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Authors

Puchades, Lorena
Chau, Stephanie
Dodson, John A
et al.

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Association of Cardiac Abnormalities to the Frail Phenotype in Cirrhotic Patients on the Waitlist: From the Functional Assessment in Liver Transplantation (FrAILT) Study

Lorena Puchades, MD[1], **Stephanie Chau, BS**[2], **John A. Dodson, MD, MPH**[3], **Yara Mohamad, MD**[2], **Rachel Mustain, BS**[2], **Adrienne Lebsack, MPH**[2], **Victoria Aguilera, MD, PHD**[1,4], **Martin Prieto, MD, PHD**[1,4], and **Jennifer C. Lai, MD, MBA**[2]

[1]Department of Gastroenterology, Hepatology Unit, Hospital Universitari i Politècnic La Fe, Valencia, Spain

[2]Department of Medicine, Division of Gastroenterology and Hepatology, University of California-San Francisco, San Francisco, CA

[3]Department of Medicine, Division of Cardiology, New York University Langone Medical Center, New York

[4]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Valencia, Spain

Abstract

Background—Frailty is a syndrome of decreased physiologic reserve that results from compromise of multiple physiologic systems including cardiovascular. We aimed to determine the association between the frail phenotype and cardiac abnormalities in liver transplant (LT) candidates through evaluation of transthoracic echocardiography (TTE) indices.

Methods—Included were consecutive outpatients listed for LT who underwent a frailty assessment from 1/1/14–6/30/16 (using the Liver Frailty Index) and a 2-dimensional/doppler TTE exam. Patients were categorized as robust, intermediate frail, or frail by the Liver Frailty Index

CORRESPONDENCE INFORMATION: Jennifer C. Lai, MD, MBA, Department of Medicine, Division of Gastroenterology and Hepatology, University of California-San Francisco, San Francisco, CA, 513 Parnassus Avenue, UCSF Box 0538, San Francisco, CA 94143, Jennifer.lai@ucsf.edu, Academic office: (415) 476-2777.

AUTHORSHIP:

Puchades: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content.
Chau: Study design; acquisition of data, interpretation of data; critical revision of the manuscript for important intellectual content.
Dodson: Study design; interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content.
Mohamad: Study design; interpretation of data; critical revision of the manuscript for important intellectual content.
Mustain: Study design; interpretation of data; critical revision of the manuscript for important intellectual content.
Lebsack: Study design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.
Aguilera: Study design; interpretation of data; critical revision of the manuscript for important intellectual content.
Prieto: Study design; interpretation of data; critical revision of the manuscript for important intellectual content.
Lai: Study concept and design; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; statistical analysis and study supervision.

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based on scores of <3.2, between 3.2–4.5 or ≥4.5. Linear regression assessed associations between the Liver Frailty Index and TTE indices.

Results—Of 335 patients, 19% were robust, 65% intermediate frail, and 16% frail. TTE indices of left atrial (LA) dilatation differed significantly by frailty status: median LA dimension (p=0.03), LA volume index (LAVIcc/m^2; p<0.001) and %LAVI>34cc/m^2 (p= 0.001). In linear regression adjusted for age, sex, hypertension and diabetes, the Liver Frailty Index was positively associated with LA dimension (coeff 0.20, 95%CI 0.07–0.34), LAVIcc/m^2 (coeff 0.01, 95%CI 0.005–0.02), ejection fraction (coeff 1.59, 95%CI 0.32–2.85) and pulmonary artery systolic pressure (coeff 0.01, 95%CI 0.003–0.02) and negatively associated with LV hypertrophy (coeff −0.22, 95%CI −0.37, −0.06).

Conclusion—In LT candidates, frailty is associated with cardiac structural and functional changes, independent of known risk factors. Our study provides evidence to support that measures of frailty in cirrhotic patients encompass abnormalities of the cardiovascular system and may inform assessments of cardiovascular reserve in this population.

INTRODUCTION

Frailty is a distinct biologic syndrome of decreased physiologic reserve and increased vulnerability to health stressors [1], which is prevalent in patients with cirrhosis awaiting liver transplantation [2,3]. Originally conceptualized in the field of geriatrics, frailty is thought to result from dysregulation of multiple systems, including cardiovascular, endocrine, and neurologic. However, little is known about whether these same systems contribute to frailty in patients with cirrhosis, who are, in general, younger than the geriatric population.

Of particular interest is the role that cardiovascular dysfunction plays in the frail phenotype in patients with cirrhosis. In contrast to hypertensive and ischemic heart disease classically seen in older adults without known liver disease, cardiovascular abnormalities in cirrhotic patients are characterized by hyperdynamic circulation with high cardiac output, decreased arterial pressure and total peripheral resistance [4]. Beginning in the late 1980s, occasional reports of unexpected deaths due to heart failure following liver transplantation [5], transjugular intrahepatic portosystemic shunt (TIPS) insertion [6], and surgical portocaval shunts [7] led to increased attention to cardiac dysfunction related to cirrhosis. Subsequently, the literature has established that the presence of cirrhosis *per se* is associated with cardiovascular abnormalities that worsen overall prognosis and peri-operative outcomes, regardless of the cause of liver disease [8–22].

In older adults without liver disease, cardiac abnormalities identified on transthoracic echocardiogram (TTE) have been associated with the frail phenotype [23–25]. Whether these cardiovascular abnormalities associated with cirrhosis result in worsening physiologic reserve, as measured by objective assessments of frailty, remains largely unknown. Therefore, we aimed to determine the association of the frail phenotype with cardiac structure and function in patients with cirrhosis through evaluation of TTE indices. We hypothesized that frailty would be associated with echocardiographic characteristics in patients with cirrhosis.

METHODS

Study Design

We performed a cross-sectional study at a single, high-volume liver transplant center with patients enrolled in the Functional Assessment in Liver Transplantation (FrAILT) Study from January 1, 2014 to June 30, 2016 who had a 2-dimensional (2D) and doppler TTE within 365 days of their frailty assessment. The TTE indices we considered as the key parameters of this study were left chamber measurements [left atrial (LA) and left ventricle (LV) dimensions, volume and mass], ejection fraction (EF) and the descriptive statement of doppler evidence of diastolic dysfunction (DD).

Study Population

The Functional Assessment in Liver Transplantation (FrAILT) Study enrolls consecutive adult patients with cirrhosis who are actively listed for liver transplantation and are seen as outpatients at the University of California, San Francisco (UCSF) Liver Transplant Clinics [26]. Patients were eligible for enrollment in the FrAILT Study if they had a Model for End-Stage Liver Disease (MELD) score ≥12 or if they were ≥60 years of age. Patients were excluded if they had severe hepatic encephalopathy, as defined by the time to complete a Numbers Connection Test of > 120 seconds, given concerns over their ability to fully cooperate with the frailty testing.

For this specific study, the eligibility criteria were as follows: a) enrollment in the FrAILT Study from January 1, 2014 to June 30, 2016 and b) receipt of a standardized 2-dimensional (2D) and doppler TTE within 365 days of the frailty assessment.

Variables and Data sources/Measures

Baseline characteristics—Information regarding (i) demographics: age, sex, ethnicity, height, weight and BMI; (ii) baseline liver-related data: etiology of liver disease (HCV, Alcohol, NASH, Cholestasic, HBV, other), laboratory tests (creatinine, albumin, MELD, MELDNa and Child Pugh Score), presence of HCC, dialysis, ascites and/or moderate hepatic encephalopathy (defined as a Numbers Connection Test score between 60–120 seconds); (iii) cardiovascular comorbidities: hypertension, diabetes (type 1 or type 2) and coronary artery disease (CAD) and (iv) frailty parameters, were collected on all patients from the patient's electronic health record by study personnel at the time of the frailty assessment. Patients were classified as having hypertension or diabetes if this was listed in their past medical history or they were prescribed medication(s) to manage these diseases. History of CAD was determined from medical chart. Ascites was ascertained from the physical examination or discussion of ascites in the management plan.

Frailty assessment—Frailty was assessed using 3 simple, performance-based tests: dominant hand grip strength, timed chair stands, and balance. The Liver Frailty Index, an index to objectively measure frailty specific to patients with cirrhosis; was calculated from the scores of these 3 tests (http://liverfrailtyindex.ucsf.edu/). Patients with a Liver Frailty Index in the bottom 20%ile (<3.2) of the FrAILT Study cohort were classified as "robust"

and those with a Liver Frailty Index in the top 80%ile (≥ 4.5) of the FrAILT Study cohort were classified as “frail”, based on our prior published study [26].

TTE measurements—All patients included in this study underwent cardiovascular assessment by a standard 2D and doppler TTE as part of their pretransplant protocol either within our center or at outside institutions. In total, TTE reports were collected from 64 centers; 28% were performed at our own institution. We only analyzed data from TTE reports that contained the basic information recommended by the American Society for Echocardiography [27]. For patients with more than 1 eligible TTE, we analyzed the TTE closest to the date of the frailty assessment.

We evaluated the following TTE indices: (i) measurements of cardiac left chambers morphology (LA and LV dimensions, volume and mass); (ii) measurements of cardiac systolic function (EF); (iii) measurements of cardiac DD (statement of doppler evidence of DD) and (iv) Estimated Pulmonary Artery Systolic Pressure (PASP). These specific TTE indices were selected because they have previously been associated with adverse cardiac-related outcomes in patients with cirrhosis [5–22]. Regarding their assessment methods, left chamber measurements were collected and indexed to body surface area as recommended by the American Society for Echocardiography and the European Association of Cardiovascular Imaging, in order to allow comparison among individuals with different body sizes [28]. If left atrial volume index (LAVI) or left ventricular mass index (LVMI) measurements were not provided, we calculated them using the height and weight included in the TTE report and the area-length method and the 2D echocardiography necropsy-validated formula [22], respectively through an online calculator provided by the Canadian Society of Echocardiography (http://csecho.ca/mdmath). Systolic function was classified according to the EF, as “normal” if EF in the range of 53–73%, “depressed” if EF < 53% or hyperdynamic if EF > 73% [28]. Parameters of DD were collected including, primary measurements of mitral inflow [peak early filling (E wave) and late diastolic filling (A wave) velocities and E/A ratio], tissue doppler annular early (e’) and late (a’) diastolic velocities and E/e’, an additional time ratio [29]. To aid the assessment of LV diastolic dysfunction, additional morphologic and functional information were also collected including LAVI ≥ 34cc/m^2, presence of LV hypertrophy (defined as a finding in the TTE report or a LVMI > 115g/m^2 for men and > 95g/m^2 for women), and PASP estimated (derived from Bernoulli equation with the tricuspid regurgitation (TR) jet [29]. According to guidelines in force during the study period for identifying DD in subjects with normal EF, the mitral inflow E velocity to tissue Doppler e’ (E/e’) ratio should be calculated, whereas in patients with depressed EF, the transmitral inflow pattern by itself (E/A ratio) is usually sufficient for diagnosis [28]. Therefore, DD was defined as diagnosis of “doppler evidence of DD” included in the TTE report and classified according to the degree of DD provided by the cardiologist, in 4 different filling patterns (“normal”, “mild or impaired relaxation”, “moderate or pseudo-normal”, “severe or reversible/fixed restrictive” or “findings inconclusive to estimate” in the case of discordance with available variables).

Statistical analysis

We reported baseline and TTE characteristics using categories of frailty (by cut-offs of the Liver Frailty Index) in order to facilitate interpretation of characteristics that are generally associated with the frail phenotype. Continuous distributions were summarized as medians [interquartile range (IQR)] and discrete data were summarized as frequencies (percentages). Differences in baseline characteristics and TTE indices by frailty status were compared using chi-square or Kruskal-Wallis tests for categorical and continuous variables, respectively.

In order to precisely quantify the association between frailty and TTE indices and to control for confounding, we performed multivariate linear regression models using the Liver Frailty Index as a continuous variable, adjusted for age, sex, diabetes and hypertension, as these factors are known to be independently associated with cardiac structural abnormalities on TTE [23,25]. The primary TTE indices of interest were left chamber measurements, EF and the descriptive statement of doppler evidence of DD.

A cut-off p-value<0.05 was used to determine statistical significance. STATA v14 (College Station, Texas) was used for all statistical analyses.

This manuscript adheres to the *Strengthening The Reporting of Observational studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies* [30].

RESULTS

Participants

Of the 433 patients enrolled in the FrAILT Study during the study period, 59 (14%) were excluded because the TTE provided did not include the measurements and descriptive items recommended by guidelines [27] and 39 (9%) were excluded because they did not have a TTE within 365 days of their frailty assessment (Figure 1).

Baseline characteristics of the cohort

Baseline characteristics of the 335 patients included in this cohort are shown in Table 1a, column A. Thirty-four percent were women, and median age was 60 years (IQR 19–74). Forty-eight percent had chronic HCV infection and 38% had HCC. Median MELDNa score at testing was 18 (IQR 13–22) and Child Pugh score was 8 (IQR 6–9). Ascites was present in 25% of the cohort, and 16% had moderate hepatic encephalopathy. Hypertension, diabetes, and CAD were present in 44%, 23% and 5%, respectively. The median number of days between the frailty assessment and TTE assessment was 119 days (IQR 51–186).

Baseline measurements of frailty

The median Liver Frailty Index score was 3.82 (IQR 3.35–4.28). A total of 53 (16%) subjects were classified as “frail” (Liver Frailty Index score ≥4.5), 218 (65%) as “intermediate frail” (Liver Frailty Index score 3.4–4.5), and 64 (19%) as “robust” (Liver Frailty Index score <3.2). As for the individual components of the Liver Frailty Index score, median grip strength was 29 kg (IQR 22–37), median number of chair stands per second was

0.4 (IQR 0.3–0.6), and 85% of patients were able to complete 3 balance tests for the maximum time of 10 seconds each.

Baseline measurements of TTE

TTE characteristics are shown in Table 2, column A. Median LA dimension was 4 cm (IQR 3.6–4.4), LAVI was 30 cc/m^2 (IQR 23–38), LV end diastolic volume index was 50 cc/m^2 (IQR 41–61), LV end systolic volume index was 16 cc/m^2 (IQR 12–21) and LVMI was 85 g/m^2 (IQR 69–100). Systolic function was normal (EF between 53–73%) in 87% of patients with a median EF of 65% (IQR 63–70%). The majority (62%) had no doppler evidence of DD although 41% had a LAVI ≥ 34 cc/m^2, 31% had LV hypertrophy, and the median PASP was 28mmHg (IQR 23–33).

Demographic characteristics associated with frailty

Baseline characteristics among robust versus intermediate frail and frail subjects are shown in Table 1a, columns B, C and D, respectively. The 3 groups were similar with respect to age, sex, body size, cardiovascular risk factors, rates of dialysis and days between frailty and TTE assessments ($p > 0.05$). Frail patients had higher MELD and MELDNa scores, rates of mild/moderate and severe ascites and rates of moderate hepatic encephalopathy ($p < 0.05$). As shown in Tables 1a and 1b, patients who were classified as frail also had a lower proportion of HCC and HCV-related cirrhosis but a higher proportion of alcohol and NASH cirrhosis ($p < 0.05$).

TTE findings associated with frailty

TTE findings in the robust, intermediate and frail groups are described in Table 2, columns B, C and D, respectively. TTE indices of LA dilation (LA dimension and volume) differed significantly by frailty status. However, TTE indices of LV enlargement and hypertrophy (LV volumes and mass) showed no significant differences between the 3 categories of the Liver Frailty index. Likewise, these 3 groups had no significant differences regarding TTE indices of systolic function (EF) and DD (“doppler evidence of DD” and “proportion of LAVI ≥ 34cc/m2”). When subjects were divided into stages of systolic and DD, there were still no significant differences between frail, intermediate and robust patients.

In linear regression models adjusted for age, sex, hypertension and diabetes, the Liver Frailty Index (per 1 unit) was positively associated with LA dimension (coeff 0.20, 95% CI 0.07–0.34) and LAVI (coeff 0.01, 95% CI 0.005–0.02) but not with the proportion of patients with LAVI ≥ 34cc/m2. The Liver Frailty Index was also positively associated with EF (coeff 1.59, 95% CI 0.32–2.85) and PASP (coeff 0.01, 95% CI 0.003–0.02) and negatively associated with LV hypertrophy (coeff −0.22, 95% CI −0.37, −0.06). There were no significant associations between the Liver Frailty Index and LVMI or doppler evidence of DD (Table 3).

DISCUSSION

Frailty has recently emerged as a potent predictor of mortality in patients with cirrhosis [2–3, 26]. However, little is known of the major contributors to the frail phenotype in this population. Based on reports from the geriatric literature, we hypothesized that the frail

phenotype would be associated with cardiac structural and functional abnormalities. Indeed, we observed that, in our cohort of 335 patients with cirrhosis, patients who were frail had higher rates of LA enlargement, EF, PASP and lower proportion of LV hypertrophy compared with nonfrail patients, independent of known cardiac risk factors including age, sex, diabetes, and hypertension.

Notably, the strongest association between TTE indices and the frail phenotype was with higher LA volume and PASP. This is of particular interest given the previously described association between higher LAVI and DD in cirrhotic patients [14]. In addition, in the field of cardiology, high LAVI, as defined by LAVI ≥ 34 cc/m^2, is an independent predictor of clinically relevant outcomes including, heart failure, ischemic stroke, and death [21,27]. Similarly, elevated PASP is independently associated with cardiac events in patients with and without heart failure [31–33]. Whether these findings contribute to the increased risk of death among frail cirrhotic patients should be further investigated in a larger study with longer-term follow-up in this population.

The precise pathophysiology underlying the observed associations between cardiac structural changes and frailty is unknown, but we offer the following potential explanations based on what has been described in the literature from the fields of hepatology, cardiology, and geriatrics. First, LA enlargement reflects the cumulative effects of elevated filling pressures over time [29]. In patients with cirrhosis, this may occur as an adaptive response to the hyperdynamic circulation and the trophic effects caused by continuous activation of several neurohumoral systems such as the sympathetic nervous system or the renin-angiotensin-aldosterone system. That cirrhotic patients with DD display elevated levels of atrial natriuretic peptide provides evidence of this association [34]. Secondly, the increased EF and lower proportion of LV hypertrophy observed in frail cirrhotic patients may serve as the cardiac manifestation of the cumulative effect of portal hypertension. It is also possible that general muscle wasting contributed to the lower proportion of LV hypertrophy that we observed in the frail patients in our cohort.

There are similarities and differences in our findings in cirrhotic patients as compared to those in older adults without cirrhosis. In both older adults (without cirrhosis) and cirrhotic patients, frailty is associated with LA enlargement and PASP but, unlike patients with end-stage liver disease (ESLD), adults aged ≥ 65 years old had a lower EF and an increased LVMI [23–25]. Particularly, the lower EF seen in frail noncirrhotic patients suggests that decreased cardiologic reserve may contribute to the frail phenotype in an elderly subject without liver disease more than it does in a younger frail cirrhotic. On the other hand, the increased LVMI observed in frail geriatric patients denotes an opposite direction in cardiac remodeling in subjects with cirrhosis than in older adults with normal hepatic synthetic function. Our data suggest a hallmark of TTE findings which might differentiate frail cirrhotic patients from both nonfrail cirrhotic patients and frail noncirrhotic patients.

We acknowledge the following limitations to our study. First, the TTE examinations included in this study represent TTEs performed at multiple different institutions, as liver transplant candidates often complete their cardiac evaluations at their local facility, rather than at our transplant center. However, these were the same TTE reports that were used for

clinical decision-making at our transplant center, so the analyses that we performed using these data could be generalizable to real-life clinical practice. Second, the time frame between TTE and frailty assessment ranged anywhere from 0 to 362 days; the extent of frailty may have changed during the interim between the TTE and the actual measurement of frailty. Nevertheless, we did not observe any significant differences in the median number of days between TTE and frailty measurement by frailty category, so we do not believe that this contributed substantial bias to our results. Third, we were unable to adjust for a broad range of cardiopulmonary conditions in our cohort (eg, congestive heart failure, atrial fibrillation) – although we did adjust for hypertension – but given that all of the patients included in our cohort were approved for liver transplantation at our institution, we believe that the prevalence of clinically significant cardiopulmonary disease would be low and unlikely to substantially change our analyses. Similarly, we did not collect information on portopulmonary hypertension, but the prevalence of portopulmonary hypertension at UCSF is very low (<5%), supported by a median PASP was 28 mmHg in our cohort. Lastly, the decision of not adjusting by severity of liver disease (MELD and Child-pugh scores, albumin, sodium, platelets and ascites) was deliberate since the Liver Frailty Index captures by itself portal hypertension status and systemic hemodynamics.

Despite these limitations, our study is the first to evaluate the association of cardiac abnormalities with frailty in patients with ESLD. Moreover, it provides provocative evidence to support that measures of frailty in cirrhotic patients encompass, among other systems, abnormalities of the cardiovascular system and can be used to objectively measure underlying cardiovascular reserve in this population. Whether these TTE abnormalities associated with frailty in cirrhotic patients have the potential to predict pre, peri, and posttransplant cardiovascular events warrants further investigation. Given the progressive aging and the increasing cardiovascular comorbidities of liver transplant candidates as well as the cardiovascular abnormalities intrinsically associated with cirrhosis, we advocate for the integration of objective frailty measures, such as the Liver Frailty Index, into the routine clinical assessments of cirrhotic patients on the liver transplant waitlist.

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ABBREVIATIONS

FrAILT	Functional Assessment in Liver Transplantation
LT	Liver Transplant
UCSF	University of California, San Francisco
TTE	Transthoracic Echocardiography

MELD	Model for End-Stage Liver Disease
LA	Left Atrial
LAVI	Left Atrial Volume Index
LV	Left Ventricle
DD	Diastolic Dysfunction
EF	Ejection Fraction
PASP	Pulmonary Artery Systolic Pressure
TIPS	Transjugular Intrahepatic Porto-systemic stent Shunt
TR	Tricuspid Regurgitation
LVMI	Left Ventricular Mass Index
IQR	Interquartile Range
ESLD	End-Stage Liver Disease

References

1. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56(3):M146–56. [PubMed: 11253156]
2. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant. 2014; 14(8):1870–9. [PubMed: 24935609]
3. Lai JC, Dodge JL, Sen S, Covinsky K, Feng S. Functional decline in patients with cirrhosis awaiting liver transplantation: Results from the functional assessment in liver transplantation (FrAILT) study. Hepatology. 2016; 63(2):574–80. [PubMed: 26517301]
4. Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennec cirrhosis. J Clin Invest. 1953; 32:1025–1033. [PubMed: 13096569]
5. Rayes N, Bechstein WO, Keck H, Blumhardt G, Lohmann R, Neuhaus P. Causes of death after liver transplantation: an analysis of 41 cases in 382 patients. Zentralblatt Chir. 1995; 120:435–438.
6. Lebrec D, Giuily N, Hadenque A, Vilgrain V, Moreau R, Poynard T, et al. Transjugular intrahepatic portosystemic shunt: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. J Hepatology. 1996; 25:135–144.
7. Franco D, Vons C, Traynor O, de Smadja C. Should portocaval shunt be reconsidered in the treatment of intractable ascites in cirrhosis? Arch Surg. 1988; 123:987–991. [PubMed: 3395243]
8. Laffi G, Barletta G, La Villa G, Del Bene R, Riccardi D, Ticali P, et al. Altered cardiovascular responsiveness to active tilting in nonalcoholic cirrhosis. Gastroenterology. 1997; 113:891–898. [PubMed: 9287981]
9. Wong F, Girgrah N, Graba J, Allidina Y, Liu P, Blendis L. The effect of cirrhotic cardiomyopathy on the cardiac response to exercise in cirrhosis. Gut. 2001; 49:268–275. [PubMed: 11454805]
10. Bernardi M, Rubboli A, Trevisani F, Cancellieri C, Ligabue A, Baraldini M, et al. Reduced cardiovascular responsiveness to exercise-induced sympathoadrenergic stimulation in patients with cirrhosis. J Hepatol. 1991; 12:207–216. [PubMed: 2050999]
11. Moreau R, Hadengue A, Soupison T, Mechin G, Assous M, Roche-Sicot J, et al. Abnormal pressor response to vasopressin in patients with cirrhosis: evidence for impaired buffering mechanism. Hepatology. 1990; 12:7–12. [PubMed: 2373486]

12. Wong F, Liu P, Lilly L, Bomzon A, Blendis L. The role of cardiac structural and functional abnormalities in the pathogenesis of hyperdynamic circulation and renal sodium retention in cirrhosis. Clin Sci. 1999; 97:259–267. [PubMed: 10464050]
13. Pozzi M, Carugo S, Boari G, Pecci V, de Ceglia S, Maggiolini S, et al. Functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. Hepatology. 1997; 26:1131–1137. [PubMed: 9362352]
14. Finucci G, Desideri A, Sacerdoti D, Bolognesi M, Merkel C, Angeli P, et al. Left ventricular diastolic dysfunction in liver cirrhosis. Scan J Gastroenterol. 1996; 31:279–284.
15. Bernardi M, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, et al. QT interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. Hepatology. 1998; 27:28–34. [PubMed: 9425913]
16. Kosar F, Ates F, Sahin I, Karincaoglu M, Yildirim B. QT interval analysis in patients with chronic liver disease: a prospective study. Angiology. 2007; 58:218–224. [PubMed: 17495272]
17. Zambruni A, Trevisani F, Caraceni P, Bernardi M. Cardiac electrophysiological abnormalities in patients with cirrhosis. J Hepatol. 2006; 44:994–1002. [PubMed: 16510203]
18. Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RA. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. Liver Transpl. 2000; 6(4):443–50. [PubMed: 10915166]
19. Nazar A, Guevara M, Sitges M, Terra C, Solà E, Guigou C, Arroyo V, Ginès P. Left ventricular function assessed by echocardiography in cirrhosis: relationship to systemic hemodynamics and renal dysfunction. J Hepatol. 2013; 58:51–57. [PubMed: 22989573]
20. Sampaio F, Pimenta J, Bettencourt N, Fontes-Carvalho R, Silva AP, Valente J, Bettencourt P, Fraga J, Gama V. Systolic and diastolic dysfunction in cirrhosis: a tissue-Doppler and speckle tracking echocardiography study. Liver Int. 2013; 33:1158–1165. [PubMed: 23617332]
21. Altekin RE, Caglar B, Karakas MS, Ozel D, Deger N, Demir I. Evaluation of subclinical left ventricular systolic dysfunction using two-dimensional speckle-tracking echocardiography in patients with non-alcoholic cirrhosis. Hellenic J Cardiol. 2014; 55:402–410. [PubMed: 25243439]
22. Merli M, Calicchia A, Ruffa A, Pellicori P, Riggio O, Giusto M, Gaudio C, Torromeo C. Cardiac dysfunction in cirrhosis is not associated with the severity of liver disease. Eur J Intern Med. 2013; 24:172–176. [PubMed: 22958907]
23. Leibowitz D, Jacobs JM, Gilon D, Lande-Stessman I, Ein-Mor E, Stessman J. Cardiac Structure and Function and Frailty in Subjects Aged 85 and 86 Years. Am J Cardiol. 2016; 118(5):760–4. [PubMed: 27445215]
24. Gharacholou SM, Tashiro T, Cha SS, Scott CG, Takahashi PY, Pellikka PA. Echocardiographic indices associated with frailty in adults≥ 65 years. Am J Cardiol. 2015; 116(10):1591–5. [PubMed: 26394832]
25. Newman AB, Gottdiener JS, Mcburnie MA, Hirsch CH, Kop WJ, Tracy R, Walston JD, Fried LP, Cardiovascular Health Study Research Group. Associations of subclinical cardiovascular disease with frailty. J Gerontol A Biol Sci Med Sci. 2001; 56(3):M158–66. [PubMed: 11253157]
26. Lai JC, Covinsky KE, Dodge JL, Boscardin J, Roberts JP, Segev D, Feng S. A Novel Liver Frailty Index for Patients with Cirrhosis. Hepatology. 2017 Apr 19.
27. Gardin JM, Adams DB, Douglas PS, Feigenbaum H, Forst DH, Fraser AG, Grayburn PA, Katz AS, Keller AM, Kerber RE, Khandheria BK, Klein AL, Lang RM, Pierard LA, Quinones MA, Schnittger I, American Society of Echocardiography. Recommendations for a standardized report for adult transthoracic echocardiography: a report from the American Society of Echocardiography's Nomenclature and Standards Committee and Task Force for a Standardized Echocardiography Report. J Am Soc Echocardiogr. 2002; 15(3):275–90. [PubMed: 11875394]
28. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER12, Rudski L, Spencer KT, Tsang W, Voigt JU. 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):1–39.e14. [PubMed: 25559473]

29. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009; 22:107–33. [PubMed: 19187853]

30. von Elm, Erik MD., Altman, Douglas G DSc, Egger, Matthias MD., Pocock, Stuart J PhD, Gøtzsche, Peter C MD., Vandenbroucke, Jan P MD., for the STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. Ann Intern Med. 2007; 147(8):573–577. [PubMed: 17938396]

31. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TS. Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol. 2006; 47(12):2357–63. [PubMed: 16781359]

32. Kalogeropoulos AP1, Siwamogsatham S, Hayek S, Li S, Deka A, Marti CN, Georgiopoulou VV, Butler J. Echocardiographic assessment of pulmonary artery systolic pressure and outcomes in ambulatory heart failure patients. J Am Heart Assoc. 2014; 3(1):e000363. [PubMed: 24492947]

33. Choudhary G, Jankowich M, Wu WC. Elevated pulmonary artery systolic pressure predicts heart failure admissions in African Americans: Jackson Heart Study. Circ Heart Fail. 2014; 7(4):558–64. [PubMed: 24902739]

34. Ruíz-del-Árbol L1, Achécar L, Serradilla R, Rodríguez-Gandía MÁ, Rivero M, Garrido E, Natcher JJ. Diastolic dysfunction is a predictor of poor outcomes in patients with cirrhosis, portal hypertension, and a normal creatinine. Hepatology. 2013; 58(5):1732–41. [PubMed: 23703953]

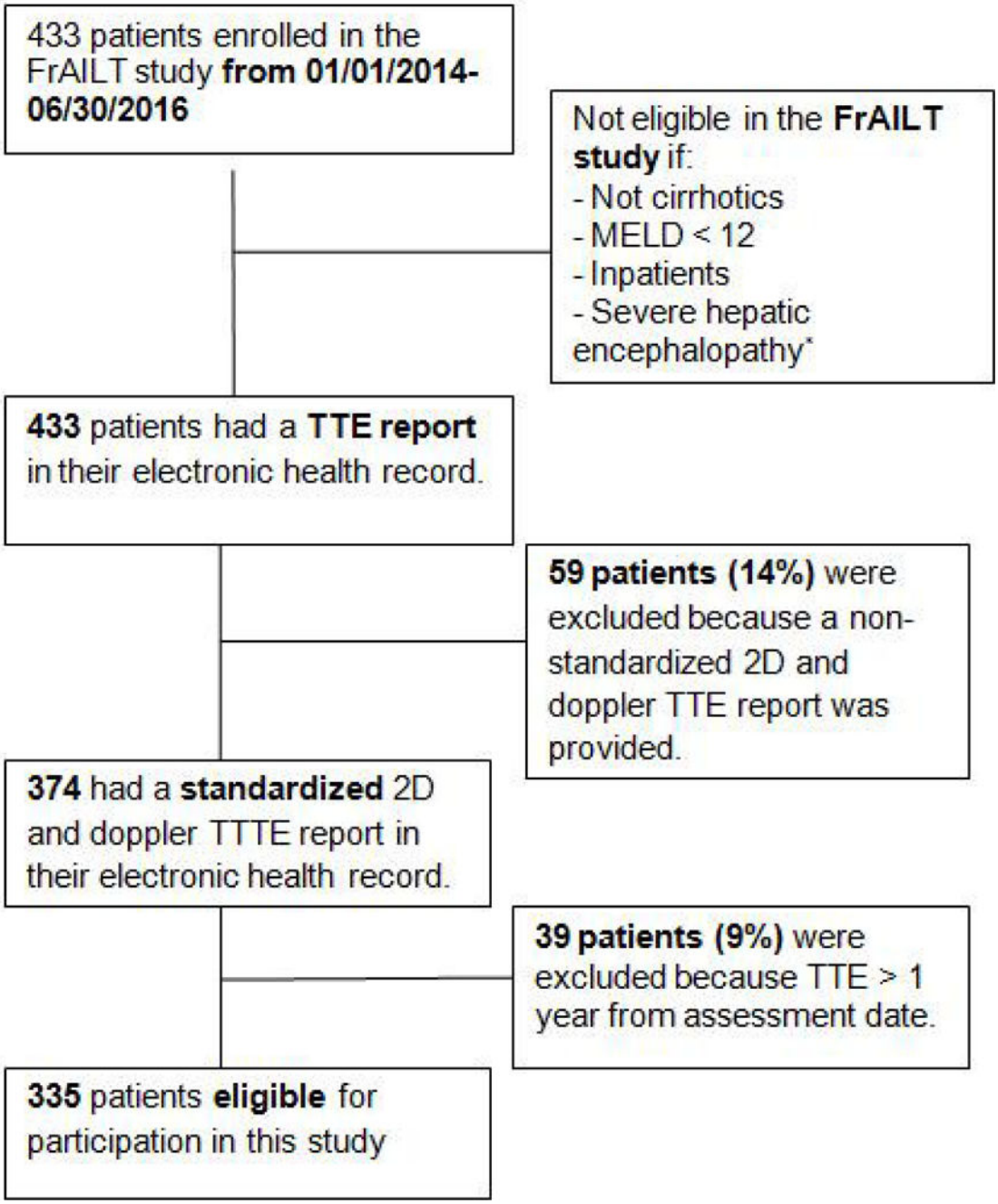

Figure 1.
Included patients flow chart

Table 1a

Baseline characteristics of 335 cirrhotic patients on the waitlist and by frailty status *

	A)	B)	C)	D)	
Characteristics τ	**All (n=335)**	**Robust (n=64)**	**Intermediate (n=218)**	**Frail (n=53)**	**P value**
Demographics					
Age, year	60 (53–65)	60 (57–66)	60 (53–65)	60 (51–65)	0.92
% Female	34%	27%	32%	44%	0.21
Ethnicity					
White	53%	60%	50%	50%	
Black	5%	6%	6%	2%	
Hispanic	25%	16%	25%	35%	0.54
Asian	9%	10%	10%	6%	
Native American	1%	0%	2%	0%	
Other	7%	8%	7%	8%	
Height, cm	172 (163–178)	173 (165–180)	170 (163–178)	172 (160–178)	0.75
Weight, kg	82 (70–97)	81 (74–96)	82 (70–95)	85 (67–98)	0.60
BMI	28 (25–33)	27 (24–32)	28 (24–32)	29 (25–33)	0.16
Baseline liver condition					
Etiology of liver disease					
HCV	48%	60%	50%	29%	
Alcohol	21%	11%	21%	33%	
NASH	11%	6%	10%	23%	0.02
Cholestasic	9%	10%	9%	6%	
HBV	5%	6%	5%	4%	
Other	6%	6%	6%	6%	

	A)	B)	C)	D)	
Characteristics $^{\tau}$	**All (n=335)**	**Robust (n=64)**	**Intermediate (n=218)**	**Frail (n=53)**	**P value**
HCC	38%	56%	41%	10%	<0.001
Laboratory tests					
MELD	15 (11–18)	12 (8–16)	14 (12–17)	18 (15–23)	<0.001
MELDNa	18 (13–22)	14 (10–18)	17 (13–21)	22 (19–27)	<0.001
Creatinine, g/dL	0.9 (0.8–1.2)	0.9 (0.7–1.0)	0.9 (0.8–1.2)	1.1 (0.9–1.8)	<0.001
Albumin, g/dL	3.0 (2.6–3.6)	3.5 (3.1–4.0)	3 (2.6–3.5)	3 (2.6–3.3)	<0.001
Dialysis	2%	2%	2%	6%	0.26
Ascites					
Absent	76%	97%	74%	60%	<0.001
Mild-Moderate	19%	3%	20%	27%	
Severe	6%	0%	6%	13%	
% Moderate Hepatic Encephalopathy $^{¥}$	16%	3%	17%	23%	0.02
Child Pugh Score	8 (6–9)	6 (5–8)	8 (6–9)	8 (7–10)	<0.001
Cardiovascular conditions					
Hypertension	44%	44%	45%	44%	0.56
Diabetes (type 1 or type 2)	23%	19%	22%	37%	0.11
Coronary Artery Disease	5%	5%	6%	2%	0.42
Frailty					
Liver Frailty Index	3.82 (3.35–4.28)	2.90 (2.69–3.08)	3.83 (3.55–4.09)	4.87 (4.69–5.25)	N/A
Days between TTE and frailty assessment	119 (51–186)	140 (79–194)	116 (52–183)	106 (31–195)	0.64

*Defined by the Frailty Index score as frail if score ≥ 4.5, intermediate frail if score between 3.2–4.5 and robust if score <3.2)

$^{\tau}$Median (interquartile range) or %

¥Defined as Numbers Connection Test Score between 60 and 120 seconds. Patients with a Numbers Connection Test score > 120 seconds were excluded from the study

Table 1b

Frailty status of 335 cirrhotic patients on the waitlist by etiologies

	Etiologies of liver disease in the entire cohort (n=335)						*Patients with HCC*
Frailty status*	**HCV (n=160)**	**Alcohol (n=72)**	**Nash (n=37)**	**Cholestasic (n=29)**	**HBV (n=16)**	**Others (n=21)**	**HCC (n=128)**
Robust	23%	10%	11%	21%	25%	21%	27%
Intermediate frail	67%	66%	57%	69%	63%	63%	69%
Frail	9%	24%	32%	10%	13%	16%	4%

*Defined by the Frailty Index score as frail if score ≥ 4.5, intermediate frail if score between 3.2–4.5 and robust if score < 3.

Table 2

Echocardiographic findings of 335 cirrhotic patients on the waitlist and by frailty status*

	A)	B)	C)	D)	
ETT variables ✝	**All (n=335)**	**Robust (n=64)**	**Intermediate (n=218)**	**Frail (n=53)**	**P value**
Measurements of cardiac morphology					
LA dimension, cm	4 (3.6–4.4)	3.8 (3.3–4.3)	4 (3.6–4.4)	4.3 (3.7–4.4)	**0.02**
LA volume index, cc/m²	30 (23–38)	27 (21–30)	31 (24–39)	32 (28–42)	**<0.001**
% LA volumen index ≥ 34cc/m²	41%	13%	46%	48%	**0.001**
LV end diastolic volume index, cc/m²	50 (41–61)	48 (38–59)	51 (42–60)	52 (43–64)	0.26
LV end systolic volume index, cc/m²	16 (12–21)	16 (11–21)	16 (12–20)	17(13–21)	0.51
LV mass index, g/m²	85 (69–100)	85 (70–101)	85 (69–101)	79 (68–91)	0.43
% LV hypertrophy ¥	31%	38%	30%	23%	0.24
Measurements of cardiac systolic function					
LV ejection fraction, %	65% (63–70)	65% (63–69)	65% (63–70)	68% (63–72)	0.06
Measurements of cardiac diastolic dysfunction					
Doppler evidence of diastolic dysfunction	38%	41%	39%	26%	0.42
Diastolic dysfunction classification					
Normal, stage 0	57%	53%	55%	64%	
Mild, stage 1 or impaired relaxation	33%	38%	34%	23%	0.34
Moderate, stage 2 or pseudonormal	5%	3%	6%	4%	
Severe, stages 3–4, reversible or fixed restrictive	0%	0%	0%	0%	
Unable to define/not assessed	5%	3%	5%	9%	
Estimated Pulmonary artery systolic pressure					

	A)	B)	C)	D)	
ETT variables [7]	**All (n=335)**	**Robust (n=64)**	**Intermediate (n=218)**	**Frail (n=53)**	**P value**
PASP, mmHg	28 (23–33)	26 (21–30)	27 (23–33)	29 (25–36)	0.09

[*] Defined by the Frailty Index score as frail if score ≥ 4.5, intermediate frail if score between 3.2–4.5 and robust if score < 3.2)

[7] Median (interquartile range) or %

[¥] Defined as a finding in the TTE report or a LVMI > 115g/m^2 for men and > 95g/m^2 for women

Table 3

TTE indices associated with the Liver Frailty Index (as a continuous variable) using linear regression models, adjusted for age, sex, hypertension and diabetes mellitus”

TTE characteristics	Regression coefficient (95% CI)	P-value
Measurements of cardiac morphology		
LA dimension	0.20 (0.07, 0.34)	**0.004**
LA volume index,cc/m^2	0.01 (0.005, 0.02)	**0.001**
LA volume index ≥ 34cc/m^2	0.11 (−0.06, 0.28)	0.21
LV end diastolic volume index, cc/m^2	0.005 (−0.002, 0.01)	0.14
LV end systolic volume index, cc/m^2	0.01 (−0.006,0.03)	0.23
LV mass index, g/m^2	−0.001 (−0.006, 0.03)	0.57
LV Hypertrophy *	−0.22 (−0.37, −0.06)	**0.007**
Measurements of cardiac systolic function		
LV ejection fraction (%)	1.59 (0.32,2.85)	**0.01**
Measurements of cardiac diastolic dysfunction		
Doppler evidence of diastolic dysfunction	−0.13 (−0.31, 0.06)	0.17
Estimated Pulmonary artery systolic pressure		
PASP, mmHg	0.01 (0.003, 0.02)	**0.008**

* Defined as a finding in the TTE report or a LVMI > 115g/m^2 for men and > 95g/m^2 for women.