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Cardiac dysfunction in patients with end-stage liver disease, prevalence, and impact on outcome: a comparative prospective cohort study

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Abstract

Background: Without firm diagnostic criteria, the exact prevalence of cirrhotic cardiomyopathy still remains unknown. Its estimation is rather a difficult task as the disease is generally latent and shows itself only when the patient is subjected to overt stress such as body position changes, exercise, drugs, hemorrhage, and surgery. In this study, we aim to assess cardiac dysfunction in patients with end-stage liver disease, study the correlation between cardiac dysfunction and Child-Pugh classification of patients with liver cell failure, and study the prevalence and impact of cardiac dysfunction on the clinical outcome of patients with child B and child C liver disease.

Results: Diastolic dysfunction was more prevalent among the patients' group ($p < 0.001$). It was absent in 28 (70%) of control group, with grade 1 diastolic dysfunction in 12 (30%). Only one patient (2.5%) had no diastolic dysfunction, 21 patients (52.5%) had grade 1 diastolic dysfunction, 12 (30%) patients had grade 2 diastolic dysfunction, and 6 patients (15%) had grade 3 diastolic dysfunction. QTc interval was significantly prolonged in the patients' group when compared to controls ($p < 0.001$). Echocardiographic parameters and QTc interval were comparable in child B and child C patients. All patients were followed up for a period of 3 months. Sixteen of 40 patients died in this period of time. Only child classification was found to significantly predict mortality, and patients with child C liver cirrhosis had worse survival when compared to patients with child B liver cirrhosis.

Conclusion: Most of the patients had cardiac dysfunction, mainly diastolic dysfunction (87.5%). The study detected the prevalence of diastolic dysfunction among end-stage liver disease when measuring E/É using TDI which proved to be more accurate than E/A ratio. Diastolic dysfunction is proved to be the most sensitive parameter in the diagnosis of cirrhotic cardiomyopathy, being the most parameter affected early. No correlation was found between cardiac dysfunction and the severity of hepatic illness, but the severity of hepatic illness affects the outcome rather than cardiac dysfunction.

Keywords: Cardiac dysfunction, End-stage liver disease, Outcome, Cirrhotic cardiomyopathy, Tissue Doppler

Background

The term "cirrhotic cardiomyopathy" has recently been redefined by the cirrhotic cardiomyopathy consortium by proposing criteria based on recent advances in echocardiography, like the use of tissue Doppler and speckled tracking. These criteria include systolic and/or diastolic

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dysfunction, in addition to ancillary supporting criteria for future research [1].

During periods of stress, overt cardiac dysfunction is unmasked. Thorough cardiac evaluation is essential before carrying out procedures like TIPS and liver transplantation, thereby minimizing bad prognosis for patients with more advanced cirrhotic cardiomyopathy [2].

Diastolic dysfunction is often found in cirrhotic cardiomyopathy. It is thought to be caused by stiffness in the ventricle and might hinder the cardiac ability to handle an increased preload. However, knowledge about the relevance of this change clinically is still incomplete, and until now, the usefulness of investigating diastolic dysfunction in the management of patients with cirrhosis had not been fully defined [3]. Studies of ventricular diastolic filling in cirrhosis support the presence of a subclinical myocardial disease with diastolic dysfunction and a decreased E/A ratio [4].

In our study, we aimed at covering the gap in knowledge regarding the prevalence of the disease. We investigated the correlation between the severity of liver disease and the presence of cirrhotic cardiomyopathy in addition to observation of the patients to detect the impact of cirrhotic cardiomyopathy on mortality.

Methods

This study was conducted as a comparative prospective cohort study on 40 non-alcoholic liver cirrhosis patients with end-stage liver disease, admitted to the intensive care unit in Theodor Bilharz Research Institute. Patients were selected and further classified according to Child–Pugh criteria into child B and child C patients and compared to 40 healthy subjects representing the control group. The patients' group was followed up for a period of 3 months. Informed consents were taken from all subjects.

We included patients with non-alcoholic liver cirrhosis, including post hepatitis B virus cirrhosis, post hepatitis C virus cirrhosis, and cryptogenic cirrhosis. Patients were further classified into child B and child C liver disease. We excluded patients with coexisting cardiac disease including ischemic heart disease, dilated cardiomyopathy, rheumatic heart disease, and congenital heart disease. We also excluded patients with alcoholic liver cirrhosis and patients with diseases affecting the cardiac function like thyroid disease, diabetes, hypertension, dyslipidemia, and renal disease. Patients with child A liver disease were not included in our study. Patients taking medication that could affect the heart like beta blockers and antiviral drugs were also excluded. Patients not willing to participate in the study were also excluded.

Eighty subjects were enrolled in the study and classified into two groups, Group A: (healthy controls) and Group B: (patient group). Group B was subdivided into child B and child C. All subjects selected for the study had a detailed clinical examination, and serum samples were obtained and tested for serum albumin, total bilirubin, prothrombin time, concentration, INR, sodium, and potassium.

Electrocardiography

A 12-lead surface ECG was obtained from all subjects in the supine position immediately before echocardiography by using *Suzuken kenz306* device. The ECG was recorded at a paper speed of 25mm/s and voltage of 1mV. All measurements were made by one observer who was not aware of the patients' characteristics.

M-mode and 2D echocardiography

M-mode and detailed 2-D echocardiography were carried out in all patients by using *Sonata plus (pm 26000724)*. Patients were examined in supine position as well as lying partially on the left side at an angle of 30°/45°. Doppler echocardiography was carried out in all the patients using the guidelines of the American Society of Echocardiography 2015 [5]. Diastolic function was assessed by measuring peak E velocity of mitral flow in cm/sec, peak A velocity of mitral flow in cm/sec, and E/A ratio. Systolic function was measured by M–mode in the parasternal long axis view and calculating EF. Myocardial performance index was calculated with the following formula: $\frac{IVCT+IVRT}{ET}$ where IVCT is isovolumetric contraction time, IVRT is isovolumetric relaxation time, and ET is ejection time [6]. LV mass index was obtained from the following formula: LV mass $= 0.8 \times 1.04 \times [(\text{IVS} + \text{LVID} + \text{PWT})^3 - \text{LVID}^3] + 0.6\text{g}$, where IVS is interventricular septal thickness at end-diastole (mm), LVID is left ventricular internal dimensions at end diastole, and PWT is posterior wall thickness at end diastole [5]. Left atrial volume index was calculated by the disk summation technique (Simpson's method). Parameters indexed to body surface area.

Tissue Doppler imaging

Diastolic function by TDI was done to assess diastolic function by E/e' calculated at the lateral mitral annulus. Systolic function by TDI was performed at lateral mitral annulus, and peak mitral annular systolic velocity (MASV) was measured.

The patient group was followed up for a period of 3 months for the occurrence of all-cause death. Surveillance was performed by medical contact and/or observation of clinical records.

Statistical analysis

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 23. We determined that a sample of 40 patients and 40 healthy subjects would provide the trial with a power of 80% in identifying cirrhotic cardiomyopathy at an alpha level of 0.05. The quantitative data were presented as mean, standard deviations, and ranges when their distribution were found parametric. Also, qualitative variables were presented as numbers and percentages. The comparison between groups with qualitative data was done by using *chi-square test* and *Fisher's exact test* instead of the chi-square only when the expected count in any cell was less than 5. The comparison between two groups with quantitative data and parametric distribution were done by using independent *t test.* The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the p value was considered significant as the following: $p > 0.05$, non-significant; $p < 0.05$, significant; and $p < 0.01$, highly significant. Cox regression analysis was used to evaluate the association of independent variables with time to outcome, expressed as 95% CI. Independent continuous variables were dichotomized according to their median values (when there was no linear relationship between them and the dependent variable) or according to well established cutoff values for defining abnormality. Survival curves were estimated according to the Kaplan–Meier method and compared by the log-rank test.

Results

Clinical and laboratory parameters in patients and controls

Bilirubin was significantly higher in patients compared to controls ($p < 0.001$). While albumin was significantly lower in patients compared to controls ($p < 0.001$), INR was significantly higher in patients compared to controls ($p < 0.001$). Sodium and potassium were comparable in both groups ($p = 0.35$) and ($p = 0.89$), respectively. 37.5% of patients ($n = 15$) had no encephalopathy. Forty percent of patients ($n = 16$) had grade 1 encephalopathy, 12.5% ($n = 5$) had grade 2 encephalopathy, and 10% ($n = 4$) had grade 3 encephalopathy. Ten percent of patients ($n = 4$) had no ascites, 35% ($n = 14$) had mild ascites, 35% ($n = 14$) had moderate ascites, and 20% ($n = 8$) had tense ascites (Tables 1 and 2).

Echocardiographic parameters in patients and controls

2D echocardiography parameters

EF was found comparable in patients and controls ($p = 0.522$). **E/A** was found comparable in patients and controls ($p = 0.174$). **MPI** was found comparable in patients and controls ($p = 0.455$). **LV mass index** was found significantly higher among patients compared to controls ($p < 0.001$). The control group had a mean value of 56.25 g/m^2 (SD ± 8.65) and range 44–73. Patients had a mean of 69.33 g/m^2 (SD ± 12.78) and range 48–93. **LA volume index** was found significantly higher among patients when compared to controls ($p < 0.001$). Controls had a mean value of 21.53 ml/m^2 (SD ± 3.85) and range 16–28. Patients had a mean value of 39.13 ml/m^2 (SD ± 4.6) and range 30–52.

Tissue Doppler echocardiography parameters

MASV (TDI) was significantly higher among patients when compared to controls ($p = 0.007$). The control group had a mean of 11.56 cm/s (SD ± 1.37) with range 9.7–14. The patient group had a mean of 12.6 cm/s (SD ± 1.93) and range of 9–16. **E/É (TDI)** by tissue Doppler was found significantly higher among patients compared to controls ($p < 0.001$). The control group had a mean of 7.63 (SD ±0.59) and range of 6.8–9. The patient group had a mean value of 12.78 (SD ± 2.73) and range of 8–18. **Diastolic dysfunction** was present more among the patient group ($p < 0.001$). It was absent in 28 (70%) of controls, with grade 1 diastolic

Table 1 Demographic data in patients and controls

	Control group (A)	Patient group (B)	Test value	*P* value
Gender				
Females	**17 (42.5%)**	**22 (55.0%)**	**5.788**	**0.055**
Males	**23 (57.5%)**	**18 (45.0%)**		
Age				
Mean ± SD	**51 ± 7**	**52 ± 7**	**0.559**	**0.542**
Range	**38–62**	**42–62**		
Cause of cirrhosis				
Hepatitis virus C	**0 (0%)**	**26 (65%)**	**NA**	**NA**
Hepatitis Virus B	**0 (0%)**	**8 (20%)**		
Cryptogenic	**0 (0%)**	**6 (15%)**		

0.05 NS non-significant, *< 0.05 S* significant, *< 0.01 HS* highly significant, *NA* not applicable

Table 2 Laboratory and clinical parameters in patients and controls

	Control group (A)	Patient group (B)	Test value	*P* value
Bilirubin				
Median (IQR)	*0.7 (0.45–0.9)*	*2.4 (2.1–3.15)*	*7.323*	*<0.001*
Range	*0.3–0.8*	*1.6–3.9*		
Albumin				
Mean±SD	*4.24 ± 0.35*	*2.83 ± 0.44*	*0.812*	*<0.001*
Range	*3.6–4.9*	*1.9–3.7*		
Sodium				
Mean±SD	*140 ±3*	*131 ± 3*	*14.380*	*0.35*
Range	*136–145*	*126–136*		
Potassium				
Mean±SD	*4.1 ± 0.4*	*3.7 ± 0.4*	*5.146*	*0.89*
Range	*3.5–4.8*	*3.2–4.4*		
INR				
Mean±SD	*1.06 ± 0.06*	*2.03 ± 0.35*	*50.727*	*<0.001*
Range	*1–1.2*	*1.4–3*		
Encephalopathy				
No	*40 (100.0%)*	*15 (37.5%)*	*36.364*	*<0.001*
Grade I	*0 (0.0%)*	*16 (40.0%)*		
Grade II	*0 (0.0%)*	*5 (12.5%)*		
Grade III	*0 (0.0%)*	*4 (10.0%)*		
Ascites				
No	*40 (100.0%)*	*4 (10.0%)*	*65.455*	*<0.001*
Mild	*0 (0.0%)*	*14 (35.0%)*		
Moderate	*0 (0.0%)*	*14 (35.0%)*		
Tense	*0 (0.0%)*	*8(20.0%)*		
Child				
Control	*40 (100.0%)*	*0 (0.0%)*	*80.000*	*<0.001*
Child B	*0 (0.0%)*	*18 (45.0%)*		
Child C	*0 (0.0%)*	*22 (55.0%)*		

0.05 NS non-significant, *< 0.05 S* significant, *< 0.01 HS* highly significant, *INR* international normalized ratio

dysfunction in 12 (30%). Only one patient (2.5%) had no diastolic dysfunction, with 21 (52.5%) had grade 1 diastolic dysfunction, 12 (30%) had grade 2 diastolic dysfunction, and 6 patients (15%) had grade 3 diastolic dysfunction.

Comparison of echocardiographic parameters between controls, child B, and child C patients

The same echocardiographic parameters were compared between the control group, child B, and child C patients (Table 3).

When comparing the three groups together (controls, child B, and child C) in echocardiographic parameters

MASV was significantly higher among child B and child C when compared to controls ($p = 0.025$). **E/É**, **diastolic dysfunction**, **LV mass index**, and **LA volume index** were significantly higher in child B, child C when compared to controls ($p < 0.001$). The rest of echocardiographic parameters, namely **EF**, **E/A**, and **MPI** were comparable in the three groups.

Echocardiographic parameters in child B and child C patients

When comparing echocardiographic data between child B and child C patients, all of the echocardiographic parameters showed no statistical significance (Table 4).

QTc interval in patients and controls

QTc interval was significantly prolonged in the patient group when compared to controls ($p < 0.001$) (Table 5) with no difference in QTc interval when comparing between child B and child C patients.

Follow-up

All patients were followed up for a period of 3 months. Sixteen of the 40 patients died in this period of time; below are the patients' characteristics according to survival at the start of a 3-month follow-up period (Table 6).

The two groups had statistically significant differences only in Albumin ($p = 0.001$), ascites ($p < 0.001$), and child score ($p = 0.006$). Other parameters were statistically insignificant.

Cox regression analysis was done to reveal independent variables of mortality. Only child classification was found to significantly predict mortality (Table 7).

Kaplan-Meier analysis showed that patients with child C liver cirrhosis had worse survival when compared to child B liver cirrhosis (Fig. 1).

Discussion

Cardiac dysfunction in cirrhosis often remains ignored. However, cirrhosis is associated with a host of cardiovascular abnormalities, including hyperdynamic circulation, portal hypertension, hepatopulmonary syndrome, and changes in several different vascular territories such as renal and cerebral vasculature [7].

The World Congress of Gastroenterology has proposed diagnostic criteria for cirrhotic cardiomyopathy in 2005 which were composed of systolic dysfunction and diastolic dysfunction indices by echocardiography. In addition to other supportive criteria, including electrophysiological changes, serum biomarkers, and changes in the cardiac geometry [8].

With advances in echocardiography and the use of speckled tracking and tissue Doppler in addition to the updates in the concept of heart failure, new diagnostic criteria were proposed by the cirrhotic cardiomyopathy consortium which includes (1) systolic dysfunction as

Table 3 Comparison of echocardiographic parameters between controls, child B, and child C

	Control group	Child B	Child C	Test value	*P* value	Sig.	Post hoc analysis by LSD	
	No. = 40	No. = 18	No. = 22				P1	P2
EF								
Mean±SD	62.48 ± 3.73	61.39 ± 5.97	62.05 ± 6.30	0.287[b]	0.751	NS	0.453	0.751
Range	55–71	52–74	52–74					
MASV by TDI								
Mean±SD	11.56 ± 1.37	12.72 ± 2.14	12.50 ± 1.79	3.878[b]	0.025	S	0.018	0.039
Range	9.7–14	9–16	10–16					
E/A								
Mean±SD	0.92 ± 0.32	1.03 ± 0.62	1.11 ± 0.70	1.053[b]	0.354	NS	0.444	0.161
Range	0.4–1.5	0.4–2.5	0.4–2.3					
E/É by TDI								
Mean±SD	7.63 ± 0.59	12.44 ± 2.64	13.05 ± 2.84	68.187[b]	0.000	HS	<0.001	<0.001
Range	6.8–9	9–16	8–18					
Diastolic Dysfunction								
Grade 0	28 (70.0%)	1 (5.6%)	0 (0.0%)	46.629[a]	<0.001	HS	<0.001	<0.001
Grade I	12 (30.0%)	9 (50.0%)	12 (54.5%)					
Grade II	0 (0.0%)	6 (33.3%)	6 (27.3%)					
Grade III	0 (0.0%)	2 (11.1%)	4 (18.2%)					
MPI								
Mean±SD	0.39 ± 0.03	0.40 ± 0.02	0.37 ± 0.09	1.125[b]	0.330	NS	0.838	0.186
Range	0.33–0.45	0.34–0.44	0–0.43					
LV Mass Index								
Mean±SD	56.25 ± 8.65	69.44 ± 13.73	69.23 ± 12.27	14.184[b]	<0.001	HS	<0.001	<0.001
Range	44–73	49–93	48–90					
LA Volume Index								
Mean±SD	21.53 ± 3.85	39.00 ± 4.23	39.23 ± 4.99	169.877[b]	<0.001	HS	<0.001	<0.001
Range	16–28	30–46	32–52					

P value > 0.05, non-significant

P value < 0.05, significant

P value < 0.01, highly significant

P1: control group vs child B

P2: control group vs child C

P3: child B vs child C

NS non-significant, *S* significant, *HS* highly significant, *EF* ejection fraction, *MASV* mitral annular systolic velocity, *TDI* tissue Doppler imaging, *E* E wave velocity, *A* A wave velocity, *MPI* myocardial performance index, *LV* left ventricular, *LA* left atrial, *SD* standard deviation

[a] Chi-square test; [b] one-way ANOVA test

defined by left ventricular ejection fraction below 50% or global longitudinal strain <18% or >22%, (2) diastolic dysfunction ≥ 3 of the following: Septal e' velocity < 7 cm/s, E/e′ ratio ≥ 15, LAVI > 34 mL/m^2, and TR velocity > 2.8 m/s [1].

Other areas were proposed for future research, namely abnormal chronotropic or inotropic response, electrocardiographic changes, electromechanical uncoupling, myocardial mass change, serum biomarkers, chamber enlargement, and cardiac magnetic resonance imaging [1].

The prevalence of cirrhotic cardiomyopathy among cirrhotic patients in the literature has been estimated between 50% and 70% in several studies [9]. In our study, the prevalence of cirrhotic cardiomyopathy according to the above definition reached 87.5% when assessing diastolic dysfunction and 17.5% when assessing systolic dysfunction.

Echocardiographic functional parameters

Systolic dysfunction

In our study, we assessed systolic dysfunction by 2D echocardiography by calculating ejection fraction (EF)

Table 4 Comparison of echocardiographic data between child B and child C patients

	Child B		Child C		Test value[a]	*P* value
	No.	%	No.	%		
EF group						
Normal	15	83.3%	18	81.8%	0.016	0.900
Abnormal	3	16.7%	4	18.2%		
MASV groups by TDI						
Normal	16	88.9%	22	100.0%	2.573	0.109
Abnormal	2	11.1%	0	0.0%		
E/A groups						
Normal	8	44.4%	8	36.4%	0.269	0.604
Abnormal	10	55.6%	14	63.6%		
E/É groups by TDI						
Normal	3	16.7%	2	9.1%	0.519	0.471
Abnormal	15	83.3%	20	90.9%		
MPI groups						
Normal	18	100.0%	22	100.0%	NA	NA
Abnormal	0	0.0%	0	0.0%		
LV mass index group						
Normal	18	100.0%	22	100.0%	NA	NA
Abnormal	0	0.0%	0	0.0%		
LA volume index groups						
Normal	1	5.6%	1	4.5%	0.021	0.884
Abnormal	17	94.4%	21	95.5%		

NS non-significant, *S* significant, *HS* highly significant, *NA* not applicable, *EF* ejection fraction, *MASV* mitral annular systolic velocity, *TDI* tissue Doppler imaging, *E* E wave velocity, *A* A wave velocity, *MPI* myocardial performance index, *LV* left ventricular, *LA* left atrial, *SD* standard deviation

[a] Chi-square test

Table 5 Electrophysiological changes (QTc interval) in patients and controls

	Control group No. = 40	Patient group No. = 40	Test value	*P* value
QTc interval				
Mean±SD	**430.20 ± 9.63**	**453.00 ± 26.04**	**−5.194[a]**	**<0.001**
Range	**416–448**	**410–495**		

SD standard deviation, *HS* highly significant

[a] Independent *t* test

and by tissue Doppler through measuring mitral annular systolic velocity (MASV).

Using M mode echocardiography, EF ≤ 55% was found in 7 patients (17.5 %), which was insignificant when compared to the control group ($p = 0.52$). No correlation was found between EF and child score ($p = 0.68$).

In accordance with a study done by Merli et al. on 74 patients and compared to 26 controls, no systolic dysfunction could be detected among them when assessing systolic dysfunction by EF with a mean EF value of 61% ($p = 0.4$). Similarly, no correlation was found between EF and child score ($p = 0.5$) [10].

Similarly, Kamal et al. studied 50 cirrhotic patients and no systolic dysfunction could be detected with mean EF 64% [11].

In our study, the normal measured systolic function may be due to afterload reduction due to a low systemic vascular resistance among cirrhotic patients. This is coherent with various studies which have shown that stroke volume and contractile indices are typically normal or even increased at rest [12].

However, under stressful stimuli such as exercise, renal failure, and hemorrhage, cirrhotic patients may show an attenuated systolic function compared to healthy controls [12].

Using **TDI**, we assessed systolic dysfunction by Mitral annular systolic velocity (MASV), it was found significantly higher than controls ($p < 0.007$), and this could be attributed to hyperdynamic circulation, with apparent increased systolic function indices at rest. No correlation was found between MASV and child score ($p = 0.67$).

In contrast to our study, Sunil et al. found that MASV was statistically insignificant when comparing

Table 6 Comparison of demographic, laboratory, echocardiographic data, and QTc interval in patients according to whether they were alive or dead at the beginning of a 3-month follow-up period

		Alive (*n*= 24)		Dead (*n*= 16)		Test used	*P*value
		Mean	SD	Mean	SD		
Age		52.2	6.9	51	6.1	***T*test**	0.57
Albumin		3	0.4	2.56	0.3		0.001
bilirubin		2.5	0.6	2.7	0.5		0.36
sodium		130	2.6	131	3.5		0.53
potassium		3.6	0.3	3.7	0.4		0.92
INR		1.9	0.3	2	0.3		0.37
EF		61	6.5	62.5	5.5		0.53
MASV		12.5	2.1	12.7	1.7		0.81
E/A		1.1	0.6	1	0.7		0.66
E/E'		12.7	2.6	12.8	3		0.94
MPI		0.4	0.03	0.4	0.02		0.84
LV mass		70.5	14.4	67.5	10		0.46
LA volume		38.8	3.9	39	5.6		0.9
QT interval		457.7	26.5	446	24.3		0.16
		N	%	*N*	%		
Gender	Male	13	54%	10	62.5%	Chi square	**0.6**
	Female	11	46%	6	37.5%		
Cause of cirrhosis	Cryptogenic	4	16.7%	2	12.5%		0.53
	HBV	6	25%	2	12.5%		
	HCV	14	58.3%	12	75%		
Encephalopathy	No	9	37.5%	6	37.5%		0.22
	Grade 1	12	50%	4	25%		
	Grade 2	2	8.3%	3	18.8%		
	Grade 3	1	4.2%	3	18.8%		
Ascites	No	4	16.7%	0	0		<0.001
	Mild	13	54.2%	1	6.3%		
	Moderate	7	29.2%	7	43.8%		
	Tense	0	0	8	50%		
Diastolic dysfunction	Grade 0	1	4.2%	0	0		0.68
	Grade 1	11	45.8%	10	62.5%		
	Grade 2	8	33.3%	4	25%		
	Grade 3	4	16.7%	2	12.5%		
Child	Child B	15	62.5%	3	18.8%		0.006
	Child C	9	37.5%	13	81.2%		

NS non-significant, *S* significant, *HS* highly significant, *N* number, *EF* ejection fraction, *MASV* mitral annular systolic velocity, *TDI* tissue Doppler imaging, *E* E wave velocity, *A* A-wave velocity, *MPI* myocardial performance index, *LV* left ventricular, *LA* left atrial, *SD* standard deviation

Table 7 Variables independently associated with poor outcome

Variables	OR	95% C.I. of OR	
		Upper	Lower
Child	5	17.2	1.44

pre-ascetic and ascetic cirrhotic patients with the controls ($p = 0.7$) which could be attributed to the relatively smaller healthy control study group among his study. No correlation was found between MASV and severity of hepatic illness similar to our study [13].

Also in contrast to our study, Merli et al. found reduced MASV in patients compared to healthy controls ($p < 0.001$). This could be attributed to the inclusion of alcoholic cirrhosis patients and the relatively smaller healthy controls study group among his study. Again, no correlation was found between severity of hepatic illness and MASV [10].

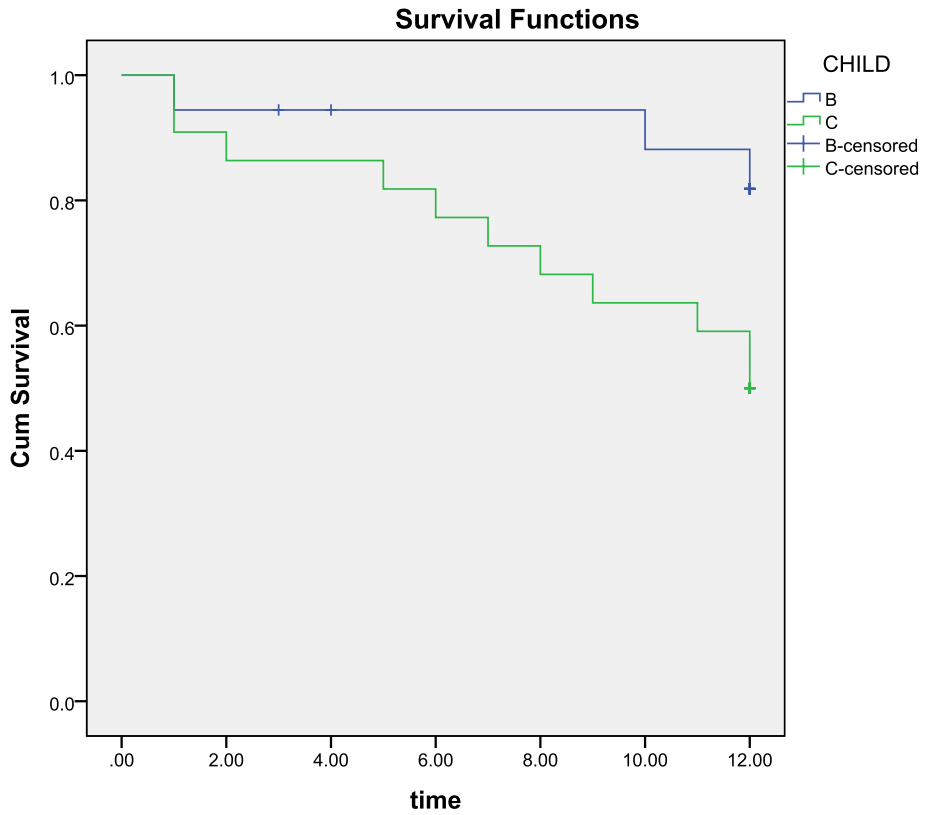

Fig. 1 Probability of survival among child B and child C

Diastolic function

The pathophysiological background of diastolic dysfunction in cirrhosis is due to increased stiffness of the myocardial wall, most likely because of a combination of myocardial hypertrophy, fibrosis, and subendothelial oedema [14].

By assessing diastolic dysfunction using 2D echocardiography by E/A ratio, it was found that there was no significant difference when comparing patients to the control group ($p = 0.174$) or correlation with child score ($p = 0.62$)

Coinciding with a similar study by Sunil et al. who measured E/A ratio on 40 patients divided into 20 patients with ascites and 20 patients with no ascites and compared them to 20 healthy controls. E/A ratio was comparable in the three groups ($p = 0.57$) [13].

However, in a relatively smaller number of studies, like the study performed by Merli et al., there was a significant decrease in E/A when compared to controls. Of note, there was a considerable number of patients with hemodynamic overload, thus influencing his results [10].

Most of the study papers have included TDI parameters in the definition of diastolic dysfunction (DD). In our study, the prevalence of diastolic dysfunction was 87% by incorporating TDI and was highly significant when comparing the E/É with the control group ($p < 0.001$).

No correlation was found between DD and child score ($p = 0.63$).

Similar to another study by Sunil et al. diastolic dysfunction by TDI was found in 70% of patients, with no correlation with severity of hepatic illness ($p = 0.09$) [13].

In another study based on TDI parameters, Arbol et al. found a DD prevalence of about 46% in cirrhotic patients, but with positive correlation between grade of DD and severity of hepatic illness. He concluded that DD was a sensitive marker of advanced cirrhosis, type 1 hepatorenal syndrome development, and a predictor of mortality. However, the study included alcoholic cirrhosis, and male sex predominance among the selected patients is noted in contrast to our study selection criteria [15].

Myocardial performance index

In our study, we assessed systolic and diastolic function together using myocardial performance index. It is considered a measure of global left ventricular function. It is calculated by the summation of isovolumetric contraction time and isovolumetric relaxation time divided by the ejection time [16].

All of the patients were within normal range of MPI with insignificant values when compared to the control group ($p = 0.455$) and insignificant correlation when comparing child B and child C patients ($p = 0.19$). This may be due to the slight affection of cardiac function of patients with liver cirrhosis when at rest.

Echocardiographic geometrical changes

Left atrial volume index

In the absence of primary atrial disease, mitral valve pathology, and overt left ventricular systolic dysfunction, left atrial volume index (LAVI) is thought to be a more stable measurement of diastolic dysfunction as it may express long term exposure to elevated left ventricular filling pressures which hinders complete atrial emptying and thereby increases left atrial volume [16].

In our study, left atrial volume index among patients when compared to controls was found significantly high ($p < 0.001$).

No statistical difference was found when comparing child B and child C ($p = 0.86$).

Our study was similar to the results found by Merli et al. in the study performed on 74 patients with liver cirrhosis and 26 controls, where LAVI was 32.7 ± 8.3 in patients compared to 24 ± 8.5 ($p < 0.0001$). No correlation was found between increased child score and LAVI ($p = 0.5$) [10].

Another study by Sampaio et al. found higher LAVI among patients when compared to controls [17] which was consistent with other studies [18, 19].

LV mass

LV mass is an important risk factor and a strong predictor of cardiovascular events. The tendency of increase in LV mass observed in cirrhotic patients may be attributed to excessive mechanical overload due to hyperdynamic circulation [20].

When assessing left ventricular mass in our study, it was found significantly higher among patients when compared to the control group ($p < 0.0001$). No statistical correlation was found when comparing child B and child C ($p = 0.95$).

This coincides with the recent study carried out on 80 patients, which showed a significant increase in LV mass compared to the control group ($p = 0.02$), with no correlation between LV mass and child score [21].

This is similar to the study done by Merli et al. on 74 cirrhotic patients who also found a significant increase in LV mass when compared to controls [10].

Electrophysiological changes

Prolongation of the QT interval in liver cirrhosis appears to be a result of a combination of ion-channel dysfunction, plasma membrane abnormalities, and receptor pathway defects and may also worsen after general interventional procedures and hepatic transplantation. However, the administration of β-blockers is effective for reducing the QT interval [22].

In our study, QT interval was prolonged in 55% of patients and was significantly higher among cirrhotics when compared to controls ($p < 0.001$), but we did not find a correlation between the severity of liver disease and the degree of QT prolongation.

In another study, a prospective study by Zambruni et al. found a longer QTc interval in patients with a more compromised liver function. Patients with a QTc interval > 440 ms were 27% of those with child A vs. 56% of those with child B/C ($p = 0.02$), while patients without ascites had 35% with a prolonged QTc interval vs. 62% in patients with ascites ($p = 0.03$) [23].

The same results to the study done by Zambruni et al. were obtained in other studies [24, 25]. The correlation of QTc prolongation with the severity of liver disease in contrast to our study could be attributed to the relatively small sample size in our study and the inclusion of alcoholic cirrhosis in the other studies [23].

Comparison of echocardiographic and electrophysiological parameters between child B and child C patients

It was of great notice when comparing both child B and child C echocardiographic and electrophysiological parameters rather than insignificant differences. Our results were similar to several studies on both geometric and functional echocardiographic parameters, like the study performed by Merli et al. on 74 patients who found no difference between child scoring and left atrium and ventricle measurements, in addition to no statistical differences in regards to systolic and diastolic function parameters [10].

And the study by Silverste et al. done on 184 patients that showed no correlation between MELD scoring (one of the scoring systems for assessment of the severity of liver disease) and left atrial diameter, left ventricular diastolic diameter, and both systolic and diastolic function parameters [9].

However, in a number of studies [4, 26, 27], diastolic dysfunction grade had a positive correlation with the severity of hepatic illness which of note is the lack of unified diagnostic criteria for the diagnosis of diastolic dysfunction and the use of E/A ratio with different cut-off values which is highly dependent on preload as mentioned earlier.

During the follow-up of the patient group for 3 months, 16 patients died (40%). Cox regression analysis was done to reveal predictors of mortality. Liver

functions assessed by child score emerged as the only independent predictor of mortality.

Survival was not affected by the parameters of cirrhotic cardiomyopathy, particularly diastolic dysfunction. This occurs in concordance with similar studies, like the study performed by Alexopoulou et al. who found no correlation between diastolic dysfunction and survival among cirrhotics [28].

This may be in contrast to a similar study by Cazzaniga et al. The absence of association of survival with cirrhotic cardiomyopathy might be because of the small number and/or the large proportion of our patients with mild diastolic dysfunction and therefore the low power of our study to detect such an effect. In addition, the effect of diastolic dysfunction on survival might be more evident in patients with TIPS, like the 32 patients included in the report by Cazzaniga et al. and less evident in patients with decompensated cirrhosis but without porto-systemic shunts like the 40 patients in our study [3].

Conclusion

Our study detected diastolic dysfunction among end-stage liver disease when measuring E/É using TDI, which proved to be more accurate than E/A ratio. Diastolic dysfunction proved to be the most sensitive parameter in the diagnosis of cirrhotic cardiomyopathy, being the earliest parameter affected. Left atrial volume index was higher in the patient group indicating the effect of chronic diastolic dysfunction. Left ventricular mass index was also higher signifying the postulated pathophysiological alterations among cirrhotic patients. QTc interval one of the cirrhotic cardiomyopathy supportive criteria was also prolonged. No correlation was found between echocardiographic parameters or QTc interval and child score. No correlation was found between parameters of cirrhotic cardiomyopathy and survival.

Abbreviations

EF: Ejection fraction; E/A: Early and late atrial filling; MPI: Myocardial performance index; LV: Left ventricle; SD: Standard deviation; LA: Left atrium; MASV: Mitral annular systolic velocity; TDI: Tissue doppler imaging; ECG: Electrocardiography; INR: International normalized ratio; IVCT: Isovolumetric contraction time; IVRT: Isovolumetric relaxation time; ET: Ejection time; IVS: Interventricular septal thickness; LVID: Left ventricular internal dimensions; PWT: Posterior wall thickness; LAVI: Left atrial volume index; DD: Diastolic dysfunction.

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Authors' contributions

Dr. FM and Dr. WR created the concept and design of the study, and Dr. MR and Dr. MD were responsible for the acquisition of laboratory and clinical data. Echocardiography, data analysis, and interpretation were done by Dr. KhH and Dr. HA. Drafting and revision of the manuscript were done by Dr. MR and Dr MD. The authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on a reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the research ethical committee at Theodor Bilharz Research Institute. Verbal and written consents were taken from all participants before inclusion after approval of the research ethical committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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