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Research paper

Liver stiffness as measured by transient elastography is a predictor of outcomes in patients with chronic heart failure with reduced, mid-range, and recovered left-ventricular ejection fraction

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ABSTRACT

Background: Transient elastography is a noninvasive method for assessing liver stiffness (LS), which can reflect right-sided filling pressure associated with passive liver congestion in patients with HF.
Methods: A prospective, single-center observational study in which LS was measured in consecutive ambulatory patients with heart failure with reduced, mid-range, and recovered left ventricular ejection fraction, between March 2018 and June 2019. Mean follow up was 219 ± 86 days. The primary endpoint was time to first event, which was defined as a composite of cardiovascular death or HF hospitalization.
Results: Eighty-five patients were included in the final analysis. Mean age was 62 ± 10 and 68% were male. Mean ejection fraction and median NT-proBNP were, respectively, 38.7 ± 14.3% and 1140 pg/mL (interquartile range 224.3–2810.3). The median LS for the entire population was 6.3 (2.5-41.2) kPa. LS correlated with NT-proBNP ($r = 0.46$; $p < 0.0001$), total bilirubin ($r = 0.47$; $p < 0.001$), direct bilirubin ($r = 0.43$; $p = 0.0001$), gama-glutamyl-transpeptidase ($r = 0.54$; $p < 0.0001$), and alkaline phosphatase ($r = 0.39$; $p = 0.0004$). A Receiver Operating Characteristic (ROC) curve was performed and a cut point of 5.9 kPa showed sensitivity of 80% and specificity of 64.1% with area under the curve of 0.73. Using Cox proportional hazard model (independent variables: LS as a continuous variable, age, gender, NT-proBNP, LVEF, and creatinine), only LS was independently associated with the primary endpoint (hazard ratio 1.05, 95% confidence interval 1.01-1.09; for each increment of one unit of LS).
Conclusion: LS correlates with biomarkers of myocardial stretch and several liver function tests and is an independent predictor of outcomes in ambulatory patients with HF.

1. Introduction

Heart failure (HF) is a clinical syndrome that courses with congestion manifested by lower limb edema, hepatomegaly, jugular venous distension, pulmonary crackles, orthopnea, nocturnal paroxysmal dyspnea, and fatigue. Additionally, patients with HF may present with signs of low cardiac output [1]. Impairment of cardiac function may lead to hepatic dysfunction [2], and identifying hepatic congestion is important for prognosis and guiding treatment. This evaluation can be performed by clinical, radiological, serological, or echocardiographic parameters [3]. Ultrasound hepatic elastography (HE) has emerged as a reproducible method to assess elasticity in liver cirrhosis by measuring the liver

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; CAP, controlled attenuation parameter; GGT, gamma-glutamyl transpeptidase; HF, Heart Failure; HE, Hepatic elastography; HFrEF, HF with reduced ejection fraction; HFmrEF, HF with mid-range ejection fraction; HFrecEF, HF with recovered ejection fraction; LS, liver stiffness; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type nautriuretic peptide; TE, transient elastography; US, abdominal ultrasonography; ROC, receiver operating characteristic; RO-AHFS, Roman Registry of Acute Heart Failure.

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shear wave velocity. However, recent studies have shown that loss of liver elasticity may indicate congestion in HF patients [4–6].

The prevalence of liver congestion in severe HF ranges from 15% to 65% [7,8]. Extensive fibrosis can be seen in chronic or severe cases [2,9], and increasing fibrosis stage can be extrapolated by increased liver stiffness (LS) as assessed by transient elastography [10]. Prognosis depends on the underlying cardiac disease, and increased LS is also associated with adverse outcome [11]. Atrophy or necrosis in the central third of the hepatic lobule and adjacent to the central vein can be found in liver biopsy in patients with HF. Furthermore, the portal areas become surrounded by a ring of fibrous tissue passing from the central vein to the central vein, which gives the appearance of reversed lobulation. This lesion is a frank cardiac cirrhosis [9].

LS has been shown to predict outcomes in hospitalized patients with HF. The role of this method in outpatients is scarce. Therefore, we aimed to analyze the prognostic role of LS as measured by transient elastography in ambulatory patients with chronic heart failure.

2. Methods

The investigation conforms with the principles outlined in the *Declaration of Helsinki* (*Br Med J* 1964; **ii:** 177). The study was submitted to the Research Ethics Committee of our hospital. The researchers obeyed the precepts established in Resolution No. 466, of December 12, 2012, of the National Health Council.

2.1. Patients

Between March 2018 and June 2019, 85 consecutive ambulatory patients from a heart failure center at a university hospital were included. Inclusion criteria were the presence of signs or symptoms of heart failure and at least one echocardiogram in the last five years showing left ventricular ejection fraction (LVEF) of <50%. According to the LVEF in the current echocardiogram, patients were classified into three groups: 1) HF with reduced ejection fraction (HFrEF, LVEF <40%); 2) HF with mid-range ejection fraction (HFmrEF, LVEF 40–49%); and 3) HF with recovered ejection fraction (HFrecEF, LVEF ≥50%). Exclusion criteria were known primary liver disease, acute hepatitis with elevated transaminases levels greater than 5 times the upper normal limits, end-stage chronic kidney disease, advanced cancer, severe ascites, and the presence of cardiac devices (due to safety concerns). All patients underwent a physical examination and clinical signs of congestion were evaluated using bedside assessment, which included the evaluation of the presence of orthopnea, jugular venous distension, ascites, hepatomegaly, and edema. Data were collected prospectively.

2.2. Transient hepatic elastography

Transient HE was performed on the day of ambulatory visit using the Fibroscan 502 Echosens (Paris, France), according to the standard protocol, in the supine position. Measurements were performed in the 9-11th intercostal spaces in the mid- or posterior axillary lines. At least 10 measurements were performed in each patient, and a success rate (the ratio of valid shots to the total number of shots) of >80% was considered acceptable. The results are expressed in kilopascals (kPa) and ranged from 1.5 to 75 kPa. Currently, no HF-specific cutoff values to grade congestive hepatopathy have been defined. For patients with primary liver diseases, the European Association for the Study of the Liver; Asociación Latinoamericana para el Estudio del Hígado Clinical Practice guidelines define LS ≤5.0 as normal, 5–13 as fibrosis, and >13 kPa as cirrhosis [12]. The controlled attenuation parameter (CAP) was used to assess the degree of steatosis. Values between 100 and 400 dB/m indicate mild steatosis and >400 dB/m indicate moderate to severe steatosis [12].

2.3. NT-proBNP

NT-proBNP was analyzed in whole blood within 6 h after collection. The dosage of NT-proBNP was determined using the Elecsys® system (Roche, Basel, Switzerland). The detection range of the system was 5–35,000 pg/mL. Patients with values above that cut had an actual NT-proBNP value determined by dilution with 2 test kits.

2.4. Liver function testing

Liver function tests included aspartate aminotransferase (AST, normal upper limit 40 U/L), alanine aminotransferase (ALT, 30 U/L), alkaline phosphatase (AP, 120 U/L), gamma-glutamyl transpeptidase (GGT, 65 U/L), and direct and indirect bilirubin (total bilirubin, 26 mg/dL).

2.5. Hepatic serologies

Serologies for hepatitis A, B, and C were performed using the Siemens Centaur XP device and with their chemiluminescent kits. According to the test results the patient was classified into one of the following categories: acute phase, chronic transmission, immunological window, post-vaccination or natural transmission.

2.6. Echocardiography

Transthoracic echocardiography was performed using the Siemens Acuson Cypress 20™ Cardiovascular System. LVEF was calculated using the Simpson method. The examinations were performed according to the recommendations of the European Association of Echocardiography and the American Society of Echocardiography.

2.7. Abdominal ultrasonography

Upper abdominal ultrasonography (US) was performed in patients with hepatic elastography >7.0 KpA (arbitrarily defined), to rule out primary causes of hepatic functional alterations using the compression technique graded through Philips HDI ultrasound device −4000 with low - and high-frequency transducers.

2.8. Clinical outcomes

Patients were followed up in our HF clinic with visits every month. When necessary, structured phone contacts with the patient or family members were made. All patients were followed up for at least 6 months. The endpoint was time-to-first-event, which was composed of a combination of cardiovascular death or HF hospitalization.

2.9. Statistical analysis

Categorical variables are presented as absolute and percentile values. Continuous variables are presented as mean and standard deviation, with the exception of non-normal variables, which are presented as median and interquartile range. The Kolmogorov-Smirnov test was used to evaluate the normality of the variables. For the correlation of the elastography data with the clinical and laboratory findings, a Pearson correlation test was performed for normal distribution, and Spearman test was performed for variables with no normal distribution. Receiver operating characteristic (ROC) curve analysis was used to determine the best liver elasticity cutoff for predicting events. Kaplan-Meier event-free survival curves were constructed and compared using the log-rank test. Cox proportional-hazards model was used to investigate the prospective association between liver stiffness and events during follow-up. Data were analyzed at a significance level of 5%. This was a convenience sample of consecutive patients, and no sample calculation was performed.

3. Results

Table 1 shows the baseline characteristics of the patients. As noted, there was a predominance of older men. Twenty-five patients (33%) had ischemic etiology, sixty-five patients (87%) were hypertensive, twenty-five had diabetes (33%), and most were NYHA functional class II. The mean ejection fraction was 38.7 ± 14.3%, and the majority had HFrEF.

Forty-four patients were taking enalapril (average daily dose 20 ± 12 mg), twenty-three patients on losartan (average dose 100 ± 15 mg), seventeen patients on sacubitril-valsartan (all 400 mg/day), eighty-six patients on spironolactone (all 25 mg/day), nine patients on ivabradine (all 10 mg/day), seventy-nine patients on carvedilol (mean dose 44 ± 10 mg), six patients on bisoprolol (10 ± 0 mg/day), nine patients on digoxin (0.125 ± 0), and fifty patients on furosemide (40 ± 58), of which twenty-two in used altered LS.

Sixty-eight patients (90%) had hepatitis A. Two patients had positive serology for hepatitis C virus, and ten patients for hepatitis B virus and sixteen were protected by the hepatitis B vaccine. Of these patients, only two with chronic hepatitis B had a previously known diagnosis. Of the 10 patients with hepatitis B virus, only two had positive anti-HBc and anti-HBe, with no positive anti-HBs for cure criteria. Chronic patients were excluded from the elastography analysis.

Twenty-eight (30%) patients out of the 93 patients in the screening period had LS >7.0 kpA and underwent the abdominal US to rule out primary liver disease. Of these, two patients had nodular heterogeneity and were referred for abdominal magnetic resonance imaging for investigation (both patients were excluded from the analysis). In the remaining patients, resonance findings were consistent with homogeneous hepatomegaly, suggesting congestive hepatopathy.

The median LS for the entire population was 6.3 (ranging from 2.5 to 41.2) kPa, with a success rate greater than 80%. Fig. 1 shows the linear correlation between liver elastography cardiac and liver function biomarkers. As observed, LS correlated positively with NT-proBNP ($r = 0.46$; $p < 0.0001$), total bilirubin ($r = 0.44$; $p < 0.0001$), direct bilirubin ($r = 0.43$; $p = 0.0001$), GGT ($r = 0.54$; $p < 0.0001$), and alkaline phosphatase ($r = 0.39$; $p = 0.0004$).

Fig. 2 shows the ROC curve. A cutoff point of 5.9 kPa had the best accuracy to predict the primary outcome of death or hospitalization, showing a sensitivity of 80% and specificity of 64.1%, and area under the curve of 0.73 (95% confidence interval 0.62 to 0.82). Clinical and laboratory data in patients above and below this cutoff are shown in Table 2. As demonstrated, patients with higher LS values had lower LVEF, lower serum albumin levels, and were more likely to have abnormal liver and renal function tests. NT-proBNP levels were significantly higher in patients with altered elastography. However, no difference was observed regarding clinical signs of congestion.

Table 1
Baseline characteristics of the study population (n = 85).

Characteristics	Results
Age (years)	63 ± 12
Male sex	58 (68%)
Left ventricle diastolic diameter (mm)	61 ± 18
Left ventricle systolic diameter (mm)	49 ± 14
LVEF in the HFrEF group (n = 46)	29.5 ± 6.5
LVEF in the HFmrEF group (n = 23)	41 ± 3.7
LVEF in the HFrecEF group (n = 16)	55.5 ± 7.2
Ischemic etiology	17 (18%)
Hypertension	64 (68%)
Diabetes mellitus	25 (26%)
Current smoker	20 (21%)
Alcoholism	21 (22%)
COPD/Asthma	17 (18%)
NYHA functional class	2 ± 1
Systolic blood pressure (mmHg)	120 ± 24
Diastolic blood pressure (mmHg)	72 ± 12
Heart rate (bpm)	72 ± 16
Ascites	10 (12%)
Hepatomegaly	9 (10%)
Lower limb edema	16 (19%)
Jugular venous distension	18 (11%)
BMI ($kg.m^{-2}$)	27 ± 5

BMI = body mass index; COPD = chronic obstructive pulmonary disease; HFrEF = heart failure with reduced left ventricle ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFrecEF = heart failure with recovered ejection fraction; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association.

The mean follow-up period was 219 ± 86 days. During this period, 3 deaths and 20 HF hospitalizations were observed. Among the 3 deaths, 1 occurred in a patient below the LS cutoff (4.0 kPa) and 2 occurred in patients with LS above the cutpoint (6.1 and 11.5 kPa). Fig. 3 shows the Kaplan-Meier event-free survival curves for patients with LS values above and below the cutoff identified by the ROC curve. The mean event-free survival time for patients above and below this cutoff was 215.2 ± 20 vs. 301.7 ± 7.3 days ($p < 0.0001$). Using the Cox proportional hazard model (independent variables: LS as a continuous variable, age, sex, NT-proBNP, LVEF, and creatinine), only LS was independently associated with the primary outcome (hazard ratio 1.5, 95% CI 1.01-1.09 for each increment of one LS unit).

The CAP values for the entire population were 219.3 ± 60.6 dB/m. A positive correlation was observed between CAP and body mass index (BMI; $r = 0.43$; $p = 0.0001$), and an inverse correlation was observed between CAP and NT-proBNP ($r = -0,37$; $p = 0,0007$). Patients with CAP ≤169 dB/m had worse outcomes, with a 6-month event-free survival probability of 56% vs. 81% above this cutoff ($p = 0.0087$).

4. Discussion

In the present study, we found a low prevalence of liver comorbidities in patients with chronic HF. In addition, we found a large number of patients with high LS, which was not associated with primary liver disease, suggesting that these results are consistent with hepatic congestion caused by HF. To the best of our knowledge, this is the first study to assess liver stiffness as a prognostic marker in stable patients with chronic HF. All previous studies were conducted on acute decompensated HF or patients with HF hospitalization within the last month.

Many patients with severe HF have abnormal liver function tests, which are usually attributed to chronic liver congestion or ischemic liver disease in acute HF [13,14]. Our data confirmed this finding since the prevalence of associated liver disease was low.

Hepatic elastography was initially proposed to evaluate primary liver disease [12,15]. Liver stiffness has been investigated in congestive states, such as HF. Many patients with decompensated HF have high LS values upon admission, which has been associated with congestion, cardiac liver cirrhosis, and increased mortality. The mortality rate in acute HF patients with LS above 8.0 kPa has been reported to be 20.8% [16]. There is no defined cutoff for LS in this scenario, and values from 8.0 to 14 have been reported in studies on acute HF [4–6,16–20].

The majority of studies suggest that patients with acute HF have high liver stiffness values, usually above 7.65 kPa, which correlates with NT-proBNP levels. These values decrease after decongestion [20]. Natriuretic peptides are released from the heart in response to ventricular stretch and other hemodynamic and inflammatory stimuli, and high levels are observed in advanced HF and congestive states [21]. In our study, carried out in ambulatory chronic HF patients, the same relationship was observed, suggesting that even in chronic stable patients with HF, LS can reflect the degree of congestion. As a matter of fact, one experimental animal study [22] and one study in children referred for right heart catheterization [23] have demonstrated that LS correlates with central venous pressure.

An important correlation between LS and echocardiographic markers of increased venocapillary pressure has also been reported. In one study, LS was a useful index to assess systemic volume status, correlating with the large inferior vena cava diameter, serum direct bilirubin, and B-type natriuretic peptide levels. They could predict the

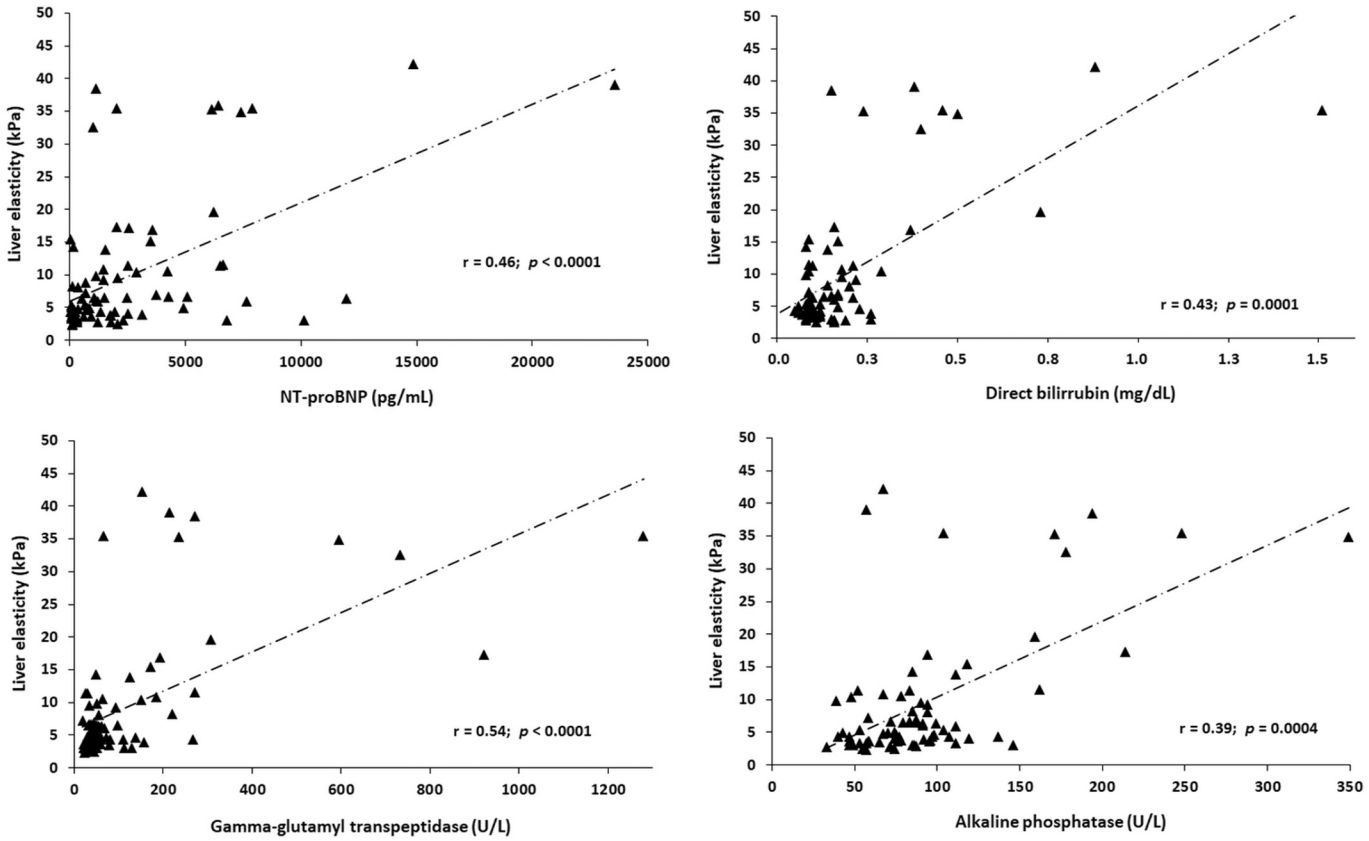

Fig. 1. Correlation of liver stiffness with NT-proBNP and liver function biomarkers.

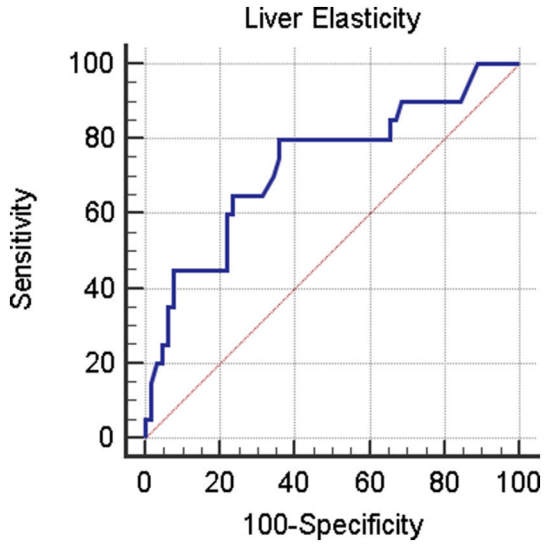

Fig. 2. Use of ROC curve to determine the performance of liver stiffness in discriminating events. For a cutoff >5.9 kPa, the sensitivity was 80% and specificity was 64.1%. Area under the curve = 0.73 (95% confidence interval 0.62 to 0.82).

severity of HF and the presence of liver congestion at discharge [19].

In patients with passive hepatic congestion, biochemical parameters of liver function are frequently elevated, usually 2 to 3 times the upper normal reference level. This finding may be due to increased cardiac filling pressures or low cardiac output with impaired organ perfusion [24]. In the present study, gamma-glutamyl transpeptidase and direct bilirubin were above reference levels, correlating with LS, and ratifying the expected changes in hepatic congestion even in ambulatory HF patients [5,6,10,18]. Of note, these variables correlated with the degree of systemic congestion and greater severity of the disease, as assessed by NT-proBNP [13].

Sloveva et al. demonstrated a moderate association of liver stiffness with clinical congestion and volumetric overload, as assessed by bioimpedance electrical vector analysis (BIVA). In that study, LS did not correlate with the degree of histologic liver fibrosis [5,6]. In another study, LS correlated with the severity of HF, as assessed by natriuretic peptide levels, in patients with acute HF [10]. This relationship between liver function and the severity of HF was also confirmed in the Roman Registry of Acute Heart Failure (RO-AHFS), where transaminases were higher in patients receiving higher doses of intravenous diuretics and in those using inotropes and vasopressors, being an independent predictor of worsening renal function and admission to intensive care [25].

There are several inflammatory interactions between the liver and the heart that involve congestion, ischemia, fibrosis, and even cirrhosis in the different stages of HF [2,7,8]. However, HE cannot differentiate transient changes from elevated venous pressures from the fibrosis that happens in later stage of the disease [22,23].

Hepatic fibrosis is a frequent finding in patients with severe HF. In one study, where liver biopsy was performed in patients considered for ventricular assist devices or heart transplant, hepatic fibrosis was found in 79.7% of the patients and, of these, 47% had severe fibrosis (grade 3 or 4) [26]. Patients with no or mild fibrosis on transjugular liver biopsy were more likely to undergo ventricular assist device or heart transplant than patients with severe fibrosis.

Hepatic ischemia reperfusion in HF and hepatic congestion are mechanisms of liver injury, related to activation of Kupffer cells, polymorphonuclear cells, intracellular calcium overload, cytokines and chemokines, oxidative stress, mitochondrial damage, disruption of liver microcirculation, and the absence of valves in hepatic veins allows

Table 2
Clinical characteristics of the study population according to liver stiffness values (n = 85).

Characteristics	E > 5.9 kPa (n = 37)	E ≤ 5.9 kPa (n = 48)	p-Value
Functional class (NYHA)	2.0 ± 0.65	2.0 ± 0.59	0.59
LVEF (%)	35 ± 10.8	38 ± 13.2	0.26
Jugular venous distension	11 (28%)	7 (17%)	0.22
Ascites	7 (19%)	7 (17%)	0.81
Hepatomegaly	7 (19%)	5 (10%)	0.23
Lower limb edema	11 (28%)	11 (13%)	0.08
Furosemide dose (mg)	40 ± 62.6	40 ± 55.2	1.00
Furosemide	24 (65%)	23 (48%)	0.12
Hemoglobin (g/dL)	12.9 ± 1.9	13.2 ± 1.6	0.43
Hematocrit (%)	39.5 ± 5.57	40.05 ± 5.46	0.67
Platelets (10^3/mm^3)	179.5 ± 58.9	199 ± 76.6	0.20
Leukocytes	6400 ± 2292	6000 ± 1642.2	0.35
Albumin (g/dL)	3.55 ± 0.55	3.8 ± 0.28	0.007
Blood Glucose (g/dL)	102.5 ± 83.2	105 ± 43.2	0.85
Glycated Hemoglobin	6.5 ± 2.27	5.9 ± 1.11	0.11
AST (U/L)	25 ± 13	23.5 ± 8.3	0.51
ALT (U/L)	28 ± 37	26 ± 16.7	0.73
ALP (U/L)	89 ± 62.2	74 ± 23.5	<0.0001
GGT (U/L)	93 ± 63.9	44 ± 46.9	0.0001
Total bilirubin (mg/dL)	0.60 ± 0.80	0.45 ± 0.31	0.23
Direct bilirubin (mg/dL)	0.20 ± 0.30	0.10 ± 0.05	0.02
Indirect bilirubin (mg/dL)	0.41 ± 0.46	0.33 ± 0.58	0.49
INR	1.27 ± 7.35	1.2 ± 0.74	0.94
Urea (mg/dL)	45.5 ± 28.6	44.5 ± 46.1	0.90
Creatinine (mg/dL)	1.40 ± 1.10	1.03 ± 0.40	0.03
Sodium (mEq/L)	138 ± 3.09	138 ± 2.05	1.00
Potassium (mEq/L)	4.5 ± 0.42	4.6 ± 0.52	0.34
Triglycerides (mg/dL)	88.3 ± 63.4	108 ± 71.3	0.18
Total cholesterol (mg/dL)	173 ± 45.5	181 ± 55.2	0.47
LDL (mg/dL)	102 ± 29.9	105 ± 43.4	0.72
HDL (mg/dL)	40.5 ± 20.1	45 ± 19.6	0.30
Troponin (ng/mL)	0.04 ± 0.03	0.01 ± 0.38	0.63
NT-proBNP (pg/mL)*	2012.2 (1125.4–4861.3)	634.1 (93.2–1137.1)	<0.0001

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transpeptidase; HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction. * Median and interquartil range.

increased inferior vena cava pressure. The major damage occurs in zone 3 of the Rappaport acinus, which surrounds the central vein, a consequence of centrilobular congestion and perivenular in the periportal region. After these, deposition and spread of connective tissue can lead to cirrhosis [27].

Due to the poor clinical correlation of signs of systemic congestion with elastography data, it can be inferred that subclinical congestion may be present or other inflammatory mechanisms may be related to the "cardiac liver," leading to worse prognosis in chronic HF. Recently, it has been shown that the liver X receptor is related to the development of heart failure and comorbidities and may be considered as an essential regulator of lipid and glucose metabolism and inflammation associated with fibrosis remodeling [7].

Based on the results of the present study, LS may be a method for assessing the risk of death or hospitalization in patients with HF and may be useful for monitoring treatment response, as an early marker of prognosis. The primary endpoint in this study was driven primarily by HF hospitalization. As a result, we conclude that HE is an accurate method to predict hospitalizations in chronic HF, but the performance to predict death is less clear.

Some limitations of our study must be addressed. First, this is a single-center study, and one should be careful when generalizing the data. Second, a small number of patients were included, which may have caused beta-type errors due to the lack of study power. Therefore, the results of this study need to be confirmed in a larger population of chronic HF.

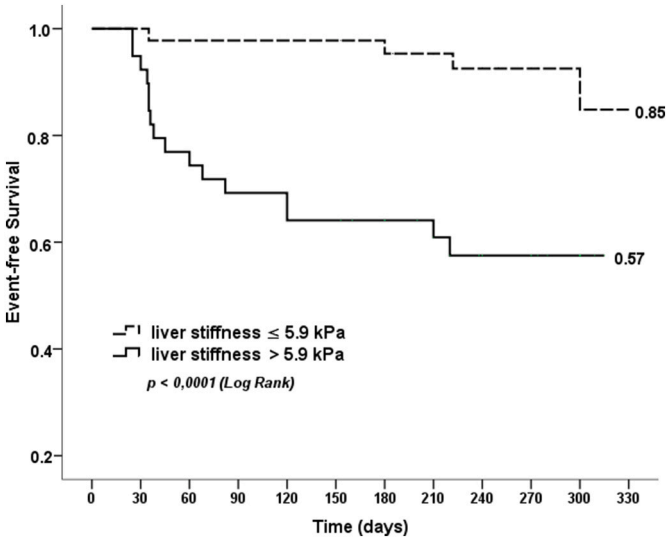

Fig. 3. Kaplan-Meier event-free survival curves stratified by high or low liver stiffness values.

5. Conclusion

In the present study, LS correlated with NT-proBNP and various markers of liver function and was an independent predictor of cardiac mortality and hospitalization in patients with ambulatory chronic HF with reduced, mid-range, and recovered ejection fraction.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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