

**Systemic vascular resistance and fluid status in patients with decompensated liver cirrhosis with or without functional renal failure in Egypt**Ashraf Abd El-Khalik Barakat<sup>1</sup>, Fatma Mohammad Nasr<sup>1</sup>, Amna Ahmed Metwaly<sup>1</sup>, Maged El-Ghannam<sup>2</sup><sup>1</sup> Intensive Care Department, Theodor Bilharz Research Institute, Giza, Egypt<sup>2</sup> Gastroenterology and Hepatology Department, Theodor Bilharz Research Institute, Giza, Egypt**Type of article:** Original**Abstract**

**Background:** Functional renal failure and cardiovascular dysfunction are common complications of liver cirrhosis. This study aimed to evaluate cardiac performance, systemic vascular resistance (SVR) and fluid status in patients with decompensated liver cirrhosis either with or without functional renal failure.

**Methods:** Sixty patients diagnosed as having decompensated liver cirrhosis were divided into two groups. Group 1 included 30 patients with decompensated liver cirrhosis with ascites and with creatinine values  $\leq 1.5$  mg/dl. Group 2 included 30 azotemic decompensated cirrhotic patients with diagnostic criteria of hepatorenal syndrome (HRS). Also, 20 healthy subjects, of matched age and sex to the Group 1 and Group 2 patients, were included in the study as the control group. All patients and normal controls were subjected to clinical examination, laboratory evaluation, ECG, abdominal ultrasonography and echocardiographic studies.

**Results:** The echocardiographic and ECG data showed significant increase in LAD ( $P < 0.01$ ,  $P < 0.01$ ), AoD ( $P < 0.05$ ,  $P < 0.01$ ), interventricular septum thickness (IVST) ( $P < 0.01$ ,  $P < 0.01$ ), posterior wall thickness (PWT) ( $P < 0.01$ ,  $P < 0.01$ ), EDD ( $P < 0.01$ ,  $P < 0.01$ ), ESD ( $P < 0.05$ ,  $P < 0.01$ ), left ventricular (LV) mass ( $P < 0.01$ ,  $P < 0.01$ ), and Corrected QT (QTc) ( $P < 0.01$ ,  $P < 0.01$ ) interval with significant decrease in SVR ( $P < 0.01$ ,  $P < 0.01$ ). Additionally, there was significant decrease in IVC diameter in both patients groups compared to the control group ( $P < 0.01$ ,  $P < 0.01$ ).

**Conclusion:** Patients with decompensated liver cirrhosis have low SVR, and Doppler echocardiography provides an easy noninvasive tool to assess this finding. Also, these patients demonstrate small inferior vena cava (IVC) diameter with normal collapsibility, which indicates low effective plasma volume. Measuring IVC diameter and collapsibility are of value in the prediction of intravascular fluid status in liver cirrhosis. This is especially true with renal dysfunction. Early addition of oral vasoconstrictors in decompensated patients may correct the SVR and circulatory dysfunction and hinder HRS occurrence.

**Keywords:** Fluid status, Hepatorenal syndrome (HRS), Inferior vena cava (IVC) collapsibility, Liver cirrhosis, Systemic vascular resistance (SVR)

**1. Introduction**

Chronic liver diseases are amongst the top leading causes of death worldwide (1-3). Chronic liver diseases are characterized by unrelenting progression of liver inflammation and fibrosis over a prolonged period of time, usually more than 20 years, which may eventually lead to cirrhosis (4). Renal dysfunction is a common complication of liver cirrhosis with ascites, occurring in 20% of patients with cirrhosis who are admitted to a hospital (5). Most cases of renal dysfunction in cirrhosis are functional in nature (6). A wealth of evidence indicates that impairment in circulatory function is the main cause of renal dysfunction in cirrhosis. Some studies (7, 8) have found that patients with cirrhosis and ascites without hepatorenal syndrome show a typical circulatory pattern of increased total plasma volume, cardiac index and heart rate, along with reduced peripheral vascular resistance and arterial pressure. When hepatorenal syndrome develops, the mechanisms of further derangement of cardiovascular function become even

**Corresponding author:**

Fatma Mohammad Nasr. Intensive Care Department, Theodor Bilharz Research Institute, Giza, Egypt.

Tel: +20.1003542204, Email: fatma\_elwakeel@live.com

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more complex because a decreased cardiac function is also involved. Furthermore, studies performed by Tristani and Cohn (9) as well as Lebrec (10) have shown that a significant number of patients with hepatorenal syndrome exhibit arterial hypotension. These studies also indicated that reduced cardiac output with a tendency for peripheral vascular resistance is slightly higher in the aforementioned subjects than in ascitic subjects without hepatorenal syndrome. Cardiac failure in cirrhosis, named portal or cirrhotic cardiomyopathy (CCM), has a functional background and may disappear after liver transplantation. It comprises systolic and diastolic dysfunctions, mainly of the left heart chamber, and electromechanical abnormalities including a prolongation of the Q-T interval. Diastolic heart dysfunction precedes abnormalities of systolic cardiac performance (11). The histopathology of CCM is nonspecific and more evident in patients with ascites (12). Paracentesis may improve diastolic and systolic functions (13). The most common way to study LV systolic and diastolic functions is by echocardiography. For the analysis of diastolic function, the mitral E/A ratio has been analyzed in most reported studies of CCM, concluding that a ratio  $\leq 1$  is associated with increased mortality risk. A mitral E/A ratio  $\leq 1$  is present in 50–70% of patients with end stage liver disease (ESLD); this becomes more evident with disease progression (14, 15). By providing noninvasive correlates of intracardiac pressure and flow, Doppler echocardiography may offer a complete hemodynamic assessment to help guide diagnosis and treatment of patients who are critically ill.  $MRV/TVI_{LVOT} > 0.27$  had a 70% sensitivity and a 77% specificity to identify systemic vascular resistance (SVR)  $> 14$  WU.  $MRV/TVI_{LVOT} < 0.2$  had a 92% sensitivity and an 88% specificity to identify SVR  $< 10$  WU. Normal SVR  $> 10$  Wood units (WU) and  $< 14$  WU (16). The diameter of the IVC and the calculation of the caval index should be measured 3 cm from where it enters the right atrium. The inspiratory and expiratory diameter of the IVC can then be measured on the M-mode image, at the smallest and largest locations, respectively. In patients with decreased intravascular volume, the diameter of the IVC will be decreased and the percentage of collapse will be greater than 50%. With complete collapse, the IVC may become difficult to visualize. Volume overload patients with increased intravascular volume will have a large IVC diameter and minimal collapse on inspiration. In severe cases, there may not be any notable respiratory variation seen in M-mode (17).

The general objective of this study was to evaluate circulatory dysfunction in patients with decompensated liver cirrhosis either with or without functional renal failure. The specific objectives were to evaluate: 1) cardiac performance by echocardiography and electrocardiography, 2) systemic vascular resistance, and 3) fluid status in both patients groups and subsequently compare them to normal subjects and to each other.

## 2. Material and Methods

Sixty adult patients with cirrhosis and ascites were recruited from the Gastroenterology and Hepatology Department of the Theodor Bilharz Research Institute. The Ethical Committee of TBRI approved the study, and was conducted in accordance with Helsinki Declaration (1975). All participants gave written informed consent. The study was carried out in 2014 and 2015. Patients diagnosed as having liver cirrhosis caused by HCV infection were included in the study. These diagnoses were determined by clinical, biochemical and morphological sonographic criteria. Patients were divided into two groups. Group 1 included 30 patients (50%) with decompensated liver cirrhosis, with ascites and with creatinine values  $\leq 1.5$  mg/dl. Group 2 included 30 azotemic cirrhotic patients (50%) with ascites, with creatinine values  $> 1.5$  mg/dl, and with diagnostic criteria of HRS. The HRS diagnosis was established based on the 2007 International Ascites Club criteria: cirrhosis with ascites; serum creatinine  $> 1.5$  mg/dl; no improvement of serum creatinine (decrease  $< 1.5$  mg/dL) after volume expansion; absence of shock; no treatment with nephrotoxic drugs; absence of parenchymal kidney disease as indicated by proteinuria  $> 500$  mg/day, microhematuria ( $> 50$  RBCs/high power field), and/ or abnormal renal ultrasound scanning (18). A third group (Group 3) consisting of 20 healthy subjects (of matched age and sex to the Group 1 and Group 2 patients) was also included in this study as a control group.

Subjects with heart disease, pulmonary disease, diabetes mellitus, hypertension (blood pressure  $> 140/85$  mmHg), hyperlipidemia, any malignancy, alcohol consumption, pregnancy, HBV co-infection and liver malignancy were excluded. None of the patients were receiving any drugs that could interfere with the cardiovascular, hepatic or renal function, however the use of diuretics and/or beta-blockers was permitted. Treatment using diuretics or beta-blockers was temporarily discontinued for 3 days before the investigations in order to eliminate a pharmacological influence on cardiac work or volume status.

All patients and normal volunteers were subjected to thorough historical and physical examination. All patients were additionally subjected to blood sampling for comprehensive blood picture, including: hemoglobin percent, liver function tests, renal function tests, serum electrolytes, lipid profiles, HBs antigen and HCV antibody. Twelve lead

surface resting ECG were additionally performed on all subjects. The QT interval duration was manually calculated from the beginning of the q wave to the end of the T wave in all 12 leads. Moreover, the maximal QT interval duration was measured among these 12 leads. QT intervals were corrected (QTc: Corrected QT interval) in accordance with the rate using the BAZET formula:  $QTc = QT / \sqrt{RR}$ .  $QTc > 440$  ms was considered prolonged (19-20). Abdominal ultrasound scanning was performed on all participants using a Toshiba Nemo 30 scanner equipped with a 3.5 MHz linear transducer. These scans were carried out by one trained investigator who, it is important to note, was unaware of all other clinical and laboratory data. All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography (21), by more than one member of the study team, with an average was taken. M-mode, two dimensional echocardiography, and Doppler ultrasound studies (pulsed, continuous wave and color flow imaging) were made using a high resolution (ALT 5000 HDI) Toshiba Nemo 30 scanner equipped with a 2.5 MHz transducer. With M-mode, measurements of interventricular septum (IVS) and left ventricle posterior wall (PWT) thicknesses, separately at end diastole and end systole, were done. Furthermore, left ventricle end-diastolic (LVED) and end-systolic (LVES) diameters were determined. The size of the left atrium was determined from the parasternal long axis view at end systole. Left ventricular ejection fraction EF% was measured from M-mode dimensions using Teichholz formula (22).

With Doppler echocardiography accompanied by electrocardiogram, flow characteristics and rates of mitral, tricuspid, aortic and pulmonary valves were evaluated. Pulsed Doppler spectral recordings were obtained in the apical 4-chamber view from a sample volume positioned at the tips of the mitral leaflets. The transmitral, pulsed Doppler velocity recordings from 3 consecutive cardiac cycles were used to derive measurements using the peak values of E and A velocities. Impaired relaxation was defined as an E/A ratio  $< 1$  (23). The left ventricular (LV) outflow time-velocity integral ( $TVI_{LVOT}$ ) in centimeters was obtained by placing a pulsed wave sample volume in the LV outflow tract when imaged from the apical 3-chamber view. A continuous wave Doppler was used to determine peak mitral regurgitant velocity (MRV) in m/s from the apical 4-chamber view. The highest velocity obtained from multiple echocardiographic views was then used. Systemic vascular resistance was calculated from the equation  $SVR = MRV / TVI_{LVOT}$  (16).

Vena cava sonography was performed in the supine position with 2-dimensional guided M-mode echocardiography, using a 3.5 mhz ultrasound probe. From a subxiphoidal long axis view, the diameters were measured immediately in end-expiration (24). Most studies agree that the measurement should be distal to the junction with the right atrium and within 3 cm of that point (25-27). The inspiratory and expiratory diameter of the IVC can then be measured on the M-mode image, at the smallest and largest locations, respectively. In patients with decreased intravascular volume, the diameter of the IVC will be decreased and the percentage of collapse will be greater than 50%. With complete collapse, the IVC may become difficult to visualize. Patients with increased intravascular volume will have a large IVC diameter and minimal collapse on inspiration. In severe cases, there may not be any notable respiratory variation seen in M-mode (17).

### 3. Results

The demographic data of the patients groups (1&2) and the control group revealed mean ages  $43.5 \pm 9.95$ ,  $41.55 \pm 10.53$  and  $43.9 \pm 8.8$  years, respectively. In Group 1; 18 were males (60%) and 12 were females (40%). In Group 2; 20 were males (66.6%) and 10 were females (33.4%). In the control group; 12 were males (60%) and 8 were females (40%). There was significant decrease in both systolic & diastolic BP with increase in pulse rate in both patient groups (Groups 1 and 2) as compared to the control group ( $P < 0.01$ ). Moreover, there was significant decrease in systolic & diastolic BP in Group 2 as compared to Group 1 ( $P < 0.01$ ) (Table1).

There was an overall significant decrease in liver span as well as a significant increase in portal vein and spleen diameter in both patient groups as compared to the control group ( $P < 0.01$ ) (Table2). The electrocardiographic data showed a statistically significant increase in heart rate and QTc in both patient groups as compared to the control group and a statistically significant increase in QTc in Group 2 as compared to Group 1 (Table 2).

The laboratory data showed a significant increase in K, ALT, AST, total bilirubin (Tbil), direct bilitubin (Dbil), WBCs and INR with a significant decrease in Na, Alb and platelets in both patient groups as compared to the control group. Additionally, there was a significant increase in creatinine, BUN and WBCs with a significant decrease in Na, Albumin & platelets in Group 2 as compared to Group 1 (Table3).

**Table 1.** Demographic and clinical data of the studied groups, patients (groups 1, 2) and control (group 3)

Variables	Group1 (n=30) (mean±SD)	Group2 (n=30) (mean±SD)	Group3 (n=20) (mean±SD)	P1	P2	P3	
Age (year)	43.5±9.95	41.55±10.53	43.9±8.8	NS	NS	NS	
Gender	Male	18 (60%)	20 (66.6%)	12 (60%)	NS	NS	NS
	Female	12 (40%)	10 (33.4%)	8 (40%)	NS	NS	NS
Systolic BP (mmHg)	109.0±21.2	90.6±11.3	123.3±8.1	< 0.01	< 0.01	< 0.01	
Diastolic BP (mmHg)	68.8±12.5	59.0±8.4	78.7±4.2	< 0.01	< 0.01	< 0.01	
Pulse (beat/minute)	96.3±7.7	94.8±8.2	70.2±10.2	< 0.01	< 0.01	NS	

P1: value between groups 1&3; P2: value between groups 2&3; P3: value between groups 1&2; NS: not significant

**Table 2.** Abdominal sonar and electrocardiography of the studied groups, patients (group1, 2) and control (group3)

Variables	Group1(n=30) (mean±SD)	Group2(n=30) (mean±SD)	Group3 (n=20) (mean±SD)	P1	P2	P3	
Liver (cm)	12.3±1.8	12.2±1.9	14.6±0.5	< 0.01	< 0.01	NS	
Portal vein ( mm)	14.8±1.6	15.1±1.4	6.44±0.5	< 0.01	< 0.01	NS	
Spleen (cm)	16.2±1.7	16.3±1.5	8.6±1.6	< 0.01	< 0.01	NS	
Ascites	moderate 5 Tense 25	moderate 2 Tense 28	No ascites				
Kidneys	Normal	Normal	Normal				
ECG	Heart rate	98.3±9.7	95.8±8.6	71.2±7.2	< 0.01	< 0.01	NS
	QTc (msec)	458.35±19.2	472.53±26.7	391.14±9.6	< 0.01	< 0.01	< 0.01

P1: value between groups 1&3; P2: value between groups 2&3; P3: value between groups 1&2; NS: not significant

**Table 3.** Laboratory data of the patients (group1, 2) and control (group3)

Variables	Group 1 (n=30) (mean±SD)	Group 2 (n=30) (mean±SD)	Group 3 (n=20) (mean±SD)	P1	P2	P3
Na (mEq/L)	131.3±4.7	122.4±3.8	141.0±2.5	< 0.01	< 0.01	< 0.01
K (mEq/L)	4.8±0.5	4.9±0.8	4.0±0.2	< 0.01	< 0.01	NS
Creat( mg/dL)	1.1±0.5	2.8 ±0.8	1.0±0.2	NS	0.01	0.01
BUN (mg/dL)	23.4±17.2	55±19.3	21.0±10.3	NS	0.01	0.01
ALT (U/L)	31.9±31.3	33.2±36.9	13.6±2.1	0.01	0.01	NS
AST(U/L)	63.9±88.7	69±92.7	13.2±4.1	0.01	0.01	NS
T bil (mg/dL)	3.3±4.4	3.8±4.5	0.5±0.1	0.01	0.01	NS
D bil (mg/dL)	1.8±2.6	1.9±2.9	0.1±0.0	0.01	0.01	NS
Alb (g/dL)	2.5±0.8	2.1±0.7	4.1±0.1 <	0.01	0.01	0.05
Cholesterol (mg/dl)	145.1±34.3	150.3±36.2	152.2±16	NS	NS	NS
TG (mg/dL)	108.6±50.5	111.9±57.7	112.3±56	NS	NS	NS
Hb (gm/dl)	10.6±2.8	10.2±1.6	11.3±1.9	NS	NS	NS
WBCs	10.5±1.2	16.3±7.2	5.2±1.3 <	< 0.01	< 0.01	< 0.01
Platelets	126.7±60.4	89.3±37.6	270.2±90.8	< 0.01	< 0.01	< 0.01
INR	1.67±0.46	1.8±0.55	1.04±0.05	< 0.01	< 0.01	NS

P1: value between groups 1&3; P2: value between groups 2&3; P3: value between groups 1&2; Alb: Albumin, ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Creat: creatinine; D bil.: Direct bilirubin; Fbs: Fasting blood sugar; Hb: hemoglobin; INR: international normalized ratio; K: serum potassium; Na: serum sodium; T bil. : Total bilirubin; TG: Triglyceride; WBCs: white blood corpuscles; NS: not significant

The echocardiographic data showed a statistically significant increase in LA, Ao, IVST, PWT, EDD (P<0.01), ESD and LV mass in both patient groups as compared to the control group and a statistically significant decrease in early to late diastolic flow ratio (E/A ratio) in both patient groups as compared to the control group. A significant increase in LA and Ao was also demonstrated in Group 2 as compared to Group 1 (Table 4). There was significant decrease in SVR and IVC diameter in both patient groups as compared to the control group. There was normal IVC collapsibility in Group 1 and 2 and insignificant decrease in IVC collapsibility in Group 2 (Table 5).

**Table 4.** Echocardiographic data of the patients (group1, 2) and control (group3)

	Group 1 (n=30) (mean±SD)	Group 2 (n=30) (mean±SD)	Group 3 (n=20) (mean±SD)	P1	P2	P3
LA (cm)	3.8±0.5	4.1±0.6	3.4±0.3	< 0.01	< 0.01	< 0.05
AO (cm)	3.1 ±0.3	3.4±0.8	2.8±0.2	< 0.05	< 0.01	< 0.05
IVST (cm)	1.0±0.3	1.0±0.4	0.9±0.1	< 0.01	< 0.01	NS
PWT (cm)	1.0±0.1	1.0±0.2	0.9± 0.1	< 0.01	< 0.01	NS
EDD (cm)	5.3±0.6	5.5±0.8	4.5±0.3	< 0.01	< 0.01	NS
ESD (cm)	3.1±0.5	3.3±0.7	2.8±0.3	< 0.05	< 0.01	NS
EF %	66.6±8.3	64.8±8.4	68.8±7.2	NS	NS	NS
LV mass (gm)	182.8±53.1	184±54.1	136.8±28.8	< 0.01	< 0.01	NS
E velocity (m/s)	0.58± 0.26	0.59± 0.26	0.62 ±0.15	NS	NS	NS
A velocity (m/s)	0.65± 0.44	0.66±0.45	0.59 ±0.17	< 0.01	< 0.01	NS
E/A	E/A 0.9± 0.3	0.9± 0.4	1.1± 0.5	< 0.01	< 0.01	NS

P1: value between groups 1&3; P2: value between groups 2&3; P3: value between groups 1&2; Ao: aortic diameter; EDD: end diastolic dimension; EF: ejection fraction; ESD: end systolic dimension; IVST: interventricular septum thickness; LA: left atrium diameter; LVM: left ventricular mass; PWT: posterior wall thickness; NS: not significant

**Table 5.** Specific echocardiographic measurements of the patients (group1, 2) and control

Variables	Group 1 (n=30) (mean±SD)	Group 2 (n=30) (mean±SD)	Group 3 (n=20) (mean±SD)	P1	P2	P3
SVR	0.13±.03	0.12±.06	0.21±.04	< 0.01	< 0.01	NS
IVC (mm)	10.3±2.1	10.8±4.3	16.4±3.2	< 0.01	< 0.01	NS
IVC coll. (%)	51.2±8.3	48.5±4.6	53.2±2.3	NS	NS	NS

P1: value between groups 1&3; P2: value between groups 2&3; P3: value between groups 1&2; Coll: collapsibility; IVC: inferior vena cava; SVR: systemic vascular resistance; NS: not significant

#### 4. Discussion

In our study we found a significant decrease in both systolic & diastolic BP with a significant increase in heart rate in both patient groups as compared to the control group. Our results are in agreement with the results of Moller and Henriksen who found Hyperdynamic syndrome in patients with cirrhosis (28). Additionally, there was a significant decrease in systolic and diastolic BP in Group 2 (hepatorenal syndrome patients) as compared to Group 1. Hemodynamic studies performed by Tristani and Cohn (9) and Lebrec (29) have shown that a significant number of patients with hepatorenal syndrome exhibit arterial hypotension. In our study, there was a significant decrease in liver span and a significant increase in portal vein and spleen diameters in both patient groups as compared to the control group. This is in agreement with studies of Mandal, Sudha Rani and colleagues (31, 32). The electrocardiographic data in our study showed a statistically significant increase in heart rate and QTc in both patient groups as compared to the control group and a statistically significant increase in QTc in Group 2 as compared to Group 1. Our study agrees with other studies that showed similar findings (13, 32, and 33). Our study showed a significant decrease in Na in both patient groups as compared to the control group. Furthermore, there was a significant decrease in Na in Group 2 as compared to Group 1. These findings agree with many studies that have concluded that hyponatremia is common in patients with cirrhosis and ESLD, that it is associated with increased risk of morbidity and mortality in these patients, and that hyponatremia is also associated with the development of hepatorenal syndrome (34, 35). Hyponatremia is associated with numerous complications in liver disease patients, including severe ascites, hepatic encephalopathy, infectious complications, renal impairment, increased severity of liver disease, increased hospital stay, and neurologic/infectious complications post-transplant (36). The laboratory data in our study showed a significant increase in ALT, AST, Tbil, Dbil, WBCs and INR and a significant decrease in Alb and platelets in both patient groups as compared to the control group. This is a common finding in patients with liver cirrhosis (37). Also, there was a significant increase in creatinine, BUN and WBCs and a significant decrease in Na, Alb and platelets in Group 2 as compared with Group 1. Our study agrees with the study done by Fisher and Brown, which showed clinical onset of HRS with pre-renal features of low urine output in the absence of diuretics, urinary sodium excretion, dilutional serum hyponatremia, moderate hyperkalemia, and a rise in plasma creatinine concentration; with a subsequent decline in creatinine clearance as well as a decrease in Alb, platelets, and

an increase in WBCs in HRS; due to increased incidence of infection specially spontaneous bacterial peritonitis in these patients (38). Our echocardiographic data showed a statistically significant increase in LA diameter, Ao diameter, IVST, PWT, EDD, ESD, LV mass and a statistically significant decrease in early to late diastolic flow ratio (E/A ratio) in both patient groups as compared to the control group and a significant increase in LA and Ao diameters in Group 2 as compared to Group 1. Our findings agree with other studies on this matter: Grose et al., found an increase in EDV in patients with cirrhosis (39); Wong et al. found an increased left ventricle wall thickening in patients with cirrhosis (40). Other studies have found that patients with cirrhosis have altered hemodynamics leading to a hyperdynamic syndrome (41, 42). Increase in the left ventricle mass is a physiological response to the increased work as reflected by increased CO. The increased CO also explains why Child B patients showed a significant higher stroke volume, end systolic volume and end diastolic volume than Child A patients during stress. These are likely the earliest changes towards the hyperdynamic syndrome seen in advanced cirrhosis with decreased SVR, increased CO, increased left ventricular mass together with subtle hormonal changes (28, 43). In an autopsy study of 133 patients with cirrhosis, cardiomegaly and left ventricular hypertrophy were found in up to 43% of the patients (44). Similar to our results, Moller and Henriksen also reported an increase in both systolic and diastolic volumes of the left ventricle in cirrhotic patients (45). Also, Finucci et al. reported that cirrhotic patients demonstrate an increase in left ventricular end-diastolic, left atrium and stroke volumes (46). In our study, we found preserved systolic function in the patient groups with no change in ejection fraction between all three groups. This is in agreement with the study of Ginès who found no difference in systolic LV function in cirrhotic patients both with and without ascites, and those without renal failure or with HRS, despite marked differences in the activity of the renin-angiotensin system and sympathetic nervous system. These features indicate an impaired response of cardiac chronotropic and inotropic function to changes in systemic hemodynamics (47). Baik et al. reported that systolic function is preserved in liver cirrhosis patients with normal or even increased ejection fraction at rest (48). Similar to our results concerning diastolic function in cirrhotic patients, Moller and Henriksen and Sawant et al. concluded that cirrhotic patients have diastolic dysfunction with left ventricular hypertrophy, left atrial enlargement, isovolumetric relaxation time prolongation, and decreased early to late diastolic flow ratio (E/A ratio) (11, 49). In our study, there was a significant decrease in SVR in both patient groups as compared to the control group. Our results agree with a recent study that observed a statistically significant inverse correlation between SVR and all validated liver disease severity models (50). The exact mechanism of vasodilation with a drop in SVR in patients with decompensated liver cirrhosis is not yet fully understood. The most common implicated chemical mediator is nitric oxide (51). It has been postulated that endotoxemia in cirrhosis induces expression of nitric oxide synthase within the vessel walls. Nitric oxide synthesized in this way is a potent vasodilator with a profound impact on mean arterial blood pressure and SVR (52, 53). This vasodilatory effect is further exacerbated by inefficient hepatic clearance of nitric oxide due to portal-systemic shunting (54, 55). Other potential local vasodilatory mediators in cirrhosis include carbon monoxide (56), prostacyclin (57), and hydrogen sulfide (58). As cirrhotic patients progress from compensated to decompensated, with or without hepatorenal syndrome (HRS), there is a progressive decline in systemic vascular resistance and decreased blood pressure. Moreover, there is a progressive rise in plasma norepinephrine (NE), plasma renin activity, and arginine vasopressin (AVP), with resultant hyponatremia during progression of cirrhosis to HRS; all known risk factors for increased mortality in cirrhosis (59). Thus, the primary systemic arterial vasodilation hypothesis, causing arterial underfilling, has been proposed to explain the pathogenesis of renal sodium and water retention in cirrhotic patients (60). Therefore, SVR could, theoretically, be a predictor for severity of liver disease (61). In our study there was a significant decrease in IVC diameter in both patient groups as compared to the control group. There was normal IVC collapsibility in normal volunteers and patients with decompensated liver cirrhosis and ascites, with creatinine  $\leq 1.5$  (IVC collapsibility  $>50\%$ ). In patients with decompensated liver cirrhosis and ascites, with creatinine  $>1.5$ , there was an impairment in IVC collapsibility (IVC collapsibility  $<50\%$ ). Our study agrees with the study of Davenport who found that IVC diameter and IVC collapsibility are of value in the prediction of intravascular fluid status in liver cirrhosis especially with acute renal injury (ARI) (62). On the other hand, the study of Kitamura and Kobayashi found that interpretation of caval physiology is hindered by conditions that restrict the physiologic variability of the IVC; such as liver cirrhosis and fibrosis, masses causing external compression, and elevated intra-abdominal pressure (63). The finding of a small-diameter IVC with large inspiratory collapse (high caval index) correlates with low volume states. This phenomenon may be observed in hypovolemic and distributive shock states. Conversely, a large IVC with minimal collapse (low caval index) suggests a high volume state (64). A recent study suggested that every 1mL/kg of intravascular fluids (IVFs) administered should change the IVC collapsibility by 0.86 - 1.00%. This anticipated change in IVC diameter can be used to gauge a patient's response to intravascular volume repletion (65). The most effective method currently available for the management of HRS is the administration of vasoconstrictor drugs. The administration of midodrine, an orally

active  $\alpha$ -adrenergic agonist, in patients with cirrhosis and ascites, improved circulatory functions. This was indicated by an increase in arterial pressure and suppression of the activity of renin angiotensin and sympathetic nervous systems. Consequently, a marked improvement of circulatory function was observed, with associated increase in renal blood flow, glomerular filtration rate and urinary sodium excretion. No significant side effects were reported in short-term studies (66, 67). The addition of systemic oral vasoconstrictors that interfere with the early circulatory dysfunction of patients with decompensated cirrhosis and with decreased SVR, without waiting for the advent of renal impairment, may postpone HRS occurrence and improve survivals.

## 5. Conclusions

In conclusion, patients with decompensated liver cirrhosis have low systemic vascular resistance and that Doppler echocardiography provides an easy noninvasive tool to assess this resistance. Follow-up of SVR by Doppler echocardiography may be a predictor for severity of liver disease. Decompensated cirrhotic patients have a small IVC diameter with normal collapsibility, which indicates low effective plasma volume. Patients with hepatorenal syndrome may have decreased IVC collapsibility. Thus, measuring IVC diameter and collapsibility are of value in the prediction of intravascular fluid status in liver cirrhosis, especially with renal dysfunction. The addition of systemic oral vasoconstrictors that interfere with the early circulatory dysfunction of patients with decompensated cirrhosis and with decreased SVR, without waiting for the advent of renal impairment, may postpone HRS occurrence and improve survivals. Patients with decompensated liver cirrhosis have LV diastolic dysfunction and prolonged QT interval in the ECG with preserved systolic function. The reduced afterload, secondary to the systemic arterial vasodilatation, compensates for both a decreased preload and contractile dysfunction. Regular re-evaluation of cardiac status should be undertaken to minimize the risk of decompensation.

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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.

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