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# Liver histopathological findings in advanced heart failure: a reappraisal of cardiac cirrhosis concept

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## Abstract

Cardiogenic liver disease is a common yet poorly characterized complication of advanced heart failure (HF), and may impact clinical management in the setting of heart transplant evaluation. In this retrospective study, we describe clinical and histopathological features of liver injury in advanced HF, with a focus on the role of liver biopsy. Included were 45 HF patients, assessed for possible heart transplant, who underwent liver biopsy for suspected liver disease. Median duration of HF symptoms was 5 years. Most patients had stiff hepatomegaly and elevated bilirubin. Viral hepatitis (19 patients, 42.2%) was the most common cause of prior known liver disease. Sinusoidal dilatation was detected in the majority of patients (64.4%). Median necroinflammatory index was 3 and median fibrosis was 1, consistent with a small burden of histologically proven liver disease. Viral hepatitis was the only variable associated with a higher grade of necroinflammation and fibrosis. Nine of the 14 (64.3%) advanced fibrosis/cirrhosis patients had a viral hepatitis infection. Fibrosis was significantly associated with splenomegaly. The MELD score was not correlated with cardiac index. A coarse liver echo-pattern had a 29% positive and 63% negative predictive value for advanced fibrosis/cirrhosis. Severe liver disease is uncommon in patients with advanced HF in the absence of splenomegaly or primary causes of liver disease. Ultrasound data need to be carefully evaluated, as it may overstate the severity of liver disease. Liver biopsy may be needed to accurately stage liver disease before excluding patients from advanced treatment strategies.

**Keywords** Heart failure · Cardiac cirrhosis · Liver biopsy · Liver ultrasound

## Abbreviations

| | |
|---|---|
| ACHF | Advanced congestive heart failure |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| VAD | Ventricular assist device |
| LDH | Lactate dehydrogenase |
| ALP | Alkaline phosphatase |
| MELD | Model for end-stage liver disease |
| MELD XI | Model for end-stage liver disease eXcluding INR |
| NYHA | New York Heart Association |
| NT-pro-BNP | N-terminal-pro B-type natriuretic peptide |
| PAPs | Pulmonary arterial pressure in systole |
| TAPSE | Tricuspid annular posterior systolic excursion |
| HAI | Histological activity index score |

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## Introduction

Advanced congestive heart failure (ACHF) is characterized by chronic increase in hepatic venous pressure and liver sinusoidal congestion. This may translate into hepatocellular

hypoxemia and necrosis followed by sinusoidal collagen deposition and subsequent liver fibrosis [1].

Although clinical and histopathologic features of cardiogenic liver disease are distinctive and historically known, relevant literature is limited and heterogeneous [2–5]. When facing HF patients with an enlarged and stiff liver, high bilirubin levels, prolonged INR or hypoalbuminemia, physicians tend to interpret such conditions as "cardiac cirrhosis." This practice has a significant impact on clinical management, and may be relevant in the setting of heart transplant evaluation and wait listing.

Recently, Mayer et al. identified diverse clinical, hemodynamic, and histologic manifestations of liver injury caused by cardiac dysfunction [6]. Hepatic fibrosis was common in this setting, though not directly related to systemic or hepatic hemodynamics. In contrast, liver cirrhosis was rarely observed [6]. The implications of these findings, however, are far from being well known.

Gelow et al. had reported a higher rate of bridging fibrosis and complete cirrhosis (up to 35%) in patients with ACHF [7]. However, other possible causes of liver disease were not assessed [7]. Notably, liver impairment translated into restricted access to ventricular assist device (VAD) implantation or cardiac transplantation and a worse outcome in those who underwent such procedures [7].

Current international guidelines [8], recommend liver biopsy in patients with HBV and/or HCV infection to exclude a severe liver disease that could preclude transplant, but no specific recommendations exist for patients without viral hepatitis.

To further contribute to this field of study, we performed a retrospective analysis in ACHF patients who underwent liver biopsy to assess whether liver histology correlates with clinical, biochemical, virological or ultrasound parameters in ACHF and to define the role of liver biopsy in the detection and staging of liver disease progression in ACHF.

## Patients and methods

### Study design and patient inclusion

This is a retrospective observational pilot study on consecutive patients with chronic ACHF, screened for cardiac transplantation at the Monaldi Hospital transplant medicine unit, Naples, from January 2008 to October 2016. During that time span, all candidates were evaluated according to a pre-defined clinical protocol, including the specific aim of assessing liver function and detecting overt or occult liver disease of any cause.

Individual patients were subjected to percutaneous liver biopsy in the presence of one or more of the following conditions: (i) presence of signs or symptoms of possible liver disease, including hepatomegaly with or without splenomegaly, pruritus, jaundice, and ascites; (ii) ultrasound (US) evidence of liver disease (coarse or bright liver echo-pattern; spleen diameter > 120 mm in the absence of systemic inflammation; portal vein diameter > 12 mm); (iii) signs of portal hypertension at upper gastrointestinal endoscopy (portal hypertensive gastropathy, gastric or oesophageal varices); (iv) persistent (> 14 days) impairment of biochemical liver function tests (e.g., serum albumin < 2.8 g/dl, total bilirubin > 2 g/dl), or evidence of hepatic inflammation [defined as alanine aminotransferase (ALT) serum levels > 1.5 × the upper normal limit (UNL)]. Patients with known prior liver disease, such as viral hepatitis, fatty liver, hemochromatosis, autoimmune liver disease, or alcohol intake > 40 g/day in men and 30 g/day in women, were also included.

Liver biopsy was not performed or data were not included for patients with liver haemangiomas, acute HF, presence of haemodynamic instability, and active thrombotic or haemorrhagic complications.

The study was led in accordance with the principles outlined in the Declaration of Helsinki of 1976 and its later amendments. All patients gave their written informed consent to undergo liver biopsy. Ethical approval for retrospective data collection was granted by our Academic Department Review Board.

### Clinical and laboratory evaluation

We collected from all patients data on medical history, physical examination findings and diagnostic investigations, including age, gender, anthropometric parameters, and renal (urea, creatinine), hepatic [AST, ALT, gamma-glutamyltransferase (γ-GT), bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), albumin] and metabolic (cholesterol, triglycerides, glucose) parameters and platelets count. Based on these data, obtained at the time of liver biopsy, the model for end-stage liver disease (MELD) score was calculated as a measure of liver dysfunction. MELD was also compared with the model for end-stage liver disease eXcluding INR (MELD XI), being many patients on anticoagulant treatment for heart disease. The AST-to-Platelets Ratio Index (APRI) test was calculated as a non invasive measure of liver fibrosis [9, 10] and compared with histological and US parameters.

Data concerning active or previous smoking habit and alcohol consumption, and details of current drug therapy at the time of liver biopsy were also collected.

Conventional cardiovascular risk factors and the etiology of heart disease were documented. HF stage was graded, based on symptoms, according to the New York Heart Association (NYHA) functional classification [11], and was supported by quantification of N-terminal-pro B-type natriuretic peptide (NT-pro-BNP) serum

levels (Elecsys-Cobas®; dynamic range 5–35,000 pg/mL). All blood tests were performed in our Hospital central laboratory.

### Cardiovascular functional assessment

Cardiac function was measured both by echocardiography and invasive hemodynamic study. All patients had performed a transthoracic mono/bi-dimensional and Doppler ultrasound examination (Philips iE33 ultrasound machine with second harmonic imaging and a 3.5 MHz transducer), through which contractility and chamber measures were collected. Records were obtained in left lateral decubitus during quiet respiration on continuous single-lead electrocardiogram (ECG) monitoring. Left ventricular volumes in systole and diastole and ejection fraction were computed from apical two- and four-chamber view, using modified Simpson's rule; right ventricular function was estimated by tricuspid annular posterior systolic excursion (TAPSE). Pulmonary arterial pressure in systole (PAPs) was estimated based on tricuspid valve regurgitation, whilst cardiovascular functional parameters, including pulmonary arterial vascular resistances in Wood units/$m^2$, pulmonary artery wedged pressure (mmHg), cardiac output (mL/min) and cardiac index (mL/min/$m^2$), were assessed by right heart catheterization. Cardiac index was measured by thermodilution. To relate TAPSE and PAPs with histological and US parameters, patients were split into two subgroups of values below and above the median.

### Hepatic histological assessment

Patients underwent an ultrasound-guided liver biopsy after appropriate attenuation/withdrawal of anticoagulant or antiplatelet medications, and, where needed, bridging with low-molecular weight heparin (LMWH). Biopsies were performed in the right liver lobe with a "Menghini" aspiration, 18 gauge, 150 mm long needle, using either an intercostal or a subcostal approach.

Liver specimens were fixed in formalin, embedded in paraffin, and finally stained with haematoxylin–eosin and Masson's trichrome stain.

Liver biopsies were examined by a pathologist (IDR) who, unaware of clinical and laboratory data, classified necroinflammation (Histological Activity Index, HAI) and fibrosis according to the Ishak scoring system [12]. Liver steatosis was instead classified according to Kleiner's modified scoring system for non-alcoholic fatty liver disease [13]. Briefly, score 1 identifies the presence of fatty deposition in 1–10% of hepatocytes, score 2 in 11–30%, score 3 in 31–60% and score 4 in > 60%.

### Statistical analysis

Data are shown as either median and interquartile range (IQR) or as mean ± standard deviation (SD) for continuous variables, and as number and percentage for categorical variables.

Differences between groups have been analyzed by Fisher's exact test for categorical variables, whilst either Mann–Whitney *U* test or Kruskal–Wallis test have been performed to compare continuous variables in two or more independent samples, respectively. HAI levels were assessed as a dichotomous variable based on the median value. Fibrosis was classified as mild for an index < 3 or moderate/severe when ≥ 3. Correlation between two numerical variables was assessed by Spearman correlation coefficient. The level of statistical significance was set at 5% and all tests were two-tailed. All the analyses were performed with SPSS software version 23.

## Results

### General characteristics of the study population

During the study period, 228 inpatients underwent screening for heart transplantat our center. Of these, 45 (19.7%) underwent liver biopsy. Baseline clinical data are summarized in Table 1. Most patients were males, did not smoke or drink alcohol, and had no diabetes mellitus. They were mostly in NYHA class II or III, except for five patients in class IV.

ACHF was due to ischemic heart disease in 14 (31.1%) patients and non-ischemic dilated cardiomyopathy in 31 patients (68.9%). Median duration of HF symptoms was 5 years [IQR 3–9.75]. The majority of patients had stiff hepatomegaly and mildly elevated bilirubin (Table 1); prior/current ascites occurred in 11 cases (25.6%), and episodes of encephalopathy had been either documented on history or observed in 2 patients (4.4%). Viral hepatitis and excessive alcohol intake were the most common causes of a prior known liver disease. No other primary causes of liver disease were reported. Median levels of liver enzymes were reported in Table 1.

Most of patients presented comorbidities: 9 diabetes mellitus, 7 thyroid dysfunction, 3 chronic obstructive pulmonary disease (COPD), 8 chronic renal failure, 5 arytmie, 1 epilepsy.

Ten patients (22.7%) were on amiodarone therapy, at a median weekly dosage of 1000 mg (IQR: 1000–1400 mg).

### Prevalence of liver histopathological changes

No major adverse events (abdominal bleeding or intrahepatic hematoma) occurred as a consequence of liver biopsy,

**Table 1** Clinical features of the study group ($n=45$)

| Parameter | All patients | HAI ≤ 3 ($n=25$) | HAI > 3 ($n=20$) | $p$ | Fibrosis < 3 ($n=31$) | Fibrosis ≥ 3 ($n=14$) | $p$ |
|---|---|---|---|---|---|---|---|
| Age, years[a] | 52 [39.5–59.5] | 50 [38–59.5] | 53 [46.2–59.5] | 0.213 | 50 [39–58] | 57.5 [46.7–61.2] | 0.113 |
| Sex, *n* (%) | | | | | | | |
| Males/females | 36 (80)/9 (20) | 20 (80)/5 (20) | 16 (80)/4 (20) | 1.000 | 23 (74.2)/8 (25.8) | 13 (92.9)/1 (7.1) | 0.236 |
| BMI, kg/m$^{2}$[a] | 25 [22–26.9] | 25.5 [22–28.4] | 24.5 [21.7–26.05] | 0.413 | 25.6 [22–26.9] | 24.5 [24–27.1] | 0.901 |
| Waist circumference, cm a | 96 [88–99.5] | 98 [90.5–105.2] | 92 [87.5–97] | 0.129 | 96.5 [88–99.7] | 95 [89.5–103.5] | 1.000 |
| Males, *n* (%) | 97 [92–103] | – | – | | – | – | |
| Females, *n* (%) | 89 [80.2–96.7] | – | – | | – | | |
| Smoking, *n* (%) | | | | 1.000 | | | 1.000 |
| Yes/no | 16 (35.6)/29 (64.4) | 9 (36)/16 (64) | 7 (35)/13 (65) | | 11 (35.5)/20 (64.5) | 5 (35.7)/9 (64.3) | |
| Alcohol drinking habit, *n* (%) | | | | 0.301 | | | 0.244 |
| Yes/No | 10 (22.2)/35 (77.8) | 4 (16)/21 (84) | 6 (30)/14 (70) | | 5 (16.1)/26 (83.9) | 5 (35.7)/9 (64.3) | |
| Glycemia, mg/dL[a] | 101 [87.7–113.5] | 102 [88–114] | 100 [86–114.5] | 0.908 | 103 [88–115.5] | 94 [83.2–107.5] | 0.240 |
| Baseline glycemia, *n* (%) | | | | 0.612 | | | 0.139 |
| < 100 mg/dL | 20 (47.6) | 12 (48) | 8 (47.1) | | 12 (40) | 8 (66.7) | |
| 100–125 mg/dL | 17 (40.5) | 11 (44) | 6 (35.3) | | 15 (50) | 2 (16.7) | |
| > 125 mg/dL | 5 (11.9) | 2 (8) | 3 (17.6) | | 3 (10) | 2 (16.7) | |
| Total cholesterol, mg/dL[a] | 145 [123.7–191.7] | 148 [131.5–211.5] | 142 [98.5–178.5] | 0.322 | 154.5 [135–211.7] | 122.5 [95.5–142.7] | 0.012 |
| Triglycerides, mg/dL[a] | 87 [58.7–115.5] | 100 [68–130] | 69 [50–109] | 0.120 | 90 [62–131] | 68 [46–102.5] | 0.094 |
| Azotemia, mg/dL[a] | 56 [43–76] | 54 [43–84] | 56 [43.7–66.7] | 0.545 | 53.5 [41.7–76.2] | 58 [45–73.5] | 0.724 |
| Creatinine, mg/dL[a] | 1.25 [1–1.6] | 1.1 [0.9–1.7] | 1.3 [1–1.6] | 0.728 | 1.1 [0.9–1.5] | 1.3 [1.1–1.7] | 0.318 |
| Albumin, g/dL * | 4 [3.6–4.3] | 4.1 [3.7–4.4] | 3.9 [3.6–4.3] | 0.518 | 4 [3.7–4.3] | 3.9 [3.5–4.4] | 0.471 |
| Bilirubin, mg/dL[a] | 1.4 [1.2–1.8] | 1.4 [1.2–1.8] | 1.4 [1.2–1.9] | 0.670 | 1.3 [1.2–1.7] | 1.6 [1.2–2.1] | 0.363 |
| NT-pro-BNP, pg/mL[a] | 2859 [1295.5–5015.5] | 2612.5 [1295.5–5015.5] | 3267.5 [1237.7–4972.2] | 0.767 | 2859 [1537–5739.2] | 2398 [407.7–4378] | 0.354 |
| INR[a] | 1.3 [1.2–1.4] | 1.3 [1.1–1.4] | 1.3 [1.2–1.3] | 0.494 | 1.3 [1.1–1.4] | 1.3 [1.2–1.6] | 0.148 |
| Etiology of CHF, *n* (%) | | | | 0.749 | | | 0.307 |
| Ischemic | 14 (31.1) | 7 (28) | 7 (35) | | 8 (25.8) | 6 (42.9) | |
| Non-ischemic | 31 (69.9) | 18 (72) | 13 (65) | | 23 (74.2) | 8 (57.1) | |
| Ejection fraction, %[a] | 25 [20–31.7] | 27 [22.5–36.5] | 20 [20–30] | 0.165 | 27 [20–34.2] | 22.5 [18.5–28.7] | 0.188 |
| Cardiac index, L/min/m$^{2}$[a] | 2.1 [1.8–2.4] | 1.9 [1.7–2.4] | 2.2 [1.9–2.4] | 0.645 | 2.03 [1.7–2.2] | 2.4 [1.9–2.9] | 0.764 |
| *P.* artery systolic pressure mmHg[a] | 48 [37.5–60] | 51 [42–61] | 46.5 [33–59.5] | 0.436 | 45 [37.5–61] | 49 [37.5–59.25] | 0.489 |
| TAPSE mm[a] | 15 [12–16] | 14.5 [12.5-16] | 15 [11.5-16] | 0.679 | 15 [12–18] | 15 [10–16] | 0.874 |
| Model for Endstage Liver Disease[a] | 12 [10–16] | 12 [10–16] | 12 [10–15] | 0.900 | 12 [10–14] | 15 [11–19] | 0.072 |
| NYHA Class, *n* (%) | | | | 0.786 | | | 0.901 |
| Class I | 0 (–) | 0 (–) | 0 (-) | | 0 (-) | 0 (–) | |
| Class II | 17 (39.5) | 8 (34.8) | 9 (45) | | 12 (41.4) | 5 (35.7) | |
| Class III | 21 (48.8) | 12 (52.2) | 9 (45) | | 14 (48.3) | 7 (50) | |
| Class IV | 5 (11.7) | 3 (13) | 2 (10) | | 3 (10.3) | 2 (14.3) | |
| Viral hepatitis, *n* (%) | | | | 0.008 | | | 0.057 |
| Yes/no | 19 (42.2)/26 (57.8) | 6 (24)/19 (76) | 13 (65)/5 (35) | | 10 (32.3)/21 (67.7) | 9 (64.3)/5 (35.7) | |

**Table 1** (continued)

| Parameter | All patients | HAI ≤ 3 ($n=25$) | HAI > 3 ($n=20$) | $p$ | Fibrosis < 3 ($n=31$) | Fibrosis ≥ 3 ($n=14$) | $p$ |
|---|---|---|---|---|---|---|---|
| Ascites, $n$ (%) | | | | 0.728 | | | 0.709 |
| Yes/no | 11 (25.6)/32 (74.4) | 7 (29.2)/17 (70.8) | 4 (21.1)/15 (78.9) | | 7 (23.3)/23 (76.7) | 4 (30.8)/9 (69.2) | |

[a]Data are shown as median [IQR]

a cutaneous hematoma developed in 2 patients. Biopsy data are summarized in Fig. 1. Sinusoidal dilatation was detected in the majority of patients (29, 64.4%), irrespective of heart disease etiology or severity. Median HAI was 3 (IQR 1–6.5) and only 6 patients had an HAI > 7. Median fibrosis was 1 (IQR 1–3), whereas median steatosis was equal to 0 [IQR 0–1]. Overall, liver histology data were consistent with a small burden of histologically proven liver disease in the study group. Only 9 patients (20%) showed bridging fibrosis, 5 (11.1%) complete cirrhosis; 11 of these 14 patients (78.6%) had non-ischemic dilated cardiomyopathy. Figure 2 shows two samples of liver histology, one with sinusoidal dilatation and very mild necroinflammation and fibrosis and the other with liver cirrhosis; a short legend reports the score ranges for inflammation and fibrosis according to Ishak et al. [12]).

## Correlates of liver histopathological findings

Table 1 shows the evaluation of factors associated with a higher grade of necroinflammation or advanced fibrosis/cirrhosis. Viral hepatitis was the only variable associated with both a higher grade of necroinflammation and fibrosis. Patients with fibrosis ≥ 3 had lower cholesterol levels. Non-significant trends were observed for greater age, higher rate of alcohol intake and hypotriglyceridemia in patients with worse liver disease (Table 1). Fibrosis grade was also significantly associated with splenomegaly ($p=0.027$), but not with ascites ($p=0.785$), hyperbilirubinemia ($p=0.424$) or amiodarone therapy ($p=0.363$) (Suppl. Figure 1).

### Etiology of heart disease

Levels of liver injury markers, HAI, fibrosis and steatosis were similar in patients with ischemic and non-ischemic cardiomyopathy, as were anthropometric and metabolic parameters and the prevalence of hepatitis virus infection (Suppl. Table 1).

### Severity of heart failure

According to the NYHA functional class, patients were divided into subgroups with either moderate (class I–II) or severe (class III–IV) HF symptoms. There were no statistically significant differences between these two groups for studied parameters (Suppl. Table 2).

We then looked at the possible association between cardiac functional parameters and liver biopsy findings. As

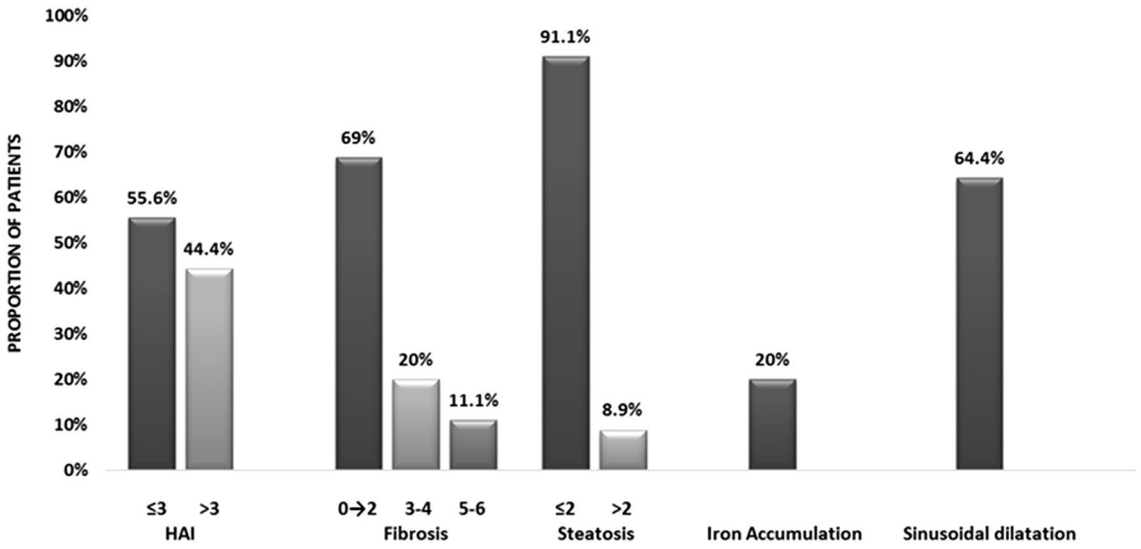


**Fig. 1** Prevalence of the most important liver histopathological findings in the study group

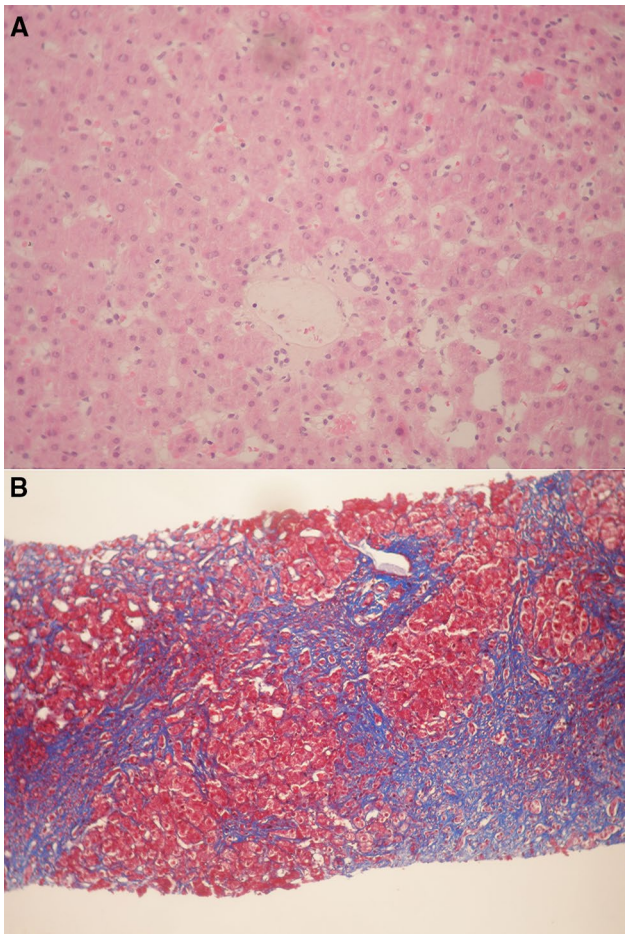


**Fig. 2** Panel A: sinusoidal dilatation, mild inflammation and absence of fibrosis Panel B: liver cirrhosis according to Ishak [12]. HAI score may range from 1 (low inflammation) to 18 (high grade inflammation). Fibrosis score may range from 1 (mild fibrosis) to 6 (overt liver cirrhosis)

shown in Suppl. Figure 2, median levels of NT-pro-BNP and cardiac index did not differ according to the severity of liver injury. Likewise, patient subgroups with low or high TAPSE and PAPs did not show significant differences in terms of liver histology parameters, including necroinflammation, fibrosis, steatosis, and sinusoidal dilatation (Table 1) In addition, TAPSE and PAPs were not associated with liver US parameters, including portal vein diameter, spleen diameter, and irregular liver margins (data not shown).

### Noninvasive parameters of liver dysfunction

The MELD and MELD-XI scores were not associated with liver histology parameters (data not shown) and did not correlate with Cardiac index (MELD, $\rho = 0.113$, $p = 0.51$, Fig. 3; MELD-XI, $\rho = 0.15$, $p = 0.248$).

The APRI test largely showed low scores (median 0.4, range 0.3–0.7) and did not correlate with histologic and US parameters (not shown).

### Viral hepatitis

Nineteen (42.2%) patients had a prior/concomitant chronic viral infection of the liver: 9 cases (47.4%) had hepatitis C virus (HCV) infection, 7 (36.8%) hepatitis B virus (HBV) infection, 2 (10.5%) HBV-hepatitis D virus coinfection, and 1 (5.3%) HBV–HCV coinfection (Suppl. Table 3). HBV-DNA was positive in 3 of the 7 HBsAg carriers (42.9%) and HCV RNA in 4 of the 9 anti-HCV positive subjects (44.4%). Alcohol intake was similar in patients with and without viral hepatitis (26.3% vs 19.2%; $p = 0.72$). Patients with viral hepatitis had significantly higher HAI and fibrosis scores but less sinusoidal dilatation on liver histology (Fig. 4, Suppl. Table 3).

MELD and MELD XI score was lower in patients with viral hepatitis than in those without (Suppl. Table 3). Indeed, 9 of the 14 (64.3%) advanced fibrosis/cirrhosis patients had a concomitant viral hepatitis infection. Finally, γ-GT levels were lower in patients with viral infection than in those without (Suppl. Table 3).

### Ultrasound findings

We compared liver histologic (HAI, fibrosis, steatosis, sinusoidal dilatation) and US parameters generally used to detect liver disease (liver margins, echo-patterns, portal vein, and spleen diameters). Overall, there was a poor correlation between histologic and US parameters (Table 2). A coarse liver echo-pattern was observed in 34 (75%) patients and it corresponded to histological signs of advanced fibrosis or cirrhosis in only 10 (29%) of these patients. In contrast, of the 14 patients with advanced fibrosis/cirrhosis on liver biopsy, 10 (71%) had a coarse liver echo-pattern. Overall, a coarse pattern had a 29% positive and 63% negative predictive value for advanced fibrosis/cirrhosis (moderate sensitivity with low specificity).

## Discussion

In a retrospective evaluation of 45 liver biopsies, we observed limited histopathological changes in patients with ACHF, despite of the presence of clinical, biochemical or US features suggesting severe liver disease. In this analysis, liver histology did not correlate with traditional liver disease markers, and was clearly associated only with prior/concomitant viral hepatitis. Hence, this study alludes to an important role for liver biopsy in the correct detection and staging of liver disease in ACHF.

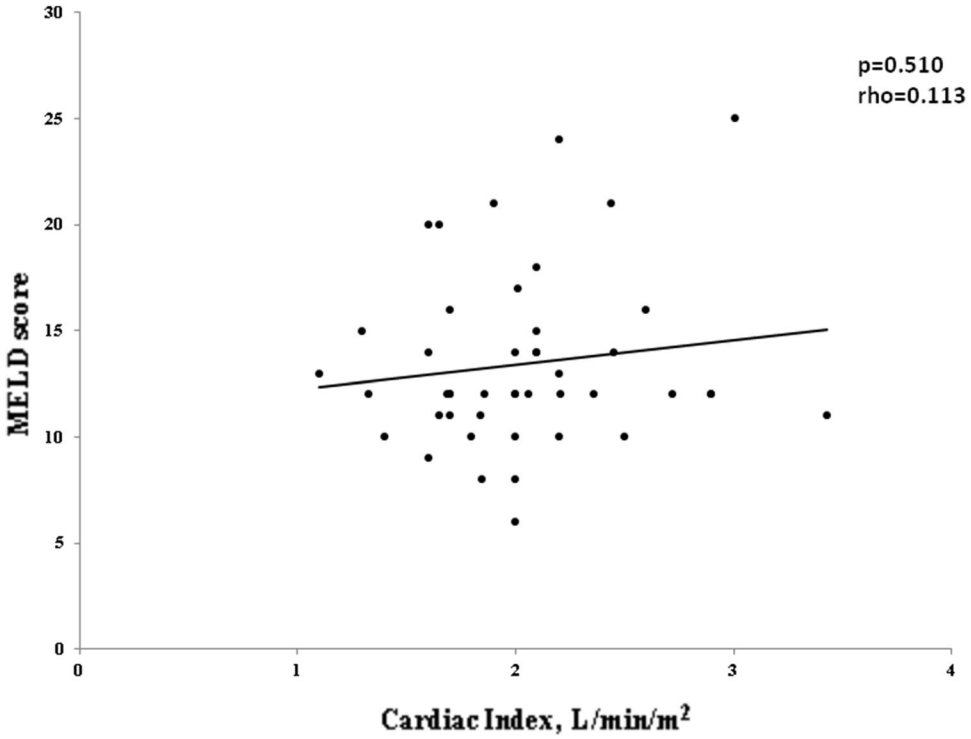


**Fig. 3** Correlation between MELD score and cardiac index in the overall patient cohort studied. The Spearman rho correlation coefficient was equal to 0.113, $p = 0.51$. The regression line is shown in black

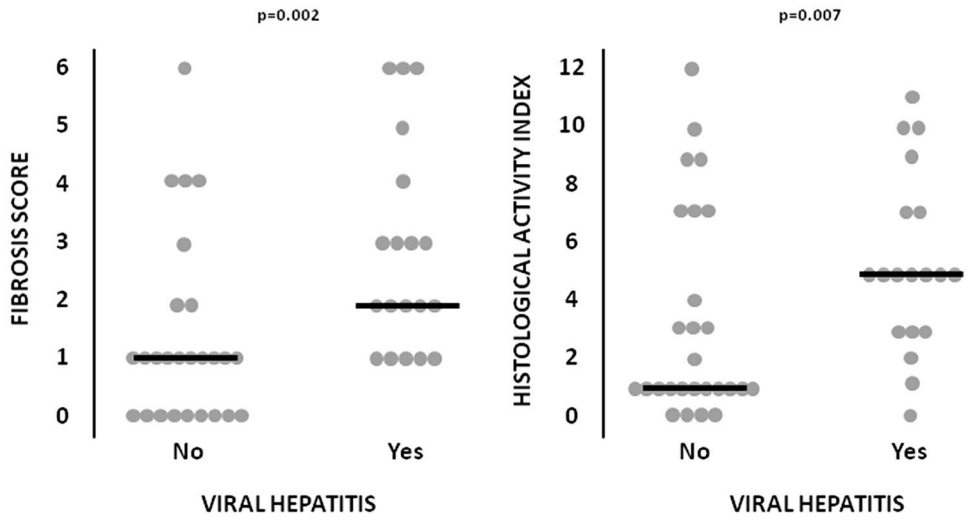


**Fig. 4** HAI and fibrosis scores according to the presence of viral hepatitis. The black horizontal bars denote the median value for each subgroup

Despite noninvasive tests consistent with the presence of advanced liver disease (including stiff hepatomegaly, elevated MELD score, hyperbilirubinemia and a coarse echo-pattern on liver ultrasound), the actual prevalence of significant liver disease, namely liver fibrosis and necroinflammation, was low. Features of liver disease were mostly observed in the sizeable subgroup of patients with concomitant viral hepatitis, that can be now cured or suppressed successfully and do not represent an exclusion criteria for heart transplant, if liver function is preserved. Among other potential causes of liver damage in this patient setting, one of the cirrhotic patients had a definite history of alcohol abuse while we could not observe a significant role for amiodarone use. It is interesting to note that histology-proven liver disease did not correlate with conditions that are usually linked to severe liver disease, such as hyperbilirubinemia and ascites. Neither the MELD/MELD XI scores nor the ultrasound data were predictive of histological liver lesions. On the other hand, none of the measures of cardiac dysfunction (BNP, cardiac index, NYHA class, TAPSE, PAPs) correlated with histological liver lesions.

Our data suggest that the changes in liver function tests in patients with ACHF do not accurately predict the actual severity of liver disease and are mostly due to functional

**Table 2** Correlation between histological and ultrasound (US) parameters (n = 45)

| Parameter | Liver margins | | | Spleen diameter, mm | | | Portal vein diameter, mm | | | Liver echo-pattern | | | Bright Liver | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Regular | Irregular | *p* | ≤ 120 | > 120 | *p* | ≤ 11 | > 11 | *p* | Coarse | Uniform | *p* | Yes | No | *p* |
| HAI, median [IQR] | 3 [1–6] | 2.5 [1.5–8.5] | 0.555 | 3 [1–5] | 5 [2.2–8.5] | 0.085 | 3 [1–5] | 5 [1.7–9] | 0.057 | 3 [1–5.5] | 5 [1–7] | 0.327 | 3 [1–7] | 3 [1–7] | 0.933 |
| Fibrosis, median [IQR] | 2 [1-2.5] | 1 [0.2–4.75] | 0.734 | 1 [0–2] | 2.5 [1–4] | 0.052 | 1 [0–2] | 2 [1–4] | 0.126 | 1 [1–3] | 1 [0–4] | 0.805 | 1 [1, 2] | 1 [0–3] | 1.000 |
| Steatosis, median [IQR] | 0 [0–1] | 0 [0–1] | 0.774 | 0 [0–1] | 0 [0–1] | 0.968 | 0 [0–0] | 1 [0–1.25] | 0.052 | 0 [0–1] | 0 [0–1] | 0.866 | 0 [0–2] | 0 [0–0] | 0.158 |
| Sinusoidal dilatation, *n* (%) | | | | | | | | | | | | | | | |
| Yes | 15 (62.5) | 14 (73.7) | 0.523 | 15 (65.2) | 10 (62.5) | 1.000 | 15 (68.2) | 10 (58.8) | 0.738 | 22 (66.7) | 7 (70) | 1.000 | 7 (63.6) | 14 (73.7) | 0.687 |
| No | 9 (37.5) | 5 (26.3) | | 8 (34.8) | 6 (37.5) | | 7 (31.8) | 7 (41.2) | | 11 (33.3) | 3 (30) | | 4 (36.4) | 5 (26.3) | |
| Iron accumulation, *n* (%) | | | 0.710 | | | 0.448 | | | 0.713 | | | 1.000 | | | 1.000 |
| Yes | 6 (24) | 3 (15) | | 6 (24) | 2 (12.5) | | 4 (17.4) | 4 (22.2) | | 7 (20.6) | 2 (18.2) | | 2 (18.2) | 4 (21.1) | |
| No | 19 (76) | 17 (85) | | 19 (76) | 14 (87.5) | | 19 (82.6) | 14 (77.8) | | 27 (79.4) | 9 (81.8) | | 9 (81.8) | 15 (78.9) | |

hepatic derangement. This has important implications for the decision to list these patients for heart transplant or implant a mechanical circulatory support device.

It was interesting to observe a reduced prevalence of ascites, sinusoidal dilatation as well as γ-GT level increase in patients with concomitant viral hepatitis. All of these are clearly features of liver congestion and appeared to be (counter-intuitively) attenuated in those patients with higher levels of liver fibrosis and necroinflammatory changes. Whether this can be related to a more stiff liver needs to be further analyzed.

Our 45 cases were fairly representative of ACHF patients with an indication for elective heart transplant, although the general usability of results could be attenuated by the relatively small sample size.

Liver biopsy is an invasive procedure, with a higher risk in patients with heart disease [14], who often need an anticoagulant treatment. In this setting of patients, liver biopsy, although not performed via the transjugular approach, was well tolerated in our experience. Liver biopsy can still be regarded as the diagnostic method of choice to assess type and grade of liver disease. Sampling errors related to liver biopsy are possible [15, 16] and can be due to inadequate length of the liver fragment, insufficient number of observable portal spaces, presence of subcapsular tissue only. In our study group the characteristics of samples analyzed fulfilled the criteria (length, number of portal spaces) to consider them appropriate for an accurate histological diagnosis.

We believe our data prompt a serious reassessment of the concept of 'cardiac cirrhosis'. By definition, cirrhosis is a condition of partial or complete architectural derangement of the liver, with formation of nodules separated by complete fibrous septa. Most of our patients had a long-standing condition of HF, documented by a 5-year median duration of symptoms, and a very stiff and enlarged liver at physical examination. However, in many of them, we could not find histological evidence of liver cirrhosis or even advanced fibrosis in the absence of additional primary causes of liver disease. This suggests that the clinical picture of 'cardiac cirrhosis' could in fact be a reversible condition secondary to heart disease, and the term 'cirrhosis' possibly misleading.

Prior studies evaluated features of cardiogenic liver disease in HF patients [2–5]. In the heart transplant setting, few patients were studied, mostly in a retrospective fashion. Liver damage was variably described as 'reversible' and specifically 'cholestatic' in nature [17], 'independent' from heart disease [18], or 'common' in advanced HF [7]. In contrast, our data resemble those of Myers et al., who found changes in liver structure (centrolobular fibrosis and, in some cases, cirrhosis) uncorrelated to hepatic venous pressures in patients with cardiomyopathy.

Generally, liver US examination is thought to have a high diagnostic accuracy when fibrosis levels are high [19–21].

To the best of our knowledge, no data are available about the use of liver US scan in patients with ACHF. Hence, we studied whether US scans could accurately detect liver fibrosis in this group of patients and be used for evaluation of liver disease stage before heart transplant. Our data show there is poor correlation between liver histology and US findings in this clinical setting and coarse echo-patterns did not correspond to histologic fibrosis or cirrhosis. Prolonged liver congestion and impaired perfusion related to HF could underlie the echo-pattern. Thus, in ACHF, a coarse liver echo-pattern should not directly suggest significant liver disease in the absence of other primary causes of liver injury. An additional indication for further testing, including liver biopsy, could be the presence of splenomegaly. Therefore, our findings corroborate and add to the current practice recommendations on evaluation of ACHF patients for heart transplantation [8].

Limitations of our study were the relatively small sample size, the retrospective design, and the absence of data on liver transient elastography. Multicentre studies with a prospective, standardized data collection, coupled with an assessment of liver function after transplant are certainly needed. Assessment of transient elastography as a noninvasive method for liver fibrosis longitudinal evaluation in comparison with ultrasound and histology could also prove interesting, provided the confounding role of liver congestion and the interference with implanted defibrillators are taken into account [22].

## Conclusions

In conclusion, severe liver disease is uncommon in patients with ACHF in the absence of splenomegaly or other causes of liver disease. Ultrasound data need to be carefully evaluated, as it may overstate the severity of liver disease. Liver biopsy is the best test to accurately stage liver disease in ACHF before excluding patients from advanced treatment strategies. However, in the absence of viral hepatitis, alcohol abuse or splenomegaly, the likelihood of finding significant liver disease is very low and the decision to perform liver biopsy should be adequately pondered.

### Compliance with ethical standards

**Conflict of interest** This work was supported by the AORN dei Colli-Monaldi Hospital, Naples, Italy. The authors have no conflict of interest to disclose.

**Statements on human and animal rights** This article does not contain any studies involving human participants or animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual partecipants included in the study.

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