.9	0.439
E/A				
Median (Min. – Max.)	0.8 (0.6 – 1.8)	0.9 (0.5 – 1.7)	0.7 (0.5 – 1.6)	0.087
TAPSE (cm)				
Mean \pm SD.	2.5 \pm 0.3	2.5 \pm 0.3	2.3 \pm 0.5	0.172
SPAP (mmHg)				
Median (Min. – Max.)	30 (23 – 50)	32 (23 – 44)	40.5 (23 – 65)	0.127
E/E'				
Median (Min. – Max.)	10.3 (4.3 – 16.3)	10.2 (6.2 – 17.5)	14.5 (5 – 18)	0.176
TR				
Median (Min. – Max.)	2.7(2.3 – 3.6)	2.8 (2.3 – 3.3)	3.1 (2.3 – 4)	0.073
Cardiomyopathy	5 (25%)	6 (30%)	7 (35%)	0.788

SD: Standard deviation, p: p-value for comparing the three studied groups, p_1 : p-value for comparing between Control and Cases S, p_2 : p-value for comparing between Control and Cases I, p_3 : p-value for comparing between Cases S and Cases I, *: Statistically significant at $p \leq 0.05$

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Also, a highly significant positive correlation was found between the child score of the patients and the corrected QT interval ($p < 0.001$) (tab 6).

Tab 5. Relationship between Child score with QTc and Cardiomyopathy in the total sample.

	Child score			P
	A (n= 11)	B (n= 32)	C (n= 17)	
QTc (ms)				
Mean \pm SD.	353.6 \pm 32.7	388.1 \pm 37.7	460.3 \pm 40.3	<0.001*
Cardiomyopathy				
No	10(90.9%)	26(81.3%)	6(35.3%)	0.001*
Yes	1(9.1%)	6(18.8%)	11(64.7%)	

p: p-value for comparison between the studied categories, *: Statistically significant at $p \leq 0.05$

Tab 6. Correlation between Child score and QTc (ms) in the total sample.

	Child score	
	r_s	p
QTc (ms)	0.685	<0.001*

r_s : Spearman coefficient, *: Statistically significant at $p \leq 0.05$

A highly statistically significant difference was found upon studying the relation between the degree of esophageal varices and the corrected QT interval ($p = 0.001$) (table 7) (Fig. 1).

Tab 7. Correlation between QTc (ms) and Varices in the total sample.

	QTc (ms)	
	r_s	p
Varices	0.429	0.001*

r_s : Spearman coefficient, *: Statistically significant at $p \leq 0.05$

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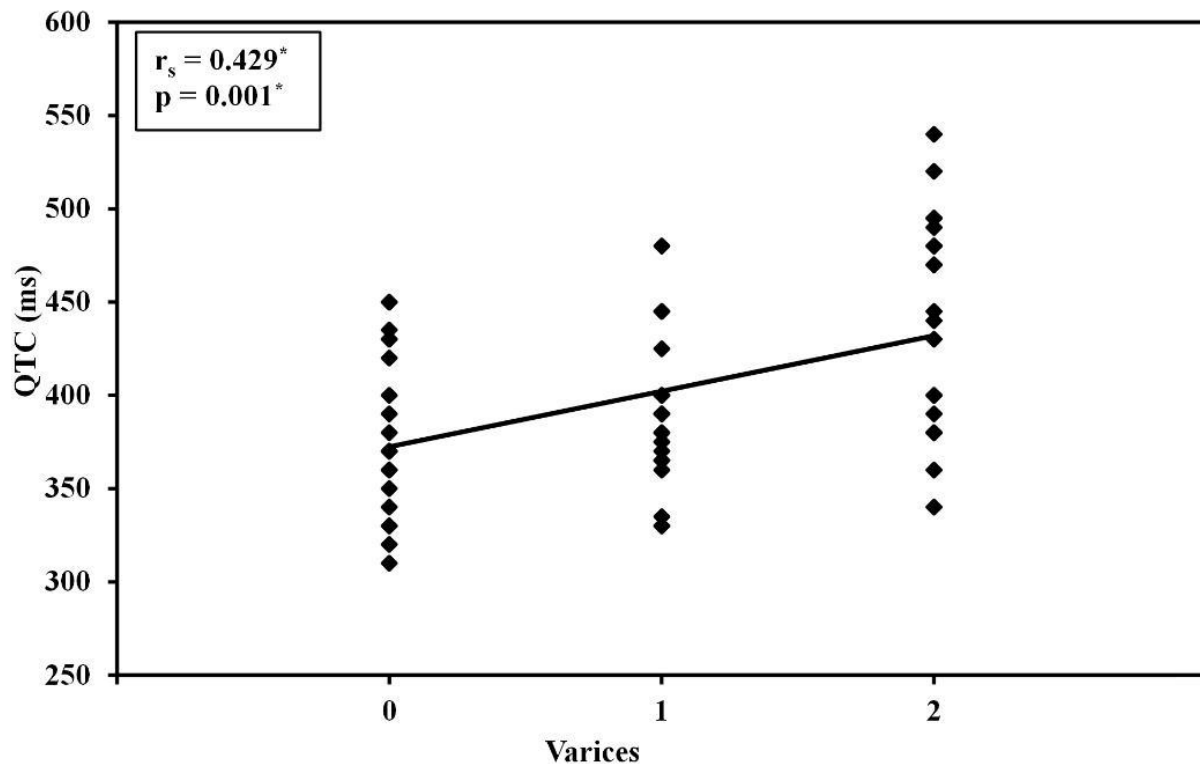


Fig 1. Correlation between QTC (ms) and varices in the total sample (n= 60)

DISCUSSION

Cirrhotic cardiomyopathy, characterized by abnormalities in electrophysiology and altered diastolic relaxation with diminished contractile response to stress, is a chronic disease that patients with cirrhosis may acquire [2].

Cirrhotic cardiomyopathy is associated with a poorer prognosis because of its associations with heart failure, ascites, hepatorenal syndrome, and lower survival after transjugular intrahepatic portosystemic shunt [24]. Our goal was to investigate the relationship between esophageal varices and cardiac alterations in patients with cirrhosis.

The study recruited sixty cirrhotic individuals who were matched by age and sex. The severity of the esophageal varices was used to categorize the patients: twenty patients were included in the

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control group as they had no varices, twenty patients had small varices, and twenty patients had large varices.

Every patient's ejection fraction fell between the usual limits. This function may be connected to afterload reduction since patients with cirrhosis have reduced systemic vascular resistance. **Wong F, 2001**, indicated that during rest, both the contractile index and stroke volume are typically routine or slightly raised. [25].

Using the 2019 criteria, CCM was identified; out of 60 cirrhotic patients, 18 patients (30%) exhibited diastolic dysfunction identified by (≥ 3 of the following) 1. Septal e' velocity < 7 cm/s; 2. E/e' ratio ≥ 15 . 3. TR velocity > 2.8 m/second; 4. LAVI > 34 mL/m²[3].

The prevalence of CCM in the study was 18/60 (30%), consistent with findings from previous studies, such as Cesari M. 2012, who reported that 29% of patients included in his study had the condition. Other studies also showed the exact prevalence [26-28].

The contradictory findings in the literature about the prevalence of CCM (ranging from 46% to 63%) are primarily attributable to the varied diagnostic standards employed in these studies. [29-32].

Regarding the association between CCM and the severity of liver disease, we found that CCM diagnosed in our cases by diastolic dysfunction was significantly prevalent in patients with advanced liver disease by CHILD classification. These results were consistent with other studies, such as Behera MK, 2021 which showed that patients with cirrhosis and left ventricular diastolic dysfunction had significantly higher child Pugh scores [33, 34]. Meanwhile, Hammami R, 2017, showed no correlation between the severity of cirrhosis and the stage of cardiomyopathy [35].

The three groups were compared for blood biochemical and radiological parameters, which show statistically significant differences for platelet count, albumin, bilirubin, portal vein diameter, spleen diameter, and grade of ascites ($p < 0.05$). These results are consistent with other studies that showed that a low platelet count was associated with higher grades of esophageal varices [36-38]. Gebregziabher HT et al. (2023) also showed that platelet count and spleen diameter performed

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well for EV diagnosis [39]. *ZEB et al. (2022)* showed that a low albumin level can predict the degree of EV [40]. *Mahmood K. et al. (2019)* concluded that low platelet count, high bilirubin level, and ascites are non-invasive predictive factors for large esophageal varices [41]. *Prihatini et al. 2005* showed that portal vein diameter could be a noninvasive parameter to detect esophageal varices in cirrhotic patients [42].

Echocardiography and ECG results were used to compare the heart condition of the three study groups. The corrected QT interval revealed a statistically significant difference between the control, small varices, and large varices groups but not between the control and small varices groups. ($p < 0.001$). Also, we found a positive correlation between prolonged QT interval and the degree of esophageal varices. Studies on the degree of esophageal varices and CCM were limited; the majority focused on cases of gastrointestinal bleeding.

According to *Seleem H. et al. (2022)*, there was a tendency for the QTc interval to be higher in the group of cirrhotic patients with large esophageal varices than in the group with small varices. However, no significant difference was seen between the two groups [43].

In addition to *Trevisani et al.'s (2012)* study examining QTc interval prolongation in cirrhotic and non-cirrhotic patients with acute gastrointestinal bleeding (AGIB), several studies assessed the QTc interval in individuals with a history of bleeding varices. Only after six months, the QTc values reverted to baseline after being observed to be extended during the bleeding period [44]. Similar results were obtained by Ytting H, 2005, who showed that portal hypertension and the prolonged Q-T interval may be related to liver disease. Furthermore, Ou M., 2021 found that QTc interval prolongation was seen in UGIB in cirrhotic patients. [45, 46].

The longer Qt interval observed in the group of patients with large varices in this study may have been caused by their significantly higher history of upper gastrointestinal bleeding. Additionally, we discovered that the CHILD classification strongly correlated the QTc interval with the severity of liver disease. These results are consistent with those of Papadopoulos VP, 2023, who demonstrated that although QTc is extended in cirrhosis regardless of sex, age, or cause, it is related

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to severity and affected by β -blockers and acute gastrointestinal bleeding. [47] Similar data were also found by Mozos I, 2011, and Patel D, 2014[48, 49].

There is still no clear explanation for the QT interval's elongation. There have been suggestions for molecular-level modifications. Additional factors include myocardial ischemia, changed electrolytes, and alterations to the autonomic nervous system, which can affect the heart rate and electromechanical coupling. Furthermore, it has been suggested that anomalies in gonadal hormone metabolism contribute to the development of QT prolongation in advanced cirrhosis [50].

Regarding the remaining CCM criteria, no statistically significant variations were seen between the groups under analysis. According to a study by *Marconi et al., 2017* esophageal varices may be predicted using echocardiographic measures, including LA volume, LV mass index, and TDI S'-wave velocity. Furthermore, a decrease in the TDI peak S'-wave velocity, a rise in LV mass, and LA dilatation may serve as early warning signs of portal hypertension and help identify patients who are at a higher risk of developing the condition and its associated complications [51].

According to *Seleem H. et al. 2022* research, patients with high-grade EV had significantly lower E/E' ratios and significantly higher LA volumes than those with low grades [43].

We concluded that only a prolonged QT interval was significantly associated with large varices in cardiac alterations and their linkage with the degree of esophageal varices.

The current study has several limitations, such as its small sample size and the absence of a stress test (such as a pharmacological or physical exertion test) that would have improved its understanding of subclinical systolic dysfunction.

Conclusion

Only a prolonged QT interval was significantly associated with large varices regarding cardiac alterations and their linkage with the degree of esophageal varices.

Abbreviations:

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CCM: cirrhotic cardiomyopathy

QTc: corrected QT interval

EV: esophageal varices

GLS: global longitudinal strain

TTE: transthoracic echocardiography

EF: ejection fraction

SVR: systemic vascular resistance

ALT: Alanine aminotransferase.

AST: Aspartate aminotransferase.

INR: International Normalized Ratio.

SD: Standard deviation.

ROC Curve: Receiver operating characteristic curve.

Footnotes.

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Ethical consideration

The ethical committee's approval, with adherence to the Helsinki Declaration, was obtained before the start of the study, approval code 36264PR41/1/23.

Original research

Consent for publication: All patients included in this research gave written informed permission to publish the data contained within this study.

Data and materials availability: The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions

K H A was responsible for conception and revision, and NMM and EMH were accountable for interpreting and analyzing data. K H A, NMM, and EMH wrote the manuscript, which was revised and approved by all co-authors.

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