Annals of Gastroenterology (2023) **36,** 564-572

Prevalence of cirrhotic cardiomyopathy according to different diagnostic criteria: alterations in ultrasonographic parameters of both left and right ventricles before and after stress

Dimitrios S. Karagiannakis[a], Katerina Stefanaki[b], George Anastasiadis[c], Theodoros Voulgaris[a], Jiannis Vlachogiannakos[a]

Medical School of National and Kapodistrian University of Athens, "Laiko" General Hospital; School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital; "Laiko" General Hospital, Athens, Greece

Abstract

Background We estimated the frequency of cirrhotic cardiomyopathy (CCM) using all of the proposed diagnostic criteria, to describe the whole spectrum of cardiac alterations, and to investigate the role of stress in unmasking latent cases of CCM.

Methods Ninety consecutive patients were recruited. CCM was evaluated using the Montreal, the American Society of Echocardiography 2009 criteria, and the 2019 modified criteria of the CCM consortium. A dobutamine stress test was also performed.

Results Left ventricular diastolic dysfunction (LVDD) was identified in 72 (80%), 36 (40%), and 10 (11.1%) patients based on the above criteria, respectively. None of the patients had right ventricular systolic dysfunction, either at rest or after stress. The dobutamine stress test revealed left systolic dysfunction in 4 (4.5%) patients. There was agreement among the 3 criteria that the presence of LVDD was not associated with the severity of liver disease, using Child-Pugh stage. However, patients with Child-B/C had longer QTc intervals (P=0.004), higher levels of brain natriuretic peptide (P=0.016), and greater echocardiographic E/e' ratio (P<0.001) and E/e'(s) (P=0.003), compared to Child-A patients, while a significant correlation was demonstrated between Child-Pugh score and E/e' (P<0.001), or E/e'(s) (P=0.002).

Conclusions The prevalence of LVDD seems to be lower than previously considered. Right ventricular function seems to remain unimpaired. A dobutamine stress uncovered only a small percentage of patients with left systolic dysfunction. Nevertheless, the aggravation of several sonographic variables during stress, particularly in Child-B/C patients, potentially indicates a higher risk for clinical heart failure during stressful invasive interventions.

Keywords Cirrhotic cardiomyopathy, diastolic dysfunction, systolic dysfunction, dobutamine stress test, liver cirrhosis

Ann Gastroenterol 2023; 36 (5): 564-572

Conflict of Interest: None

Correspondence to: Dimitrios S. Karagiannakis MD, PhD, Academic Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, "Laiko" General Hospital, 17 Agiou Thoma street, 11527, Athens, Greece, e-mail: dkarag@med.uoa.gr

Received 6 April 2023; accepted 5 July 2023;
published online 20 July 2023

DOI: https://doi.org/10.20524/aog.2023.0824

A preprint version of this manuscript has been registered with the public server medRχiv (DOI: https://doi.org/10.1101/2022.11.02.22281851)

Introduction

In cirrhosis, liver dysfunction and the presence of portal hypertension result in splanchnic arterial vasodilation due to the overproduction, impaired degradation, and portosystemic shunting of vasodilator factors. The splanchnic arterial vasodilation and the reduced systemic vascular resistance leads to low blood pressure and reduced central blood volume with central or "effective" hypovolemia [1]. In order to compensate, the sympathetic nervous system is activated, leading to increased heart rate and output and to a hyperdynamic circulation. However, as liver dysfunction and portal hypertension aggravate, the splanchnic vasodilation worsens, and the increased heart rate and contractility are unable to further counterbalance the patient's hemodynamic circulation.

As a consequence, the renin-angiotensin-aldosterone axis is activated and vasopressin is released, to increase the blood pressure and the arterial blood volume [1]. Nonetheless, the hemodynamic state still remains extremely susceptible to factors that might influence the splanchnic arterial vasodilation, such as bacterial infections and overproduction of proinflammatory cytokines [2]. Furthermore, it seems that, along with the progression of the liver disease and the exacerbation of portal pressure, cardiac dysfunction also develops, leading to further arterial hypoperfusion and circulatory impairment [3]. This clinical entity is called "cirrhotic cardiomyopathy" (CCM) and is characterized by altered diastolic relaxation, electrophysiological abnormalities and impaired contractility, under physiological or pharmacological stress, all occurring in the absence of other known causes of cardiac disease [4-6]. Diastolic dysfunction seems to precede, while systolic dysfunction is rarely present at rest, as the ejection fraction (EF) is usually preserved because of the arterial vasodilation and the concomitant reduced afterload. Any systolic abnormality is often unmasked under physiological or pharmacological stress [7]. Until now, the clinical significance of CCM has been clarified only in cases of transjugular intrahepatic portosystemic shunt (TIPS) insertion, or liver transplantation [8,9], while its role in the prognosis of patients who do not undergo any invasive procedure remains debatable [10-13]. Moreover, there is disagreement amongst researchers about the prevalence of CCM, as different diagnostic criteria have been used for its evaluation in the studies published so far [14-16]. In 2016, the American Society of Echocardiography and the European Association of Cardiovascular Imaging proposed new guidelines for the diagnosis of left ventricular diastolic dysfunction (LVDD) in patients with normal EF [17], and recently Izzy *et al* modified these to make them more suitable for patients with cirrhosis [18]. The aim of this study was to evaluate the prevalence of CCM according to all of the proposed guidelines and to underline the differences between them. Furthermore, we aimed to investigate whether a dobutamine echocardiographic stress test, as well as the evaluation of right cardiac function, might uncover missing cases of CCM.

Patients and methods

Patients

Over a period of 18 months (July 2020-December 2021), consecutive patients aged from 18-80 years who attended our clinic with cirrhosis of any etiology and severity were considered for inclusion in the study. The diagnosis of cirrhosis was based on clinical and laboratory findings, endoscopy and imaging studies, and was confirmed by liver elastography. Only patients with liver stiffness ≥13 kPa by 2-dimensional shear wave elastography were finally included [19]. Exclusion criteria were history of arterial hypertension, chronic cardiac, pulmonary or renal disease, diabetes mellitus, active bacterial infection, recent gastrointestinal bleeding (<1 month), hepatocellular carcinoma, recent or active ethanol abuse (<6 months) [20], and treatment with drugs that could affect cardiac function or circulatory parameters, such as vasoactive drugs or nitrates. Active bacterial infection was ruled out by history, clinical examination, blood tests, culture of urine, chest radiograph, and in ascitic patients by culture and white cell count of ascitic fluid. Large-volume paracentesis was not performed in our ascitic patients during the last month before their recruitment in the study. Patients with alcoholic cirrhosis had prolonged periods of abstinence, confirmed by detailed history, discussion with relatives, and non-scheduled plasma alcohol determinations during their visits. Patients under treatment with β-blockers for the prevention of variceal bleeding had temporarily discontinued them at least 15 days prior to their cardiological assessment.

The study protocol conformed to the ethical guidelines in the 2000 revision (Edinburgh) of the 1975 Declaration of Helsinki, and was approved by the Ethics Committee of the "Laiko" General Hospital of Athens, Greece. Written consent was obtained from each patient.

Electrocardiography and echocardiography protocol

The resting electrocardiogram (ECG) was recorded by a conventional electrocardiograph (Cardioline ar 600, Italy). QT intervals were corrected (QTc) with Bazett's formula. Pulsed wave (PW) Doppler echocardiography with tissue Doppler imaging (TDI) (General Electric, Vivid 3, USA) was used to estimate the following cardiac parameters: heart rate (HR), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial volume (LAvol), left ventricular EF at rest, cardiac index (CI), systemic vascular resistance index (SVRI), peak early filling velocity during early ventricular diastole (E wave), late diastolic filling velocity during atrial systole (A wave), E/A ratio (E/A), deceleration time of the E wave (DT), isovolumetric relaxation time (IVRT), early diastolic mitral annular velocity from the septal side (e' septal), early diastolic mitral annular velocity from the lateral side (e' lateral), average early diastolic mitral annular velocity (e'av), E/e'av ratio (E/e'av), pulmonary artery systolic pressure (PASP), tricuspid regurgitation velocity (TRV), tricuspid annular plane systolic excursion (TAPSE), and systolic right ventricular function (SRV). After the assessment of cardiac function at rest, a dobutamine stress test was performed and CI after stress [CI(s)], early diastolic mitral annular velocity from the septal side after stress [e' septal(s)], E/e'av after stress [E/e'av(s)], TAPSE after stress [TAPSE(s)], systolic right ventricular function after stress [SRV(s)] and tricuspid regurgitation velocity after stress [TRV(s)], were evaluated. Three long-axis and 3 short-axis slices (basal, mid-ventricular and apical) were acquired in order to cover 16 myocardial segments [21]. Serum

[a]Academic Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, "Laiko" General Hospital (Dimitrios S. Karagiannakis, Theodoros Voulgaris, Jiannis Vlachogiannakos); [b]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, "Alexandra" General Hospital (Katerina Stefanaki); [c]Department of Cardiology, "Laiko" General Hospital (George Anastasiadis), Athens, Greece

brain natriuretic peptide (BNP) was estimated (BNP test kit-immunofluorescence assay; Getein Biotech, Inc). Dobutamine was infused intravenously at 3-min stages. The initial dose was 2.5 μg/kg/min, followed by a gradual increase to 5, 7.5, 10, and 20 μg/kg/min and, if needed, atropine injection to reach the maximum cardiac strain. Repeated short-axis and long-axis images were acquired at the end of each stage. During the dobutamine test, the patients' symptoms, HR, blood pressure and ECG were monitored. All examinations were performed by a single, experienced cardiologist (GA). The results were stored digitally and analyzed offline twice at different times. Differences were rarely found between the 2 measurements. If this happened, the average values were used.

Criteria for the diagnosis of LVDD

[a] Criteria of Montreal (2005) [22]:
E/A<1, or DT>200 msec, or IVRT> 80 msec
[b] Criteria of the American Society of Echocardiography (2009) [23]:
e' septal<8 cm/sec, e' lateral<10 cm/sec, LAvol≥34 mL/m^2
[c] Criteria of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (2016) [17], modified in 2019 by the CCM consortium [18]:
e' septal<7 cm/sec, E/e' septal≥15 cm/sec, LAvol>34 mL/m^2, TRV>2.8 m/sec

LVDD is defined as 3 of the above 4 parameters being abnormal. If there are 2 abnormal and 2 normal parameters, the LVDD cannot be assessed (indeterminate state), whereas if 1 parameter is normal and 3 abnormal, LVDD is excluded.

Left ventricular diastolic function was further assessed after a dobutamine stress test, to uncover any latent diastolic dysfunction not apparent at rest.

Criteria for the diagnosis of left ventricular systolic dysfunction (LVSD)

According to the Updated Recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging for Cardiac Chamber Quantification by Echocardiography in Adults [24], and the modified criteria of the CCM consortium (2019) [18], LVSD is defined by an EF≤50% at rest, or an absolute global longitudinal strain (GLS) by speckle-tracking echocardiography <18% at rest, while stress testing is no longer recommended. However, in the current study we did not measure GLS, as the technique was not available in our department, whereas a dobutamine stress test was necessary in order to assess left ventricular diastolic function during stress, as described above, and could also be used to assess right ventricular systolic function as described below. Thus, the diagnosis of LVSD was based on EF≤50% at rest, or on an inadequate increase in EF (ΔEF) or CI (ΔCI) of less than 10% at peak dobutamine infusion [22].

Criteria for the diagnosis of right ventricular systolic dysfunction (RVSD)

TAPSE<17 mm, or SRV<9.5 cm/sec at rest, or TAPSE(s) <17 mm, or SRV(s) <9.5 cm/sec during the dobutamine stress test [25,26].

Statistical analysis

Statistical analysis was performed using SPSS (SPSS software; SPSS Inc, Chicago, IL, USA). Quantitative variables were compared using the independent Student's *t*-test or the Mann-Whitney test for normally and non-normally distributed variables, respectively. Data are presented as mean ± standard deviation, or median (range) respectively. Qualitative variables were compared using the corrected chi-squared test or a 2-sided Fisher's exact test, as appropriate. The concordance of different diagnostic criteria was determined using the proportion of agreement, and inter-rater agreement kappa (k), which was interpreted as follows: <0.20, poor; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, good; and 0.81-1.00, very good. The relationship between parameters was estimated using Spearman's correlation coefficient. All tests were 2-sided and P-values <0.05 were considered to be significant.

Results

Demographic and clinical data

Over the study period 107 cirrhotic patients visited our clinic. Seventeen of them were excluded, as 3 were diagnosed with liver cancer, 5 had known heart disease (coronary artery disease, valvular disorders, etc.), 4 had arterial hypertension, and 5 had diabetes mellitus. Therefore, 90 patients were finally recruited, of whom 60 (66.7%) were male and 30 (33.3%) female. The median age was 55 (33-78) years. The patients' demographics are summarized in Table 1.

LVDD

According to the Montreal criteria [a], 72 (80%) patients had LVDD. Using the criteria of 2009 [b], 36 (40%) patients were diagnosed with LVDD. The agreement between the 2 methods was "good" (k value: 0.754; reclassification rate 11%, P<0.001). Based on the latest criteria of 2019 [c], 4/90 (4.45%) patients had LVDD, while 10/90 (11.1%) were characterized as "undetermined". The latter group of patients was further evaluated according to the proposed algorithm and 6 of the 10 were subsequently diagnosed with LVDD. Therefore, 10 of the 90 (11.1%) patients were diagnosed with LVDD at the end of the evaluation. The percentage of patients detected with LVDD did not change after the administration of dobutamine, as no new case of LVDD was revealed during stress. The agreement between the latest criteria

Table 1 Patients' characteristics

Characteristics	Patients (n=90)
Sex	
Male	60 (66.7%)
Female	30 (33.3%)
Age (years)	55 (33-78)
Etiology of cirrhosis	
Alcohol	48 (53.3%)
HBV/HCV	36 (40%)
NAFLD	6 (6.7%)
Child-Pugh score	6 (5-14)
Child-Pugh stage	
A	52 (57.8%)
B/C	36 (40%)
Unavailable	2 (2.2%)
MELD score	11 (6-27)

Variables are expressed as median (range) values

HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; MELD, model for end-stage liver disease

of 2019 [c] and those of Montreal [a] was "fair" (k value: 0.338; reclassification rate: 23%, P<0.001), while the agreement between the criteria of 2019 [c] and those of 2009 [b] was again "fair" (k value: 0.316; reclassification rate: 28.9%, P<0.001).

The presence of LVDD according to the Montreal criteria was not associated with the Child-Pugh stage (A vs. B/C; P=0.21) or the patient's sex (P=0.575), while it had a trend towards association with a non-alcoholic etiology of liver disease (P=0.071). The presence of LVDD according to the 2009 criteria [b] was significantly associated with male sex (χ^{2} 4.583; P=0.032) and a non-alcoholic etiology of liver disease (χ^{2} 5.030; P=0.032), but not with Child-Pugh stage (P=0.575). Based on the recent guidelines [c], the development of LVDD was not significantly associated with sex (P=0.447), etiology of cirrhosis (alcoholic vs. non-alcoholic) (P=0.505), or Child-Pugh stage (P=0.306).

LVSD and RVSD

Regardless of the criteria applied, LVSD was not detected at rest, as none of our patients had EF≤50%. Four patients (4.45%) were found to be incapable of increasing their CI adequately (ΔCI<10%) during the dobutamine stress test. No RVSD was noticed at rest, as not even a single patient had TAPSE<17 cm/sec, or SRV<9.5 cm/sec. No new case of RVSD was identified after stress testing, as TAPSE(s) and SRV(s) remained over 17 cm/sec and 9.5 cm/sec, respectively, in all patients.

Comparison of the ultrasonographic parameters between patients diagnosed with LVDD according to the latest guidelines [c] and those without

Patients with LVDD had significantly prolonged QTc (P=0.002), increased A (P=0.007), lower E/A (P=0.025), increased IVRT (P<0.001), lower e' septal (P<0.001), larger LAvol (P<0.001), higher TRV (P=0.009), and lower SVRI (P=0.04), compared to patients without LVDD. The former group of patients tended to be older (P=0.072), with higher BNP levels (P=0.081) and a lower e' lateral (P=0.064) compared to patients without LVDD, but the differences did not reach statistical significance. Regarding the dobutamine stress test parameters, patients with LVDD had statistically significantly lower e' septal(s) (P=0.012), lower SRV(s) (P<0.001), lower CI(s) (P=0.022), lower ΔCI (P=0.009) and lower ΔSRV (P<0.001), in comparison to patients without LVDD. The 2 groups had no differences in Child-Pugh (P=0.581) or model for end-stage liver disease (MELD) score (P=0.223). Table 2 summarizes the differences between the 2 groups of patients.

Differences in echocardiographic parameters between compensated and decompensated cirrhotic patients

Patients with Child-Pugh stage B/C had statistically longer QTc (P=0.004), greater E (P=0.032), higher BNP levels (P=0.016), higher A (P=0.001), higher E/e'av (P<0.001), greater SRV (P=0.018), higher CI (P<0.001), greater PASP (P=0.003), higher TRV (P=0.028), lower SVRI (P<0.001), greater E(s) (P<0.001), higher E/e'av(s) (P=0.003) and greater TAPSE(s) (P=0.021), compared to patients with Child-Pugh stage A. Table 3 highlights the differences in the comparing variables between the 2 groups.

Correlations between Child-Pugh score and sonographic parameters

A statistically significant positive correlation was verified between Child-Pugh score and QTc (rho=0.356, P=0.001), E (rho=0.29, P=0.006), BNP (rho=0.347, P=0.001), A (rho=0.379, P<0.001), E/e'av (rho=0.418, P<0.001), CI (rho=0.54, P<0.001), PASP (rho=0.278, P=0.009), E(s) (rho=0.418, P<0.001), E/e'av(s) (rho=0.321, P=0.002) and TAPSE(s) (rho=0.291, P=0.01), while a trend towards a positive correlation with TRV was determined (rho=0.209, P=0.051). A significant negative relationship was found between Child-Pugh score and SVRI (rho=-0.595, P<0.001).

Discussion

In cirrhosis, a hyperdynamic circulation is developed along with the aggravation of liver dysfunction and portal hypertension. Furthermore, in some patients a blunted cardiac function, defined as CCM, is also present, further enhancing the circulatory dysfunction of cirrhosis [7]. The prevalence of this entity remains controversial, as several studies have shown conflicting results [14-16]. Different criteria applied for the evaluation of CCM could probably explain this disagreement. According to the Montreal criteria [a], the

Table 2 Differences between patients with or without left ventricular diastolic dysfunction (LVDD)

Parameter	No LVDD	LVDD	P-value
Age (years)	55 (33-78)	70 (45-77)	0.072
HR (bpm)	76 (59-110)	81 (59-95)	0.979
QTc (msecs)	433 (368-492)	465 (449-497)	0.002
EF (%)	65 (56-75)	64 (57-74)	0.632
E (cm/sec)	76.5 (50-128)	64 (58-105)	0.354
BNP (pg/mL)	24.3 (5-286)	106 (5-369)	0.081
A (cm/sec)	76 (42-127)	101 (64-114)	0.007
E/A (ratio)	1 (0.6-2)	0.6 (0.56-1.4)	0.025
DT (ms)	220 (121-317)	233.5 (220-253)	0.182
IVRT (ms)	105 (70-130)	120 (118-127)	<0.001
TAPSE (mm)	24 (21-37)	23 (21-27)	0.109
e' septal (cm/sec)	8.9 (5.3-15.3)	6.5 (5-6.9)	<0.001
e' lateral (cm/sec)	12.4 (7.5-19.7)	10.5 (7-16.5)	0.064
E/e'av (ratio)	7.2 (3.7-13.6)	6.9 (6.6-10.6)	0.329
SRV (cm/sec)	16.5 (11.9-28)	15.4 (13.2-18.7)	0.248
CI (L/min/m^2)	3 (2.1-5.1)	3.3 (2.4-4.3)	0.08
LA (ml/m^2)	22.8 (12.1-36.2)	38.3 (24-42.9)	<0.001
LVEDD (mm)	50 (40-62)	49 (42-62)	0.562
LVESD (mm)	31 (22-37)	33 (24-37)	0.628
PASP (mmHg)	31.5 (18-43)	35 (30-45)	0.117
TRV (m/sec)	2.5 (1.8-3)	2.9 (2.5-3)	0.009
SVRI (dyn/sec/m^2/cm^{-5})	2425.5 (1355-3607)	1963 (1517-2606)	0.04
Child-Pugh score	6 (5-14)	7 (5-9)	0.581
MELD score	11 (6-27)	11 (8-16)	0.223
E(s) (cm/sec)	76 (50-182)	69 (49-137)	0.292
e' septal(s) (cm/sec)	10.5 (5.5-20.5)	8.3 (7.5-12.7)	0.033
e' lateral(s) (cm/sec)	13.5 (7.3-22)	12.9 (9.3-21)	0.355
E/e'av(s) (ratio)	6.3 (3.3-10.2)	6.9 (3.8-9.7)	0.258
TAPSE(s) (mm)	29 (21-34)	27 (23-28)	0.012
SRV(s) (cm/sec)	26.3 (16-41)	17.2 (12.3-25)	<0.001
CI(s) (L/min/m^2)	5.2 (2.4-10.5)	4 (3.5-8)	0.022
ΔSRV (cm/sec)	0.5 (0.03-1.8)	0.12 (-0.07 – 0.34)	<0.001
ΔTAPSE (mm)	0.14 (-0.18 – 0.42)	0.95 (0.04-0.17)	0.337
ΔCI (L/min/m^2)	0.8 (-0.04 – 2.5)	0.3 (0.13-0.86)	0.009
ΔE/e'av	-0.11 (-0.43 – 0.6)	-0.38 (-0.44 – 0.06)	0.681

Variables are expressed as median (range) values

HR, heart rate; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LA vol, left atrium volume; EF, ejection fraction at rest; CI, cardiac index; SVRI, systemic vascular resistance index; E, peak early filling velocity during early ventricle diastole; A, late diastolic filling velocity during atrial systole; DT, deceleration time of E wave; IVRT, isovolumetric relaxation time; e' septal, early diastolic mitral annular velocity from the septal side; e' lateral, early diastolic mitral annular velocity from the lateral side; e'av, average early diastolic mitral annular velocity; PASP, pulmonary artery systolic pressure; TRV, tricuspid regurgitation velocity; TAPSE, tricuspid annular plane systolic excursion; SRV, systolic right ventricular function; CI(s), CI after stress; e' septal(s), early diastolic mitral annular velocity from the septal side after stress; TAPSE(s), TAPSE after stress; SRV(s), SRV after stress; TRV(s), TRV after stress

prevalence of LVDD, which is the primary component of CCM, has been reported as up to 70% [7]. In a previous study from our group, using the 2009 criteria, a prevalence close to 37% was documented [15]. The current study showed a lower

Table 3 Comparison of patients according to the Child-Pugh stage

Parameter	Child-Pugh A	Child-Pugh B/C	P-value
Age (years)	57 (33-78)	57.5 (38-77)	0.476
HR (bpm)	77 (59-110)	78.5 (59-91)	0.646
QTc (msec)	428 (368-490)	454 (416-497)	0.004
EF (%)	65 (56-75)	65 (57-70)	0.125
E (cm/sec)	72 (53-119)	90 (51-128)	0.032
BNP (pg/mL)	18.5 (5-145)	46 (6.8-369)	0.016
A (cm/sec)	72 (42-120)	87 (53-127)	0.001
E/A (ratio)	1 (0.6-1.9)	0.9 (0.56-1.85)	0.234
DT (msec)	219 (121-262)	227.5 (169-272)	0.301
IVRT (msec)	111 (83-130)	100.5 (70-127)	0.172
TAPSE (mm)	24 (21-29)	25 (21-37)	0.066
e' septal (cm/sec)	8.9 (5.3-15.3)	8.4 (5-14.2)	0.164
e' lateral (cm/sec)	12.2 (8.8-19.7)	11.5 (7-17)	0.61
E/e' av (ratio)	6.7 (4.5-11.2)	9.3 (3.7-13.6)	<0.001
SRV (cm/sec)	15.3 (12.2-22.1)	17.1 (11.9-28)	0.018
CI (L/min/m^2)	2.9 (2.1-5.1)	3.3 (2.1-4.7)	<0.001
LA vol (ml/m^2)	23.3 (12.1-42.9)	24.4 (18.1-39.3)	0.164
LVEDD (mm)	49.5 (40-62)	51 (42-62)	0.232
LVESD (mm)	31 (22-37)	31 (24-37)	0.877
PASP (mmHg)	30 (18-45)	35 (30-43)	0.003
TRV (m/sec)	2.5 (1.8-3)	2.7 (2.3-3)	0.028
SVRI (dyn/sec/m^2/cm^{-5})	2527.5 (1396-3607)	1811 (1355-3580)	<0.001
E(s) (cm/sec)	74 (49-116)	83 (50-182)	<0.001
e' septal(s) (cm/sec)	10.2 (6.8-18.8)	10.5 (5.5-20.5)	0.396
e' lateral(s) (cm/sec)	13.2 (10-18.4)	13.9 (7.3-22)	0.659
E/e'av(s) (ratio)	6.1 (3.8-7.9)	8 (3.2-10.2)	0.003
TAPSE(s) (mm)	28 (21-34)	29 (23-34)	0.021
SRV(s) (cm/sec)	24 (12.3-41)	26.3 (13.3-41)	0.61
CI(s) (L/min/m^2)	5.1 (2.4-8)	5.3 (3.1-10.5)	0.3
ΔSRV (cm/sec)	0.53 (-0.07-1.8)	0.43 (0.001-1.32)	0.27
ΔTAPSE (mm)	0.13 (-0.18-0.42)	0.12 (-0.14-0.33)	0.853
ΔCI (L/min/m^2)	0.8 (-0.04-2.5)	0.66 (0.13-1.76)	0.241
ΔE/e'av	-0.07 (-0.44-0.3)	-0.15 (-0.43-0.06)	0.263

Variables are expressed as median (range) values

HR, heart rate; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LA vol, left atrium volume; EF, ejection fraction at rest; CI, cardiac index; SVRI, systemic vascular resistance index; E, peak early filling velocity during early ventricle diastole; A, late diastolic filling velocity during atrial systole; DT, deceleration time of E wave; IVRT, isovolumetric relaxation time; e' septal, early diastolic mitral annular velocity from the septal side; e' lateral, early diastolic mitral annular velocity from the lateral side; e'av, average early diastolic mitral annular velocity; PASP, pulmonary artery systolic pressure; TRV, tricuspid regurgitation velocity; TAPSE, tricuspid annular plane systolic excursion; SRV, systolic right ventricular function; Cis(s) CI after stress; e' septal(s), early diastolic mitral annular velocity from the septal side after stress; TAPSE(s), TAPSE after stress; SRV(s), SRV after stress; TRV(s), TRV after stress

prevalence of LVDD when, instead of the Montreal guidelines [a], those of 2009 [b] or the 2019 guidelines [c] were applied. Razpotnik *et al* have also reported this correspondence between the prevalence of LVDD and the criteria used for its evaluation. Thus, according to the Montreal criteria [a] the authors found a prevalence of 67%, which dropped to 35% and 7.5%, respectively, when the 2009 [b] and 2019 [c] criteria were applied [27].

The difference in prevalence of LVDD among the 3 criteria raises questions about which is the most accurate

for patients with cirrhosis. The recent 2019 [c] algorithm is more complicated, but probably more appropriate for the estimation of LVDD in cirrhotic patients, as it combines several factors that are less dependent on the alterations of preload and afterload that are affected in cirrhosis [18]. Nevertheless, it seems that, regardless of its good specificity, its sensitivity and negative predictive value (NPV) are moderate. Obokata *et al* reported sensitivity rates of 34% and an NPV of 53% in patients with diastolic dysfunction and preserved EF [28]. Ommen *et al* showed that the E/e', one of the components of the 2019 criteria, had excellent specificity in identifying increased filling pressures. Nevertheless, they also found that many patients with increased filling pressures had normal E/e'. This finding raised concerns about the sensitivity of this parameter. The authors concluded that an elevated E/e' strongly supports the existence of high left filling pressures and high pulmonary capillary wedge pressure, and thus LVDD, but a normal E/e' does not exclude LVDD [29].

The addition of a stress test has been considered to increase the sensitivity and the NPV of the method [28]. Moreover, it has been shown that abnormalities in diastolic function, possibly not apparent or mild at rest, are often induced or exacerbated during stress [30,31]. Therefore, we reevaluated diastolic cardiac function after the administration of dobutamine. Notably, not even a single patient without LVDD at rest, according to the 2019 criteria [c], fulfilled the criteria of LVDD during stress.

Concerning left ventricular systolic function, none of our patients was diagnosed with LVSD at rest. However, LVSD was revealed in a minority of them (4.5%) during stress, as they did not manage to increase their CI adequately (ΔCI<10%). As RVSD may be present in patients with otherwise normal left ventricular systolic function and preserved EF, we also evaluated the right ventricular systolic function [32,33]. Interestingly, no RVSD was verified at rest or during stress, though patients with LVDD had significantly lower TAPSE(s), SRV(s) and ΔSRV during stress, indicating a tendency towards RVSD.

Apart from the differences among the 3 guidelines, they all agree that the presence of LVDD is not associated with the severity of liver disease as expressed by the Child-Pugh stage. In a previous study from our group, using the 2009 criteria [b], we had already shown that patients with LVDD did not differ in their Child-Pugh or MELD score in comparison to those without LVDD [15]. Likewise, in the present study, patients with LVDD according to the latest criteria [c], had no significant differences in Child-Pugh or MELD score compared to those without LVDD. However, the significantly longer QTc, higher BNP and greater E/e'av and E/e'av(s) observed in Child-Pugh B/C patients, in addition to the significant correlation between the Child-Pugh score and each of the above parameters, indicate an aggravated LVDD in this group of patients. Apart from LVDD, the higher values of PASP, SRV and TAPSE(s) also demonstrate a more defective right ventricular systolic function. These findings are of great importance, as Child-Pugh B/C individuals are usually treated with TIPS implementation or liver transplantation, procedures with a poor outcome in the presence of cardiac dysfunction [34-36]. Consequently, these more advanced cirrhotic patients may need further cardiac evaluation, apart from the TDI test, before undergoing invasive interventions [37]. Cardiovascular magnetic resonance imaging (MRI) using dobutamine stress, which is considered a superior method, could probably be helpful in these cases [38]. However, its high cost and low availability rule out its use on a routine basis. Probably, the subgroup of Child-Pugh B/C patients with a concomitant prolonged QTc and/or high BNP, should have prioritization for a stress cardiac MRI preoperatively, as these parameters have been implicated in higher post-procedure mortality rates [39-41].

Our study had some limitations. First, the absence of a control group. However, our purpose was not to compare the prevalence of cardiac dysfunction between cirrhotic and non-cirrhotic patients, but to elucidate the prevalence of CCM in cirrhotic patients according to the different diagnostic algorithms. Second, systolic dysfunction was not evaluated by measuring GLS, which seems capable of identifying abnormal contraction patterns in the setting of an apparently normal EF [42]. Furthermore, Lang *et al* have shown that more than half of cirrhotic patients are diagnosed with LVSD when this method is applied [27]. This is a major limitation of our study. However, as has already been mentioned, GLS was unfortunately not available in our center.

On the other hand, our study has some strengths. To our knowledge, it is the first time that both left and right ventricular function have been evaluated in cirrhotic patients. Moreover, left ventricular diastolic function and right ventricular systolic function were estimated not only at rest, but also during stress.

In conclusion, the prevalence of LVDD is lower when estimated using the more recent guidelines, whereas the evaluation of left ventricular diastolic function after stress does not seem to increase the number of patients diagnosed with LVDD. However, Child-Pugh B/C patients present significant aggravation of left ventricular diastolic parameters during stress. Regarding LVSD, it seems to be absent at rest if assessed by TDI, while a small number of cases are revealed during the dobutamine stress test. Similarly, no RVSD is detected at rest. However, significant worsening of right ventricular systolic parameters during stress is demonstrated in subjects with LVDD. Our results increase the concerns about missing cirrhotics with cardiac alterations when the proposed guidelines are applied. It is probably better to evaluate diastolic cardiac function not only at rest, but also during stress, particularly when subjects with more advanced liver disease are being investigated. In addition, the systolic cardiac capacity must be estimated after the evaluation of both left and right ventricular systolic function, but further studies are needed in order to confirm this issue.

Summary Box

What is already known:

- There is a disagreement among the studies published so far regarding the prevalence of cirrhotic cardiomyopathy (CCM) due to the use of different diagnostic algorithms
- The optimal approach for the evaluation of CCM remains unclear
- It has not yet been investigated whether possible right ventricular dysfunction contributes to the development of CCM

What the new findings are:

- The most recent guidelines seem to have higher specificity but lower sensitivity compared to the previous ones
- According to the latest guidelines, the prevalence of left ventricular diastolic dysfunction was estimated to be <15%, lower than previously reported
- A dobutamine stress test revealed only a small percentage of patients with left systolic dysfunction
- Right ventricular diastolic and systolic function appear to remain intact, not only at rest but also during stress

References

1. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology* 2006;**43** (2 Suppl 1):S121-S131.
2. Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology* 2005;**41**:422-433.
3. Vlachogiannakos J, Saveriadis AS, Viazis N, et al. Intestinal decontamination improves liver haemodynamics in patients with alcohol-related decompensated cirrhosis. *Aliment Pharmacol Ther* 2009;**29**:992-999.
4. Møller S, Henriksen JH. Cirrhotic cardiomyopathy. *J Hepatol* 2010;**53**:179-190.
5. Alqahtani SA, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. *Semin Liver Dis* 2008;**28**:59-69.
6. Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. *J Hepatol* 2006;**44**:994-1002.
7. Karagiannakis DS, Papatheodoridis G, Vlachogiannakos J. Recent advances in cirrhotic cardiomyopathy. *Dig Dis Sci* 2015;**60**:1141-1151.
8. Debernardi Venon W, Lo Pumo S, Imperatrice B, et al. Transjugular intrahepatic portosystemic shunt in refractory ascites: clinical impact of left ventricular diastolic dysfunction. *Eur J Gastroenterol Hepatol* 2021;**33**:e464-e470.
9. Carvalheiro F, Rodrigues C, Adrego T, et al. Diastolic dysfunction in liver cirrhosis: prognostic predictor in liver transplantation? *Transplant Proc* 2016;**48**:128-131.
10. Ruíz-del-Árbol L, Achécar L, Serradilla R, et al. Diastolic dysfunction is a predictor of poor outcomes in patients with cirrhosis, portal hypertension, and a normal creatinine. *Hepatology* 2013;**58**:1732-1741.
11. Karagiannakis DS, Vlachogiannakos J, Anastasiadis G, Vafiadis-Zouboulis I, Ladas SD. Diastolic cardiac dysfunction is a predictor of dismal prognosis in patients with liver cirrhosis. *Hepatol Int* 2014;**8**:588-594.
12. Alexopoulou A, Papatheodoridis G, Pouriki S, et al. Diastolic myocardial dysfunction does not affect survival in patients with cirrhosis. *Transpl Int* 2012;**25**:1174-1181.
13. Merli M, Torromeo C, Giusto M, Iacovone G, Riggio O, Puddu PE. Survival at 2 years among liver cirrhotic patients is influenced by left atrial volume and left ventricular mass. *Liver Int* 2017;**37**:700-706.
14. Torregrosa M, Aguadé S, Dos L, et al. Cardiac alterations in cirrhosis: reversibility after liver transplantation. *J Hepatol* 2005;**42**:68-74.
15. Karagiannakis DS, Vlachogiannakos J, Anastasiadis G, Vafiadis-Zouboulis I, Ladas SD. Frequency and severity of cirrhotic cardiomyopathy and its possible relationship with bacterial endotoxemia. *Dig Dis Sci* 2013;**58**:3029-3036.
16. Almeida JG, Fontes-Carvalho R, Sampaio F, et al. Impact of the 2016 ASE/EACVI recommendations on the prevalence of diastolic dysfunction in the general population. *Eur Heart J Cardiovasc Imaging* 2018;**19**:380-386.
17. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;**29**:277-314.
18. Izzy M, VanWagner LB, Lin G, et al; Cirrhotic Cardiomyopathy Consortium. Redefining cirrhotic cardiomyopathy for the modern era. *Hepatology* 2020;**71**:334-345.
19. Barr RG, Wilson SR, Rubens D, Garcia-Tsao G, Ferraioli G. Update to the Society of Radiologists in Ultrasound Liver Elastography Consensus Statement. *Radiology* 2020;**296**:263-274.
20. Guillo P, Mansourati J, Maheu B, et al. Long-term prognosis in patients with alcoholic cardiomyopathy and severe heart failure after total abstinence. *Am J Cardiol* 1997;**79**:1276-1278.
21. Cerqueira MD, Weissman NJ, Dilsizian V, et al; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;**105**:539-542.
22. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;**28**:2539-2550.
23. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;**22**:107-133.
24. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**:1-39.
25. Modin D, Møgelvang R, Andersen DM, Biering-Sørensen T. Right ventricular function evaluated by tricuspid annular plane systolic excursion predicts cardiovascular death in the general population. *J Am Heart Assoc* 2019;**8**:e012197.
26. Kharbanda RK, Moore JP, Taverne YJHJ, Bramer WM, Bogers AJJC, de Groot NMS. Cardiac resynchronization therapy for the failing systemic right ventricle: A systematic review. *Int J Cardiol* 2020;**318**:74-81.
27. Razpotnik M, Bota S, Wimmer P, et al. The prevalence of cirrhotic cardiomyopathy according to different diagnostic criteria. *Liver Int*

2021;**41**:1058-1069.
28. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation* 2017;**135**:825-838.
29. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. *Circulation* 2000;**102**:1788-1794.
30. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. *BMJ* 2000;**321**:215-218.
31. Chattopadhyay S, Alamgir MF, Nikitin NP, Rigby AS, Clark AL, Cleland JG. Lack of diastolic reserve in patients with heart failure and normal ejection fraction. *Circ Heart Fail* 2010;**3**:35-43.
32. Puwanant S, Priester TC, Mookadam F, Bruce CJ, Redfield MM, Chandrasekaran K. Right ventricular function in patients with preserved and reduced ejection fraction heart failure. *Eur J Echocardiogr* 2009;**10**:733-737.
33. Gorter TM, van Veldhuisen DJ, Bauersachs J, et al. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:16-37.
34. Billey C, Billet S, Robic MA, et al. A prospective study identifying predictive factors of cardiac decompensation after transjugular intrahepatic portosystemic shunt: the Toulouse algorithm. *Hepatology* 2019;**70**:1928-1941.
35. Mester RA, Stoll WD. Cirrhotic cardiomyopathy and cardiac failure after liver transplantation: a case series. *Transplant Proc* 2021;**53**:2354-2357.
36. Liu H, Jayakumar S, Traboulsi M, Lee SS. Cirrhotic cardiomyopathy: Implications for liver transplantation. *Liver Transpl* 2017;**23**:826-835.
37. Dimitroglou Y, Aggeli C, Alexopoulou A, Mavrogeni S, Tousoulis D. Cardiac imaging in liver transplantation candidates: current knowledge and future perspectives. *J Clin Med* 2019;**8**:2132.
38. Sampaio F, Lamata P, Bettencourt N, et al. Assessment of cardiovascular physiology using dobutamine stress cardiovascular magnetic resonance reveals impaired contractile reserve in patients with cirrhotic cardiomyopathy. *J Cardiovasc Magn Reson* 2015;**17**:61.
39. Koshy AN, Gow PJ, Testro A, et al. Relationship between QT interval prolongation and structural abnormalities in cirrhotic cardiomyopathy: a change in the current paradigm. *Am J Transplant* 2021;**21**:2240-2245.
40. Li S, Hao X, Liu S, Gong Y, Niu W, Tang Y. Prolonged QTc interval predicts long-term mortality in cirrhosis: a propensity score matching analysis. *Scand J Gastroenterol* 2021;**56**:570-577.
41. Kwon HM, Moon YJ, Kim KS, et al. Prognostic value of B-type natriuretic peptide in liver transplant patients: implication in posttransplant mortality. *Hepatology* 2021;**74**:336-350.
42. Cimino S, Canali E, Petronilli V, et al. Global and regional longitudinal strain assessed by 2-dimensional speckle tracking echocardiography identifies early myocardial dysfunction and transmural extent of myocardial scar in patients with acute ST elevation myocardial infarction and relatively preserved LV function. *Eur Heart J Cardiovasc Imaging* 2013;**14**:805-811.