

**Cardiac dysfunction in liver cirrhosis: A tissue Doppler imaging study from Egypt**Fatma Mohammad Nasr<sup>1</sup>, Amna Metwaly<sup>1</sup>, Ashraf Abdel khalik<sup>1</sup>, Hesham Darwish<sup>1</sup><sup>1</sup> Intensive Care unit, Theodor Bilharz Research Institute, Giza, Egypt**Type of article:** Original**Abstract**

**Background:** Patients with liver cirrhosis suffer from various cardiac abnormalities, which may influence their outcome. Tissue Doppler recording of the mitral and tricuspid annular diastolic velocities can be used to assess diastolic function accurately. There has been very little published information regarding RV diastolic function in liver cirrhosis. This study is aimed at evaluating right and left ventricular systolic and diastolic functions in post hepatitis C liver cirrhosis patients using conventional echocardiography and tissue Doppler imaging.

**Methods:** This study was conducted on 75 adults from inpatient and outpatient services of the Theodor Bilharz Research Institute (TBRI) hospital. They were divided into two groups: Group 1 included 50 patients with post hepatitis C liver cirrhosis; and Group 2 included 25 normal adults serving as a control group. All patients and normal volunteers were subjected to clinical examination, laboratory evaluation, abdominal ultrasonography and echocardiographic studies with tissue Doppler imaging for evaluation of left and right ventricular systolic and diastolic functions.

**Results:** The mitral flow showed significant increase in A wave velocity, as well as DT and IVRT with a significant decrease in E/A ratio in Group 1 compared to Group 2 ( $P<0.01$ ). The tricuspid flow also showed a significant increase in A wave velocity ( $P<0.01$ ) and DT ( $P<0.05$ ) in addition to a significant decrease in E wave velocity and E/A ratio ( $P<0.01$ ) in Group 1 as compared to Group 2. At the mitral annulus, we found a significant increase in average Aa velocity, E/Ea ratio and average systolic wave velocity S, in addition to a statistically significant decrease in the average Ea velocity and average Ea/Aa ( $P<0.01$ ) in Group 1 as compared to Group 2. At the tricuspid annulus, there were significant increases in the average Aa velocity ( $P<0.01$ ), S velocity ( $P<0.01$ ) and E/Ea ( $P<0.05$ ) together with a statistically significant decrease in the average Ea/Aa and average Ea velocity ( $P<0.01$ ) in Group 1 compared to Group 2.

**Conclusion:** It is important to evaluate the cardiovascular function in every patient with cirrhosis, especially if the patient is a candidate for any intervention that may affect haemodynamics.

**Keywords:** Tissue Doppler Imaging, liver cirrhosis, systolic function, diastolic function

**1. Introduction**

Cirrhosis is a chronic liver disease characterized by diffuse fibrosis and regeneration nodules following hepatocellular necrosis in the liver (1, 2). Abelmann et al. (3) claimed that cardiac function is impaired in cirrhosis, and they were the first to define hyperdynamic circulation in patients with alcoholic cirrhosis. In the majority of cirrhotic patients, diastolic dysfunction precedes systolic dysfunction, which tends to manifest only under conditions of stress (4). Because of the feasibility and relatively preload-independence of tissue Doppler recording of the early diastolic mitral annular velocity (Ea) in conjunction with the mitral inflow velocity (E), tissue Doppler has become the most sensitive equipment for assessing left ventricular diastolic function and filling dynamics. Myocardial relaxation is impaired in almost all patients with diastolic dysfunction, which is best assessed by the Ea velocity of the mitral annulus using tissue Doppler imaging (TDI). While early diastolic trans-mitral velocity (E) increases progressively as LV filling pressure increases, the mitral annular Ea velocity remains decreased at all stages of diastolic dysfunction (5).

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Some studies have confirmed that tricuspid E/Ea (E is the early tricuspid inflow velocity and Ea is the early tricuspid annular diastolic velocity) is useful for the noninvasive estimation of RV filling pressure and for detecting serial changes under a wide range of clinical conditions (6, 7). Also, Utsunomiya et al. concluded that the tricuspid E/Ea ratio provides a reliable estimation of RV filling pressure and predicts cardiac events in patients with pulmonary arterial hypertension (8). There has been very little published information regarding RV diastolic function in liver cirrhosis. Soyoral et al. (9) found decreased E/A ratio by conventional Doppler in cirrhotic patients and concluded that cirrhosis disrupts right ventricle diastolic function. Dadhich et al. found insignificant decrease in Ea/Aa at the tricuspid annulus in cirrhotic patients compared to normal subjects (4). To our knowledge, no studies have explored E/Ea at the tricuspid annulus in liver cirrhosis patients.

Myocardial systolic velocity of the mitral and tricuspid annuli are important and frequently overlooked components of systolic function that can be sensitively quantified with TDI. Systolic annular (Sa) velocity measures long-axis ventricular motion because the longitudinally oriented endocardial fibers are most parallel to the ultrasound beam in the apical views. So, mitral and tricuspid annular motions are a good surrogate measure of overall longitudinal left ventricular (LV) and right ventricular contraction and relaxation (10, 11). The general objective of this research was to evaluate the right and left ventricular systolic and diastolic functions in patients having post hepatitis C liver cirrhosis using conventional echocardiography and tissue Doppler imaging. A more specific objective was to explore some TDI parameters like mitral and tricuspid Sa, E/Ea, and Ea/Aa in liver cirrhosis and to compare it with that of normal subjects.

## **2. Material and Methods**

### *2.1. Study setting and eligibility criteria*

This study was carried out in 2013 and 2014 and included 75 adults from inpatient and outpatient services of Theodor Bilharz Research Institute Hospital (TBRI) selected to represent two groups:

- 1) Group 1: included 50 patients having liver cirrhosis (all of them post hepatitis C virus infection).
- 2) Group 2: included 25 normal adults as control group matched for age and sex and with normal liver ultrasonography, normal liver function tests and negative hepatitis markers.

Patients with heart disease (congenital heart disease, valvular heart disease, restrictive cardiomyopathy, hypertrophic cardiomyopathy, pericardial constriction or myocarditis) were excluded. Patients with diabetes mellitus, hypertension, acute or chronic kidney disease, anemia with hemoglobin less than 10 gm% were also excluded. All patients were provided by informed consent, and the ethical committee of hospital approved this study and was conducted in accordance with Helsinki Declaration (1975).

### *2.2. General methods*

All patients and normal volunteers were subjected to thorough medical history and physical examination, liver function tests, renal function tests, serum electrolytes, HBs antigen, and HCV antibody. Abdominal ultrasound scanning was also performed to all participants by a member of the study team who was unaware of all other clinical and laboratory data. This scan was completed using a Toshiba Nemo 30 scanner equipped with a 3.5 MHz linear transducer. Liver cirrhosis (Post hepatitis C virus cirrhosis) was diagnosed based on the results of laboratory tests (hepatitis C virus antibody, low serum concentrations of albumin, high INR and low platelet count) and abdominal ultrasonographic findings (irregularity of the liver surface).

### *2.3. Echo-Doppler study*

All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography (12). These measurements were completed by two blinded members of the study team and measurements were averaged. M-mode, two dimensional echocardiography and Doppler ultrasound studies (pulsed, continuous wave, color flow and tissue Doppler imaging) were made using a high resolution (x11-15305) sonata plus ultrasound scanner equipped with a 2.5 MHz transducer. Left ventricular mass was calculated according to Devereux and associates convention:  $LVM\text{ gm} = 1.04 \times \{(LVED + IVST + PWT)^3 - LVED^3\} \times 0.8 + 0.6$  (13) where LVED was the left ventricular end diastolic diameter, IVST is the interventricular septum thickness, and PWT was the left ventricular posterior wall thickness.

Mitral inflow velocities were obtained by pulsed wave Doppler in the apical four-chamber view with a 1- to 2-mm sample volume placed at the tips of the mitral valve leaflets during quiet respiration. Mitral E and A wave velocities

(cm/s) and deceleration time DT (measured in milliseconds from E-wave peak to the decline of the velocity to baseline) were measured offline and averaged over two or three cardiac cycles. The E/A ratios were calculated. Isovolumic relaxation time (IVRT measured in milliseconds) was measured using a continuous wave Doppler signal, which intersects both the left ventricular outflow and the mitral valve motion. Thus presenting the time interval from aortic valve closure to mitral valve opening (onset of mitral valve velocity profile). Tricuspid inflow velocities were also obtained by pulsed wave Doppler in the apical four-chamber view with a 1- to 2-mm sample volume placed at the tips of the tricuspid valve leaflets during quiet respiration. Tricuspid E and A wave velocities (cm/s) and deceleration time (milliseconds) were measured offline and averaged over two or three cardiac cycles. The E/A ratios were then calculated.

#### *2.4. Doppler tissue imaging*

Pulsed wave Doppler tissue imaging velocities were obtained from the apical four-chamber view during quiet respiration by placing a sample volume in the lateral and septal mitral annulus. Cursor line was more aligned with examined wall (15–20°) to decrease incidence of angle error. The peak early diastolic mitral annular velocities (Ea, cm/s) and peak late diastolic mitral annular velocities (Aa, cm/s) were measured from the time-myocardial velocity waveforms of 2–3 consecutive cardiac cycles and the average was recorded. The lateral and septal E/Ea ratios, measure of LV filling pressure were calculated. The same measurements were repeated in the apical two-chamber view by placing the sample volume in the anterior and inferior mitral annulus and the anterior and inferior E/Ea were calculated. An average of all the four velocities of the Ea and Aa were taken as mean velocities at mitral annulus (mean Ea and mean Aa). Furthermore the average E/Ea and Ea/Aa were estimated. The mitral peak systolic annular velocity (Sa) was measured at the four different annular sites and the average systolic velocity was calculated.

Pulsed wave Doppler tissue imaging velocities were additionally obtained from the apical four-chamber view during quiet respiration by placing a sample volume in the lateral and septal tricuspid annuli. Cursor line was more aligned with examined wall (15–20°) to decrease incidence of angle error. The peak early diastolic tricuspid annular velocities (Ea, cm/s) and peak late diastolic tricuspid annular velocities (Aa, cm/s) were then measured from the time-myocardial velocity waveforms of 2–3 consecutive cardiac cycles, and averages were recorded. The lateral and septal E/Ea ratios, a measure of RV filling pressure, were calculated. The average of the two velocities of the Ea and Aa were taken as the mean velocities at tricuspid annulus (mean Ea and mean Aa). Also the average E/Ea and Ea/Aa were estimated. The tricuspid peak systolic annular velocity was measured at the two the annular sites, and the average systolic velocity was calculated.

#### *2.5. Statistical Analysis*

Statistical analysis was performed using SPSS version 17 (SPSS Inc, Chicago, Illinois, USA). Data were expressed as the mean  $\pm$  standard deviation (SD) for numerical variables.  $P \leq 0.05$  was considered to be statistically significant.

### **3. Results**

The demographic data of the patient group and the control group revealed mean ages  $43.67 \pm 9.46$  and  $44.8 \pm 8.5$  years, respectively. In Group 1 (patient group), 33 were males (66%) and 17 were females (34%). In Group 2 (control group), 16 were males (64%) and 9 were females (36%). The echocardiographic data showed a statistically significant increase in interventricular septum thickness (IVST), posterior wall thickness (PWT) and left ventricular mass (LVM) in Group 1 as compared to Group 2. Additionally, an increase in LVIDd in Group 1 as compared to Group 2 was shown. The LA and aortic diameter was significantly increased in the patient group as compared to the control group (Table 1).

Regarding the diastolic function of the left ventricle (mitral flow) measured by conventional Doppler, there was a significant increase in A wave velocity, DT, and IVRT, together with a decrease in E/A ratio in Group 1 as compared to the control group. On the right side (tricuspid flow), there was a significant increase in A wave and DT, in addition to a significant decrease in E wave and E/A ratio in Group 1 as compared to Group 2 (Table 2).

Pulsed wave tissue Doppler at the mitral annulus showed a statistically significant increase in average Aa velocity, average E/Ea ratio, and average systolic wave velocity (S), together with significant decrease in the average Ea velocity and average Ea/Aa in the patient group as compared to the control group. At the tricuspid annulus, there were statistically significant increases in the average Aa velocity, S velocity, and E/Ea, in the addition to significant

decreases in the average Ea/Aa and average Ea velocities in the patient group as compared to the control group (Table 3).

The laboratory data showed significant increases in the levels of K, AST, ALT, total bilirubin, direct bilirubin, and INR, as well as significant decreases in Na, albumin, hemoglobin, and platelets in the patient group as compared to the control group (Table 4). The abdominal sonography revealed significant increases in portal vein diameter (PV) with significant decreases in liver span in the patient group as compared to the control group.

**Table 1.** Echocardiographic data (M –mode) of the patient and the control groups

	Group 1	Group 2	P value
IVST cm	1.03 ± 0.16	0.92 ± 0.13	<0.01
PWT cm	1.04 ± 0.12	0.92 ± 0.13	<0.01
LVM gm	192.68 ± 57.48	155.55 ± 41.61	<0.01
LVIDd cm	4.96 ± 0.64	4.80 ± 0.47	<0.05
LVIDs cm	3.16 ± 2.16	2.92 ± 0.43	NS
EF%	68.44 ± 8.34	68.31 ± 6.88	NS
LA%	3.87 ± 0.49	3.56 ± 0.42	<0.01
AO cm	3.03 ± 0.35	2.88 ± 0.32	<0.01

IVST: interventricular septum thickness; PWT: posterior wall thickness; LVM: left ventricular mass; LVIDd: left ventricular internal diameter (diastole); LVIDs: left ventricular internal diameter (systole); EF: ejection fraction; LA: left atrium diameter; AO: aortic diameter.

**Table 2.** Doppler echocardiographic data (diastolic function) of the patient and the control groups

		Group 1	Group 2	P value
Mitral valve flow	E cm/s	65.95 ± 15.98	68.80 ± 6.92	NS
	A cm/s	75.61 ± 14.23	54.16 ± 7.01	<0.01
	E/A	0.89 ± 0.24	1.30 ± 0.24	<0.01
	DT ms	202.72 ± 62.96	156.24 ± 12.57	<0.01
	IVRT ms	83.52 ± 10.31	70.12 ± 11.59	<0.01
Tricuspid valve flow	E cm/s	48.03 ± 8.43	53.69 ± 7.14	<0.01
	A cm/s	58.18 ± 7.90	46.40 ± 10.64	<0.01
	E/A	0.83 ± 0.15	1.22 ± 0.35	<0.01
	DT ms	180.18 ± 52.86	154.37 ± 35.68	<0.05

E: peak velocity of early filling; A: peak velocity of atrial filling; DT: deceleration time; IVRT: isovolumic relaxation time. ms: millisecond; cm/s: centimeter per second

**Table 3.** Echocardiographic Tissue Doppler data of the patient and the control groups

		Group 1	Group 2	P value
Mitral annulus	Ea average	9.19 ± 0.87	12.80 ± 1.37	<0.01
	Aa average	12.72 ± 2.43	9.14 ± 0.96	<0.01
	E/Ea average	7.19 ± 1.63	5.40 ± 0.51	<0.01
	Ea/Aa average	0.74 ± 0.14	1.42 ± 0.23	<0.01
	Sa average	12.68 ± 2.44	9.89 ± 1.11	<0.01
Tricuspid annulus	Ea average	9.23 ± 1.29	11.99 ± 1.76	<0.01
	Aa average	13.83 ± 2.20	11.19 ± 2.88	<0.01
	E/Ea average	5.29 ± 1.14	4.67 ± 1.00	<0.05
	Ea/Aa average	0.68 ± 0.12	1.14 ± 0.29	<0.01
	Sa average	14.26 ± 2.94	11.11 ± 0.81	<0.01

Ea average: average peak early diastolic annular velocity; Aa: average peak late diastolic annular velocity; E/Ea: peak velocity of early filling/average peak early diastolic annular velocity; Sa: average peak systolic annular velocity

**Table 4.** Laboratory data of the patients and the control groups

	Group 1	Group 2	P value
Na mEq/L	131.83 ± 4.81	141.71 ± 1.99	<0.01
K mEq/L	4.64 ± 0.70	4.06 ± 0.24	<0.01
Creatinine mg/dL	1.15 ± 0.52	1.04 ± 0.15	NS
BUN mg/dL	26.34 ± 19.43	31.41 ± 10.30	NS
ALT U/L	36.93 ± 50.69	13.94 ± 2.08	<0.01
AST U/L	62.34 ± 72.89	13.82 ± 4.07	<0.01
T bil mg/dL	2.89 ± 3.54	0.51 ± 0.11	<0.01
D bil mg/dL	1.40 ± 2.20	0.12 ± 0.02	<0.01
Albumin g/dL	2.49 ± 0.67	4.21 ± 0.10	<0.01
WBCs	5.97 ± 2.84	5.82 ± 0.47	NS
Hb g/dL	10.61 ± 1.19	13.06 ± 0.62	<0.01
Platelets	122.10 ± 57.66	292.94 ± 54.97	<0.01
INR %	1.63 ± 0.49	1.03 ± 0.03	<0.01

NS: No significant

#### 4. Discussion

In the present study we found statistically significant increases in interventricular septum thickness (IVST), posterior wall thickness (PWT), and left ventricular mass (LVM) in patients with cirrhosis as compared to the control group. These results are supported by the results of Wong et al. and De Marco et al. (14, 15). Furthermore, Bernal et al. demonstrated a high prevalence of LV hypertrophy in cirrhotic patients as compared to controls (16). This is thought to be secondary to volume expansion and activation of various neurohormonal systems (renin-angiotensin system, endothelin-sympathetic stimulation) commonly observed in these patients (17). Additionally, we found that LVIDD significantly increased in Group 1 as compared to the control group, together with insignificant increases in LVIDs. Similar to our results, Finucci et al. (18) reported that cirrhotic patients have increased left ventricular end-diastolic diameters. The study of Eldeeb et al. (19) also showed significantly higher mean LVIDD and LVIDs diameters in a Child-Pugh C group of non-alcoholic liver cirrhosis patients as compared to Child-Pugh A and Child-Pugh B patients. Moller and Henriksen (20) reported increased left ventricular diastolic volumes in cirrhotic patients. Additionally, our study showed that the left atrium (LA) was significantly increased in Group 1 as compared to Group 2, which is in agreement with the results of Finucci et al. (18) and Bernal et al. (16).

Our study showed no statistically significant differences in FF% between the cirrhotic group and the healthy controls. In agreement with our study, Ziada et al. (21) showed that LVEF% does not differ among cirrhotic groups and controls. Furthermore, Eldeeb et al. (19) reported that the mean left ventricular systolic function parameters (ejection fraction and fractional shortening) were within normal range among the patients of the three child groups. Moreover, Baik et al. (22) reported that systolic function is preserved in cirrhotic patients with normal or even increased ejection fraction at rest. This study demonstrated significantly increased aortic root diameters in cirrhotic patients as compared with the controls. Our results are in agreement with the results of Alexopoulou et al. (23) who also found increased aortic root diameter in cirrhotic patients. This could be accounted for by cardiac adaptation to an increase of blood volume.

Regarding diastolic function of the left ventricle (mitral flow) by conventional Doppler echo, we found significant increases in A wave velocity, DT, and IVRT, together with significant decreases in E/A ratio in the cirrhotic group as compared to the control group. However, no significant difference in E wave velocity was noted between the two groups. It is well established that the mitral E-wave velocity primarily reflects the LA-LV pressure gradient during early diastole and is therefore affected by preload and alterations in LV relaxation (24). The mitral A-wave velocity reflects the LA-LV pressure gradient during late diastole, which is affected by LV compliance and LA contractile function. E-wave DT is influenced by LV relaxation, LV diastolic pressures following mitral valve opening, and LV compliance (i.e., the relationship between LV pressure and volume). Alterations in LV end-systolic and/or end-diastolic volumes, LV elastic recoil, and/or LV diastolic pressures directly affect the mitral inflow velocities (i.e., E wave) and time intervals (i.e., DT and IVRT). Møller and Henriksen (25) found that many patients with cirrhosis exhibit various degrees of diastolic dysfunction, which affects ventricular filling. Diastolic relaxation is then impaired, primarily because of the stiffening and/or hypertrophy of the LV, thus leading to decreased compliance and higher diastolic pressures as compared with the control subjects. Diastolic dysfunction occurs before systolic

dysfunction and may progress to systolic dysfunction (4). A previous Egyptian study (26) was made to assess the cardiovascular effect of HCV on Egyptian patients and found significant decreases in Doppler E waves, significant increases in A waves, and significant decreases in E/A ratios. This study agrees with our results, which found significant increases in Doppler A wave velocities and significant decreases in E/A ratios. Also, the study of Saleh et al. (27) reported increases in A wave velocities and deceleration times in hepatitis C patients. Pozzi et al. (28) found that in cirrhotic patients with tense ascites, the A wave velocity is markedly increased, the E/A ratio is markedly reduced, and the deceleration time is significantly prolonged. They noticed that removal of the ascitic fluid by rapid total paracentesis reduces the A wave velocity and increases the E/A ratio to values similar to those of cirrhotic patients without ascites, however these are still viewed as abnormal when compared with healthy control subjects. Finucci et al. (18) reported increased peak A velocities and deceleration times of E wave, as well as decreased E/A ratios in Child-Pugh class B and C cirrhotic patients. Wong et al. (14) reported prolonged isovolumic relaxation time in cirrhotic patients, irrespective of the presence of ascites, with significantly reduced E/A ratios only in ascitic subjects. Accordingly, they concluded that ascitic patients had thicker left ventricular walls and lower E/A ratios, thus indicating greater impedance to venous return than with pre-ascitic cirrhotic patients.

On the right side (tricuspid flow), our study showed significant increases in A wave velocities and DT, with significant decreases in E wave velocities and E/A ratios in the cirrhotic group as compared to the control group. Our study is in agreement with that of Soyoral et al. (9) in our findings of significant increases in A wave velocities with significant decreases in E wave velocities and E/A ratios in cirrhotic patients as compared to the control group. However, Soyoral et al.'s study revealed no significant increases in DT in cirrhotic patients as compared to the controls. Right ventricular diastolic dysfunction may be due to the decrease in cardiac preload, increase in the afterload, or impairment of right ventricular relaxation or other abnormalities in compliance.

Regarding our findings from pulsed wave tissue Doppler at the mitral annulus, there were statistically significant increases in the average Aa velocities and the average systolic wave velocities Sa, in addition to significant increases in the average E/Ea ratios in the patient group as compared to the control group. We also found a statistically significant decrease in the average Ea velocity and the average Ea/Aa in the patient group as compared with the controls. Our results are in agreement with the results of Saleh et al. (27) in findings of highly significant decreases of Ea/Aa and highly significant increases of E/Ea in hepatitis C patients. However, our findings disagree with Saleh's study in that we found highly significant increases in Aa peak velocities where they found highly significant decreases in Aa velocities. The discrepancy may be explained by a higher LV filling pressure in their patient base (higher E/Ea). The main hemodynamic determinants of Aa include LA systolic function and LVEDP, such that an increase in left atrium (LA) contractility leads to increased Aa velocity, whereas an increase in left ventricular end diastolic pressure (LVEDP) leads to a decrease in Aa. The study of Dadhich et al. (4) agrees with our study in finding highly significant decreases in Ea velocity, falls of the mitral annular Ea/Aa ratios, and highly significant increases in E/Ea in the cirrhotic groups (either pre-ascitic or ascitic) as compared to the controls. An average E/Ea ratio <8 identifies patients with normal LV filling pressures, whereas a ratio >13 indicates an increase in LV filling pressures (29). When the ratio is between 9 and 13, other measurements are essential. In our study, although E/Ea was significantly higher in the patient group as compared to the control group, it was marginally below the upper normal level, which means that left ventricular filling pressure is increased in liver cirrhosis, as compared to the control group, but is still at upper normal levels. In most studies of cirrhotic patients, the right ventricular pressure, pulmonary artery pressure, left atrial, and pulmonary capillary wedge pressure are all in the upper normal limit but within the normal range during rest (30). Dadhich et al. also found insignificant increases in the mitral annular S wave velocities of cirrhotic patients (pre-ascitic and ascitic) as compared to the healthy control subjects. Sa velocity measures long-axis ventricular motion because the longitudinally oriented endocardial fibers are most parallel to the ultrasound beam in the apical views. The increased S wave velocity at the mitral annulus may be due to increased contractility from hyperdynamic circulation that is usually present in liver cirrhosis. This is due to arteriolar vasodilatation with increased cardiac output, low arterial blood pressure, and decreased systemic vascular resistance. Pouriki et al. (31) concluded that left ventricular enlargement and higher systolic velocity at the mitral annulus both represent satisfactory indirect markers of hepatopulmonary syndrome (HPS). At the tricuspid annulus, we found statistically significant increases in average Aa velocity, E/Ea ratio, and systolic wave velocity Sa, together with statistically significant decreases in the average Ea and average Ea/Aa ratio in the cirrhotic group as compared to the controls. The studies done to explore right side diastolic dysfunction by tissue Doppler in cirrhotic patients are very scanty. The study of Dadhich et al. (4) revealed a statistically insignificant increase in the tricuspid annular S wave velocity in pre-ascitic and ascitic cirrhotic patients, together with an insignificant decrease in Ea/Aa ratios as

compared to the healthy controls, however, they did not measure E/Ea ratio. To the contrary, our results revealed that cirrhosis disrupts right ventricle diastolic functions. The significant increase in E/Ea ratio means significant increases in the right ventricular end-diastolic pressures in cirrhotic patients, as Sade et al. (7) confirmed. Sade et al. furthermore confirmed that measuring tricuspid E/Ea is a useful noninvasive method for estimation of RV filling pressure and for detecting serial changes under a wide range of clinical conditions; they found that  $E/Ea \geq 4$  correlates with  $RAP \geq 10$  mmHg with sensitivity 88% & specificity 85% (but not in status post-cardiac surgery). Utsunomiya et al. (8) found that tricuspid E/Ea ratio provides a reliable estimation of RV filling pressure and predicts cardiac events in patients with pulmonary arterial hypertension. Right atrial pressure is often slightly raised in cirrhosis especially in decompensated patients. Paracentesis has been shown to lower right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure, thus indicating that the transmural pressures may be normal (30). Karabulut et al. (32) reported that right ventricular diastolic dysfunction is more common in cirrhotic patients with hepatopulmonary syndrome than those without. Our study differs in that we did not measure oxygen saturation in order to diagnose hepatopulmonary syndrome. The study of Dadhich et al. (4) revealed a statistically insignificant increase in the tricuspid annular Sa wave velocity in pre-ascitic and ascitic cirrhotic patients. This complements our study in which we also found a statistically significant increase in tricuspid annular Sa wave velocity. Sa wave velocity has been reported to be significantly correlated with right ventricular ejection fraction and to reflect longitudinal RV movement (33, 34); the right ventricle contracts predominantly along the longitudinal plane rather than the short-axis plane in healthy subjects (35). Therefore, the significantly increased S wave velocity in the present study indicates that the right ventricular contractility in cirrhotic patients is not only preserved but is also increased, which may be due to hyperdynamic circulation and increased preload. S wave velocity is load dependent and may be pseudonormal under conditions of increased volume loading.

## 5. Conclusions

Liver cirrhosis disrupts cardiac structure and function. It causes left ventricular hypertrophy with increased left ventricular mass, left atrium dilatation, and diastolic dysfunction with preserved systolic function of both the right and left ventricles. Although conventional Doppler echocardiography can be used to diagnose diastolic dysfunction of the right and left ventricles, tissue Doppler is more sensitive in diagnosing diastolic dysfunction and can better assess filling dynamics than can conventional Doppler. In cirrhotic patients, left ventricular end-diastolic pressure (LV filling pressure) or left atrial pressure (as measured by mitral annular E/Ea) is in the upper normal limit during rest. Right ventricular end diastolic pressure (RV filling pressure) or right atrial pressure (as measured by tricuspid annular E/Ea) is slightly raised in cirrhosis. Myocardial systolic velocities of the mitral and tricuspid annuli are important and frequently overlooked components of systolic function, which can be sensitively and easily quantified with TDI. Cirrhotic patients may have increased peak S wave velocities at the mitral and tricuspid annuli, which may reflect increased left and right ventricular contractility possibly due to hyperdynamic circulation and increased preload. It is important to evaluate cardiovascular function and filling dynamics in every patient with cirrhosis, especially if the patient is a candidate for any intervention that may affect haemodynamics. Echocardiography with TDI has advantage to do this, as it is feasible, non-invasive and relatively inexpensive.

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## Conflict of Interest:

There is no conflict of interest to be declared.

## Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

## References

- 1) Daniel K, Podolsky, Curt J. Isselbacher. Cirrhosis and Alcoholic Liver Disease. Harrison's Principles of Internal Medicine 14 Th Edition 1997; 2: 1704
- 2) Sherlock S. Hepatic Cirrhosis. In: Disease of the liver and biliary System, ed 10. Oxford: Blackwell Scientific Publication, 1993;358-367
- 3) Abelmann WH, Kowalski HJ, McNeely WF. The circulation of the blood in alcohol addicts; the cardiac output at rest and during moderate exercise. Q J Stud Alcohol 1954;15:1-8

- 4) Dadhich S, Goswamia A, Jainb VK, Gahlotc A, Kulamarvaa G, Bhargavaa N. Cardiac dysfunction in cirrhotic portal hypertension with or without ascites. *Annals of Gastroenterology* 2014; 27, 1-6
- 5) Thomas H., Marwick. *Myocardial Imaging: Textbook on Tissue Doppler and SpeckleTracking*. Blackwell. ISBN: 978-1- 2007; 4051-6113-8.
- 6) Horton KD, Meece RW, Hill JC. Assessment of the right ventricle by echocardiography: a primer for cardiac sonographers. *J Am Soc Echocardiogr.* 2009 ;22(7):776-792. doi: 10.1016/j.echo.2009.04.027, PMID: 19560657
- 7) Sade LE, Gulmez O, Eroglu S, Sezgin A, Muderrisoglu H. Noninvasive estimation of right ventricular filling pressure by ratio of early tricuspid inflow to annular diastolic velocity in patients with and without recent cardiac surgery. *J Am Soc Echocardiogr.* 2007; 20: 982-988. doi: 10.1016/j.echo.2007.01.012, PMID: 17555928
- 8) Utsunomiya H, Nakatani S, Nishihira M, Kanzaki H, Kyotani S, Nakanishi N, Kihara Y, Kitakaze M. Value of estimated right ventricular filling pressure in predicting cardiac events in chronic pulmonary arterial hypertension. *J Am Soc Echocardiogr.* 2009 ;22(12):1368-1374. doi: 10.1016/j.echo.2009.08.023, PMID: 19944957
- 9) Soyoral Y, Süner A, Kızır V, Arıtürk Z, Balakan O, Halil Değertekin H, The effects of viral cirrhosis on cardiac ventricular function *Eur J Gen Med* 2004; 1(2): 15-18
- 10) Vinereanu D, Khokhar A, Fraser AG. Reproducibility of pulsed wave tissue Doppler echocardiography. *J Am Soc Echocardiogr.* 1999;12:492–499.
- 11) Carolyn Y, Scott D, Solomon. Clinician Update; A Clinician’s Guide to Tissue Doppler Imaging. *Circulation.* 2006;113:396-398. doi: 10.1161/CIRCULATIONAHA.105.579268, PMID: 16534017
- 12) Gottdiener J.S. Bendnarz I., Devereaux R. et al. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. *Journal of American Society of Echocardiography* 2004; 17:1086 :1119
- 13) Devereaux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *American Journal of Cardiology* 1986; 57: 450-458.
- 14) Wong F, Liu P, Lilly L, et al. Role of cardiac structural and functional abnormalities in the pathogenesis of hyperdynamic circulation and renal sodium retention in cirrhosis. *Clin Sci* 1999; 97:259–267.
- 15) De Marco M, Chinali M, Romano C, Benincasa M, D’Addeo G, D’Agostino L, de Simone G. Increased left ventricular mass in pre-liver transplantation cirrhotic patients. *J Cardiovasc Med* 2008; 9(2):142-146. doi: 10.2459/JCM.0b013e3280c7c29c, PMID: 18192806
- 16) Bernal V, Pascual I, Lanás A, Esquivias P, Piazuelo E, Garcia-Gil FA, Lacambra I, Simon MA. Cardiac function and aminoterminal pro-brain natriuretic peptide levels in liver-transplanted cirrhotic patients. *Clin Transplant.* 2012; 26: 111–116. doi: 10.1111/j.1399-0012.2011.01438.x, PMID: 21447142
- 17) Finucci G, Desideri A, Sacerdoti D, Bolongnesi M, Merkel C et al. Left ventricular diastolic function in liver cirrhosis. *Scand J Gastroenterol.* 1996; 31: 279-284.
- 18) Eldeeb M, Fouda R, Hammady M, Rashed L. Echocardiographic Evaluation of Cardiac Structural and Functional Changes in Hepatitis C Positive Non-Alcoholic Liver Cirrhosis Patients and Their Plasma NT-ProBNP Levels. *Life Science Journal,* 2012;9(1): 786-782.
- 19) Moller S, Henriksen JH. Cirrhotic cardiomyopathy: a pathophysiological review of circulatory dysfunction in liver disease. *Heart* 2002 ; 87:9-15.
- 20) Ziada D, Gaber R, NesreenKotb N, Ghazy M, Nagy H. Predictive Value of N-terminal Pro B-type Natriuretic Peptide in Tissue Doppler-Diagnosed Cirrhotic Cardiomyopathy. *Heart Mirror Journal.* 2011; 5(1):264-270.
- 21) Baik S, Fouad T and Lee S. Cirrhotic cardiomyopathy. *Orphanet Journal of Rare Diseases.* 2007; 2:15 doi: 10.1186/1750-1172-2-15.
- 22) Alexopoulou A, Papatheodoridis G, Pouriki S, Chrysohoou C, Raftopoulos L, Stefanadis C, Pectasides D. Diastolic myocardial dysfunction does not affect survival in patients with cirrhosis. *Transplant Internation* 2012; 25 (11):1174-1181. doi: 10.1111/j.1432-2277.2012.01547.x, PMID: 22909305
- 23) Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol.*1988; 12: 426–440.
- 24) Møller S, Henriksen JH. Cardiovascular dysfunction in cirrhosis. Pathophysiological evidence of a cirrhotic cardiomyopathy. *Scand J Gastroenterol.* 2001; 36: 785-794.



- 25) Haykal M, Negm H. Cardiovascular effects of HCV in Egyptian population. *CVD Prevention and Control J* 2009; 4 (suppl.1)
- 26) Saleh A, Akira Matsumori A, Negm H, Fouad H, Onsy A, Shalaby M, Hamdy E. Assessment of cardiac involvement of hepatitis C virus; tissue Doppler imaging and NTproBNP study *Journal of the Saudi Heart Association* 2011; (23): 217–223. doi: 10.1016/j.jsha.2011.04.005, PMID: 23960652 PMCID: PMC3727462
- 27) Pozzi M, Carugo S, Boari G, Pecci V, Ceglia S, Maggolini S, et al. Functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. *Hepatology*. 1997;26:1131–1137.
- 28) Rivas-Gotz C, Manolios M, Thohan V, Nagueh SF. Impact of left ventricular ejection fraction on estimation of left ventricular filling pressures using tissue Doppler and flow propagation velocity. *Am J Cardiol* 2003;91:780–4. doi: 10.1016/S0002-9149(02)03433-1
- 29) Ginés P, Arroyo V, Rodés J, Robert W, Schrier RW. Ascites and Renal Dysfunction in Liver Disease: Pathogenesis, Diagnosis, and treatment. 2nd edition Blackwell publishing. 2005:148-149
- 30) Pouriki S, Alexopoulou A, Chrysochoou C, Raftopoulou L, Papatheodoridis G, Christodoulos Stefanadis C, Dimitrios Pectasides D. Left ventricle enlargement and increased systolic velocity in the mitral valve are indirect markers of the hepatopulmonary syndrome. *Liver International* 2011; 31(9): 1388–1394. doi: 10.1111/j.1478-3231.2011.02591.x, PMID: 21771264
- 31) Karabulut A, Iltumur K, Yalcin K et al. Hepatopulmonary syndrome and right ventricular diastolic functions: an echocardiographic examination. *Echocardiography* 2006;23(4): 271–278. doi: 10.1111/j.1540-8175.2006.00210.x, PMID: 16640703
- 32) Wahl A, Praz F, Schwerzmann M, Bonel H, Koestner SC, Hullin R, et al. Assessment of right ventricular systolic function: comparison between cardiac magnetic resonance derived ejection fraction and pulsed-wave tissue Doppler imaging of the tricuspid annulus. *Int J Cardiol* 2011;151: 58-62. doi: 10.1016/j.ijcard.2010.04.089, PMID: 20537415
- 33) Meluzin J, Spinarova L, Bakala J, Toman J, Krejci J, Hude P, et al. Pulsed Doppler tissue imaging of the velocity of tricuspid annular systolic motion; a new, rapid, and non-invasive method of evaluating right ventricular systolic function. *Eur Heart J* 2001;22:340-8. doi: 10.1053/euhj.2000.2296, PMID: 11161953
- 34) Rushmer RF, Crystal DK, Wagner C. The functional anatomy of ventricular contraction. *Circ Res* 1953;1:162-70.
- 35) Howard LS, Grapsa J, Dawson D, Bellamy, Chambers JB, Masani ND et al. Echocardiographic assessment of pulmonary hypertension: standard operating procedure. *Eur Respir Rev* 2012; 21: 125, 239–248. doi: 10.1183/09059180.00003912, PMID: 22941889.