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ORIGINAL RESEARCH

Utility of a score-based approach to liver assessment in heart transplant candidates

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KEYWORDS:
heart transplant;
congestive hepatopathy;
combined heart liver transplant;
advanced heart failure;
non-invasive risk score

BACKGROUND: While abnormalities of liver function and imaging are common in patients with end-stage heart failure, advanced fibrosis is uncommon. Liver biopsy (LB) is used to identify advanced fibrosis in heart transplant (HT) candidates but can delay or limit access to definitive therapies and cause complications. We sought to develop and determine the utility of a clinical risk score for advanced fibrosis in HT candidates.

METHODS: We conducted a retrospective, single-center review of patients evaluated for HT between 2012 and 2019 (n = 1,651) and identified those who underwent LB (n = 137) as well as a matched control cohort (n = 160). Patients with congenital heart disease were excluded. All biopsies were reviewed by a liver pathologist. Univariate logistic modeling was used to identify factors predictive of advanced liver fibrosis. Simulation using synthetic data bootstraps was performed to determine the utility of using a score-based approach to trigger LB. Kaplan-Meier curves were used to assess survival.

RESULTS: We identified 32 (23%) patients with stage 0, 79 (58%) with stage 1 to 2, and 26 (19%) with stage 3 to 4/advanced fibrosis. The factor most associated with pursuit of LB was abnormal liver parenchyma on ultrasound. We found that a score combining severe tricuspid regurgitation, alcohol use, and low-density lipoprotein improved specificity and reduced the number of LBs required. We found no difference in survival at 3 years post-HT based on pre-HT fibrosis stage.

CONCLUSIONS: A score composed of noninvasive factors may help reduce the number of patients who require LB for diagnosis of advanced fibrosis. Additional multicenter studies are needed to validate this score.
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Background

Liver dysfunction is common in the setting of end-stage heart failure.[1-3] Heart transplant (HT) candidates with abnormal liver laboratory studies or abnormal liver parenchyma by imaging warrant further evaluation as passive hepatic congestion due to chronically elevated right heart pressures can lead to irreversible sinusoidal dilation, centrilobular necrosis, and progressive fibrosis,[3,4] a risk factor for poor post-HT outcome. Therefore, assessment of liver fibrosis in HT candidates is of paramount importance as the degree of fibrosis may determine lone-HT candidacy or dictate the need for combined heart liver transplant (CHLT).[5]

Multiple clinical risk scores including combining liver biopsy (LB) stage with Model for End Stage Liver Disease Excluding international normalized ratio (MELD-XI)[6] and combining the Model for End Stage Liver Disease (MELD) with ascites[7] have been proposed to predict liver fibrosis stage in the setting of congestive hepatopathy (CH) with mixed results. Others have evaluated the utility of biomarkers including total bilirubin and albumin[4,8,9] for prediction of liver fibrosis with variable benefit in CH. Further, in Fontan patients imaging modalities, including ultrasound, computed tomography, magnetic resonance,[10,11] transient elastography,[12] and laboratory studies,[13,14] have proved inconsistent in predicting liver fibrosis. In non-CH cirrhosis, other scores, including the Lok Index, King Score, aspartate aminotransferase (AST) to platelet ratio index (APRI), fibrosis-4, and AST to alanine aminotransferase ratio (AAR), have been shown to be predictive of cirrhosis, although these have not been thoroughly evaluated in patients with CH.[15,16] The poor performance of previously proposed biochemical markers and clinical risk scores has led to a reliance on LB for HT candidate evaluation.[1,5] The LB has important limitations. First, the need to obtain an LB can delay access to definitive therapies, such as implantation of mechanical circulatory support or HT. Next, LB-explant comparison series in patients with CH have shown heterogeneity of fibrosis, making LB interpretation complex.[9,17] Furthermore, evidence has emerged that fibrosis stage on LB does not predict post-HT survival.[9,17,18] LB is also not without risk of complications.[19] While these concerns exist, LB remains the gold standard for evaluation of pre-HT liver dysfunction.

Clinical risk scores for liver fibrosis have not been evaluated in patients with CH. As such, we sought to identify noninvasive factors that predict advanced fibrosis and assess the ability of clinical risk scores to predict advanced fibrosis in a population of noncongenital HT candidates. We also sought to determine if a score-based approach could improve identification of candidates at risk of having advanced liver fibrosis requiring LB.

Methods and materials

This study was performed under an approved protocol of the Cedars-Sinai Institutional Review Board (STUDY00002007).

Patient selection

All adult patients who were evaluated for HT at Cedars-Sinai Medical Center between January 1, 2012, and December 31, 2019 (n = 1,651) were reviewed (Figure 1). Those patients who underwent LB during the pretransplant evaluation process (n = 167) were identified. A control cohort was developed by selecting at random an equal number of year matched HT candidates who did not undergo pretransplant LB (n = 167). Candidates with congenital heart disease and those with inadequate (less than 1.5 cm in length)/unavailable biopsies or absent laboratory studies/echocardiograms were excluded yielding a final cohort of 137 HT candidates with LB and 160 HT candidates without LB.

All candidates were evaluated by a heart failure/transplant cardiologist and their candidacy evaluated in a multidisciplinary meeting. If grade 3 or 4 fibrosis was identified by LB, candidates

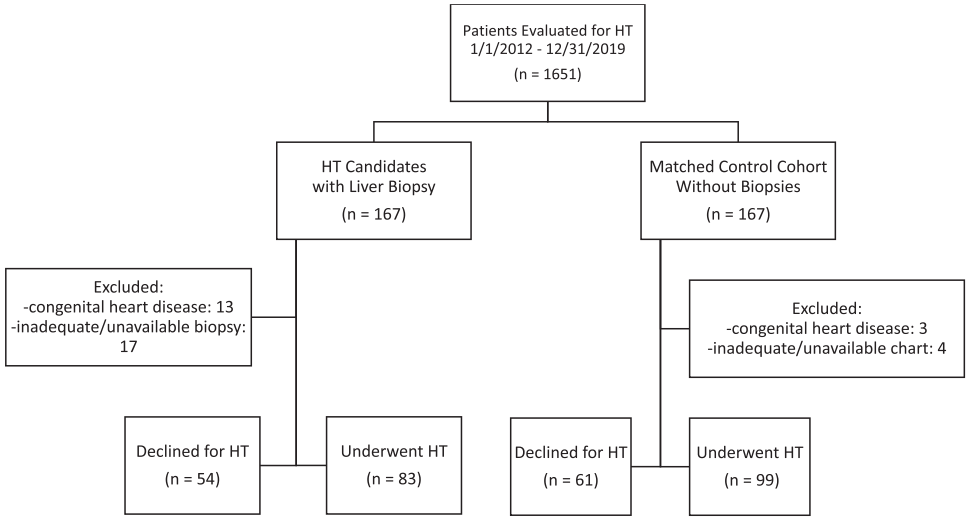

Figure 1 Cohort construction. HT, heart transplant.

were also evaluated by a transplant hepatologist. Selection criteria for HT were consistent with interneational society for heart and lung transplantation guidelines.[5] Patients with a predominance of grade 4 fibrosis on LB were considered for CHLT. In the candidates with LB, 8 received CHLT (all with advanced fibrosis). In the candidates without LB, 1 received CHLT (history of hepatitis C cirrhosis).

Biopsies and histologic assessment

Liver biopsies were retrieved from our pathology warehouse. For patients with multiple biopsies, the biopsy closest to HT was reviewed. All LB were obtained by interventional radiologists. One hundred and twenty-six biopsies were obtained via a transjugular approach with an 18-gauge needle (median number of passes = 4) and 11 biopsies via a percutaneous ultrasound-guided approach. Methods used for biopsy scoring are described in the Supplement.

Clinical variables

Candidate characteristics at the time of HT evaluation were reviewed, including transthoracic echocardiograms, right heart catheterizations, laboratory studies, and abdominal ultrasounds. Components of previously developed risk scores King score,[20] APRI,[21] Lok Index,[22] FIB-4 Score,[23] AAR,[24] Columbia Liver Risk Score,[6] MELD-XI,[25] and Varices-Ascites-Splenomegaly-Thrombocytopenia (VAST)[26] were collected (Supplementary Table 2). The minimum value for each laboratory variable during the pretransplant period was utilized for the calculation of risk scores. The median time between laboratory variables and transplant or LB is provided in Supplementary Table 3.

Statistical analysis

Methods used for statistical analysis are described in the Supplement.

Results

Baseline characteristics

The cohort of patients was grouped based on the predominant fibrosis stage on LB (Table 1). We identified 32 (23%) patients with no fibrosis, 79 (58%) with mild fibrosis (stages 1-2), and 26 (19%) with advanced fibrosis (stages 3-4). There were no significant differences in baseline demographic factors, including age, gender, comorbidities, and presence of durable left ventricular assist device. A higher percentage of patients with advanced fibrosis (31%) had a history of heavy alcohol use compared to patients with no fibrosis (9%) or mild fibrosis (8%). As expected, fewer patients with advanced fibrosis (19%) underwent lone-HT compared to those with mild fibrosis (67%), no fibrosis (53%), or the no biopsy control group (61%).

There were significant differences between the groups in the presence of ascites ($p < 0.001$) and splenomegaly ($p = 0.02$), with these most common in the advanced fibrosis group. Liver parenchyma on ultrasound was also significantly different between the groups ($p < 0.001$) with nodularity most common in the advanced fibrosis group (52%). Finally, hepatic venous pressure measurements at the time of LB showed stepwise increases with increasing fibrosis stage.

Interestingly, valvular disease was more common in the advanced fibrosis group (Table 1). Forty percent of the advanced fibrosis cohort had severe mitral regurgitation (MR), compared to 25% of the no-biopsy group, 27% of the biopsy no fibrosis group, and 18% of the mild fibrosis group ($p = 0.014$). Similarly, 64% of the advanced fibrosis group had severe tricuspid regurgitation (TR) compared to 21%, 23%, and 27% of the no-biopsy, biopsy-no fibrosis, and mild fibrosis groups, respectively. These hemodynamic impacts were also observed on right heart catheterization with significant differences in right atrial pressure ($p < 0.001$) and right atrial pressure to pulmonary capillary wedge pressure ratio ($p < 0.001$). While laboratory markers were largely similar across the groups, we did observe that the advanced fibrosis group had the lowest total bilirubin ($p = 0.003$) and low-density lipoprotein (LDL) ($p = 0.029$).

Factors associated with performance of liver biopsy and utility of ultrasound

Patients undergoing HT evaluation are selected to undergo an LB based on clinical factors suggesting an increased risk of liver fibrosis. We sought to determine the factors associated with performance of LB during the pre-HT period using univariate logistic modeling (Supplementary Table 6). Most notable were nodular liver parenchyma on abdominal ultrasound (odds ratio (OR) 7.48, 95% confidence intervals (CI) 2.33-24.01, $p = 0.001$), heterogenous liver parenchyma on abdominal ultrasound (OR 3.64, 95% CI 1.06-12.54, $p = 0.041$), and presence of ascites on abdominal ultrasound (OR 4.19, 95% CI 1.69-10.42, $p = 0.002$). Additionally, severe valvular disease was associated with obtaining an LB (severe MR [OR 3.91, 95% CI 1.03-14.88, $p = 0.046$], severe TR [OR 5.88, 95% 1.63-21.19, $p = 0.007$]). Given the strong odds of obtaining an LB in a patient with a nodular liver parenchyma, we then analyzed the performance of ultrasound parenchyma in predicting advanced fibrosis and found poor predictive ability (AUROC 0.566) (Table 2).

Prediction score analysis

Next, we assessed the performance of previously proposed noninvasive scoring systems for liver fibrosis. Area under the receiver operating curve (AUROC) for prediction of advanced fibrosis stage was calculated for the Lok index (0.472), King score (0.443), APRI (0.606), fibrosis-4 (0.465), AAR (0.519), MELD-XI (0.529), and VAST (0.677) scores (Table 2). Additionally, we assessed the previously proposed Columbia score which was developed in a similar population of HT candidates (Supplementary Figure 1).[6]

Factors associated with advanced fibrosis

In patients who underwent LB during the pre-HT period, we sought to determine the factors associated with the identification of advanced fibrosis by pathologic interpretation.

Table 1 Baseline Characteristics

Characteristic	No biopsy ($n = 160$)	Predominant fibrosis stage on biopsy: No fibrosis ($n = 32$)	Mild fibrosis (stages 1-2) ($n = 79$)	Advanced fibrosis (stages 3-4) ($n = 26$)	p-value
Age (years)	57.1 (11.0)	57.8 (11.3)	56.6 (10.7)	59.0 (9.65)	0.774
Male	120 (75.0%)	25 (78.1%)	69 (87.3%)	21 (80.8%)	0.176
NICM	80 (50.0%)	21 (65.6%)	50 (63.3%)	20 (76.9%)	0.070
Diabetes mellitus	62 (38.8%)	9 (28.1%)	25 (32.1%)	6 (23.1%)	0.315
Hypertension	69 (43.1%)	10 (31.2%)	27 (34.6%)	9 (34.6%)	0.428
BMI (kg/m^2)	25.9 (5.7%)	26.7 (5.18)	25.9 (4.89)	25.8 (4.98)	0.878
Left ventricular assist device	28 (17.8%)	12 (37.5%)	14 (17.9%)	4 (15.4%)	0.066
History of heavy alcohol use	11 (6.9%)	3 (9.4%)	6 (7.6%)	8 (30.8%)	0.007
Hepatitis C positive	4 (2.8%)	0 (0.00%)	3 (4.1%)	2 (8.3%)	0.320
Hepatitis B core antibody positive	26 (10.3%)	18 (13.2%)	1 (3.5%)	5 (7.4%)	0.378
Abdominal ultrasound findings					
Ascites	33 (25.0%)	16 (51.6%)	43 (54.4%)	18 (72.0%)	< 0.001
Splenomegaly	19 (14.4%)	9 (29.0%)	22 (27.8%)	9 (36.0%)	0.021
Liver parenchyma					< 0.001
Heterogenous	33 (25.0%)	8 (25.8%)	26 (32.9%)	8 (32.0%)	
Nodular	6 (4.55%)	12 (38.7%)	35 (44.3%)	13 (52.0%)	
Liver size					
Large	35 (26.5%)	15 (48.4%)	22 (27.8%)	11 (44.0%)	0.009
Portal pressure measurements					
Free hepatic venous pressure (mm Hg)		9.85 (5.85)	13.5 (7.98)	15.4 (7.04)	0.024
Hepatic wedge pressure (mm Hg)		13.8 (7.68)	17.0 (8.17)	19.4 (7.90)	0.051
Hepatic venous pressure gradient (mm Hg)		3.96 (4.57)	3.30 (2.94)	4.12 (3.11)	0.487
Transthoracic echocardiogram					
Ejection fraction (%)	22.7 (11.6)	22.5 (10.2)	27.8 (16.9)	26.0 (13.3)	0.041
Right ventricular function					
Severely depressed	21 (14.6%)	11 (36.7%)	17 (23.0%)	6 (27.3%)	
Mitral regurgitation					0.014
Mild	41 (28.7%)	7 (23.3%)	20 (26.3%)	3 (12.0%)	
Moderate	29 (20.3%)	13 (43.3%)	29 (38.2%)	9 (36.0%)	
Severe	36 (25.2%)	8 (26.7%)	14 (18.4%)	10 (40.0%)	
Tricuspid regurgitation					< 0.001
Mild	38 (26.0%)	7 (23.3%)	20 (26.0%)	3 (12.0%)	
Moderate	39 (26.7%)	11 (36.7%)	28 (36.4%)	3 (12.0%)	
Severe	31 (21.2%)	7 (23.3%)	21 (27.3%)	16 (64.0%)	
LVIDD (cm)	3.12 (0.72)	3.18 (0.67)	2.99 (0.77)	3.29 (0.68)	0.285
IVC collapsibility					< 0.001
None (RA pressure ~15)	39 (30.2%)	13 (48.1%)	43 (56.6%)	15 (65.2%)	
< 50% (RA pressure ~8)	39 (30.2%)	8 (29.6%)	24 (31.6%)	6 (26.1%)	
Right heart catheterization pressures					
RAP (mm Hg)	8.85 (5.34)	11.3 (5.83)	14.9 (6.62)	15.2 (7.56)	< 0.001
PAs (mm Hg)	43.8 (14.1)	44.7 (11.6)	48.2 (14.1)	41.1 (11.6)	0.105
PCWP (mmHg)	20.0 (8.84)	20.9 (9.20)	23.7 (8.82)	21.0 (8.40)	0.065
RAP to PCWP ratio	0.48 (0.26)	0.55 (0.22)	0.66 (0.30)	0.72 (0.31)	< 0.001
Laboratory values					
Albumin (g/dl)	2.99 (0.57)	2.85 (0.62)	2.90 (0.51)	3.12 (0.57)	0.219
Total bilirubin (mg/dl)	1.16 (0.57)	1.62 (1.59)	1.11 (0.41)	1.06 (0.24)	0.003
Serum creatinine (mg/dl)	0.90 (0.44)	0.90 (0.46)	1.00 (0.50)	1.14 (1.05)	0.140
Platelet count ($\times 10^9$/liter)	91.0 (53.6)	78.4 (52.3)	78.8 (32.1)	89.0 (48.1)	0.227
Sodium (mmol/liter)	129 (4.41)	128 (3.78)	128 (4.62)	128 (6.07)	0.078
Alanine aminotransferase (units/liter)	16.8 (15.4)	14.9 (11.4)	12.6 (6.43)	13.1 (7.60)	0.086

(*continued on next page*)

Table 1 (*Continued*)

Characteristic	No biopsy ($n = 160$)	Predominant fibrosis stage on biopsy: No fibrosis ($n = 32$)	Mild fibrosis (stages 1-2) ($n = 79$)	Advanced fibrosis (stages 3-4) ($n = 26$)	*p*-value
Aspartate aminotransferase (units/liter)	23.2 (35.5)	23.5 (22.9)	16.9 (6.57)	16.2 (7.87)	0.282
LDL (mg/dl)	62.6 (25.9)	69.1 (28.5)	61.1 (22.0)	48.7 (17.0)	0.029
Triglyceride (mmol/liter)	92.0 (51.5)	109 (92.3)	68.8 (27.3)	81.5 (40.8)	0.002
Patients who underwent transplant					
UNOS status at listing					0.306
Status 1-2	17 (18.7%)	3 (21.4%)	7 (15.6%)	0	
Status 3	51 (56.0%)	9 (64.3%)	33 (73.3%)	5 (100%)	
Status 4-6	23 (25.3%)	2 (14.3%)	5 (11.1%)	0	
Inotropes at listing	34 (37.4%)	5 (35.7%)	28 (62.2%)	3 (60.0%)	0.030

Abbreviations: BMI, body mass index; IVC, inferior vena cava; LDL, low-density lipoprotein; LVIDD, left ventricular internal diameter end diastole; NICM, nonischemic cardiomyopathy; PAs, pulmonary artery systolic; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RAP, right atrium pressure; UNOS, united network for organ sharing.

Demographic, hemodynamic, echocardiographic, and blood chemistry factors were evaluated with univariate logistic modeling to assess the ability to predict advanced fibrosis (Supplementary Table 7). A history of heavy alcohol use (OR 5.56, 95% CI 2.15-14.35, $p < 0.001$) and severe valvular disease was associated with increased odds of advanced fibrosis (severe MR [OR 2.55, 95% CI 1.01-6.44, $p = 0.048$], severe TR [OR 5.02, 95% CI 1.99-12.63, $p < 0.001$]). LDL was the only laboratory marker predictive of advanced fibrosis (OR 0.97 per mg/dl, 95% CI 0.94-0.99, $p = 0.009$). Of noninvasive scores, the VAST (OR 1.73 per point, 95% CI 0.95-3.12, $p = 0.070$) exhibited a trend toward statistical significance. Additional factors that exhibited a trend toward an increased odds of advanced fibrosis included ascites on abdominal ultrasound (OR 2.22, 95% CI 0.86-5.75, $p = 0.099$) and serum albumin (OR 2.22 per mg/dl, 95% CI 0.97-5.09, $p = 0.060$). Notably, nodular liver parenchyma on abdominal ultrasound was not associated with increased odds of advanced fibrosis (OR 2.01, 95% CI 0.60-6.74, $p = 0.261$).

Next, factors with $p \leq 0.05$ in univariate modeling were added to a multivariable logistic model (Table 3). Severe TR (OR 3.23, 95% CI 1.93-5.39, $p = 0.023$), a history of heavy alcohol use (OR 4.62, 95% CI 2.52-8.45, $p = 0.011$), and LDL (OR 0.96 per mg/dl, 95% CI 0.95-0.98) remained predictive of advanced fibrosis in the multivariable model (Table 4).

Simulation of score-based approach versus ultrasound-based approach

We developed a clinical risk score for advanced fibrosis composed of the 3 significant variables in the multivariable model (Supplementary Table 4). This clinical risk score was assessed in 2 simulations using synthetic data bootstraps. In the first simulation, using the clinical risk score (above the optimal cutpoint identified for each bootstrap) to trigger LB was associated with a significantly higher AUROC (0.71 vs 0.50), numerically higher sensitivity (48% vs 41%), numerically higher specificity (93% vs 73%), and a lower percentage of LB required for the cohort (10% vs 23%). In the second simulation, using the clinical risk score (above a single cutpoint of −4 points), we observed similar results.

Liver biopsy pathology and post-HT survival

Finally, we assessed post-HT survival based on both the predominant fibrosis stage (Supplementary Figure 2) and presence of nodular regenerative hyperplasia (NRH) (Supplementary Figure 3) on the pre-HT LB. CHLT recipients (1 control and 8 LB patients) were excluded from survival analysis. NRH, another histologic marker of liver damage, can

Table 2 Performance of Abdominal Ultrasound and Extant Noninvasive Scoring Systems in Predicting Advanced Fibrosis Stage

Test/Scoring System	AUC (95% CI)	Sensitivity	Specificity	Accuracy
Abdominal ultrasound: nodular liver	0.566 (0.526-0.784)	0.560	0.573	0.570
Lok Index	0.528 (0.369-0.688)	0.563	0.582	0.578
King Score	0.542 (0.403-0.681)	0.346	0.938	0.479
APRI	0.638 (0.493-0.782)	0.346	0.938	0.479
FIB4	0.578 (0.422-0.735)	0.291	0.875	0.423
AAR	0.562 (0.387-0.737)	0.500	0.764	0.704
MELD-XI	0.529 (0.369-0.690)	0.673	0.500	0.634
VAST	0.677 (0.552-0.794)	0.944	0.333	0.493

Abbreviations: AAR, AST to alanine aminotransferase ratio; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; FIB4, fibrosis-4; MELD-XI, model for end stand liver disease excluding INR; VAST, varices, ascites, splenomegaly, thrombocytopenia.

Table 3 Multivariable Analysis of Factors for Advanced Fibrosis

Factors	Odds ratio	95% Confidence intervals	*p*-value
Severe TR	3.23	1.93-5.39	0.023
Severe MR	1.25	0.73-2.14	0.682
History of heavy alcohol use	4.62	2.52-8.45	0.011
LDL (mg/dl)	0.96	0.95-0.98	0.011

Abbreviations: LDL, low-density lipoprotein; MR, mitral regurgitation; TR, tricuspid regurgitation.

be identified in patients with CH without cirrhosis. Excluding patients with advanced fibrosis, we found NRH to be common (28% biopsy: no fibrosis, 37% biopsy: mild fibrosis) in this subpopulation. Candidates that underwent combined heart-liver transplant ($n = 9$) were excluded from the survival analysis, limiting the number of patients with advanced fibrosis. We found no difference in 3-year survival based on the presence of NRH or fibrosis on pre-HT.

Discussion

In this study, we sought to identify noninvasive factors that predict advanced fibrosis and assess the ability of clinical risk scores to predict advanced fibrosis in a population of HT candidates without congenital heart disease. We found the factor most strongly associated with performance of an LB was liver nodularity on abdominal ultrasound, whereas we found that history of heavy alcohol use and severe tricuspid regurgitation were the factors most strongly associated with advanced fibrosis by pathologic interpretation in patients with CH. With the goal of developing a score-based approach to noninvasively identify patients most in need of an LB, we performed simulations using synthetic data bootstraps derived from our cohort and found that a score based on severe tricuspid regurgitation, heavy alcohol use, and LDL decreased the number of LBs needed to diagnose advanced fibrosis as compared to using abdominal ultrasound alone.

We found that fibrosis stage on LB did not predict survival at 3 years after HT. This was likely a consequence of our institutional protocol in which candidates for HT with predominance of grade 4 fibrosis on LB underwent heart-liver transplant; in 12 candidates with advanced fibrosis on LB that underwent HT, 7 candidates (58%) underwent heart-liver transplant. However, advanced liver fibrosis alone,[27] or in conjunction with other clinical factors such as MELD,[6] is a well-established risk factor for adverse outcomes after durable left ventricular assist device implantation or HT. As such, only 12 of the 26 candidates (46%) that were found to have advanced fibrosis on LB underwent HT, as compared to 64% of candidates without advanced fibrosis on LB. Thus, even though we did not identify liver fibrosis as a risk factor for post-transplant outcomes, the presence of advanced fibrosis affects the likelihood that a candidate will undergo HT and thus long-term survival.

Multiple studies have highlighted the difficulty of evaluating liver disease in end-stage heart failure. Shingina et al recently surveyed providers at CHLT centers in North America and reported disparate evaluation and listing practices, reflecting the lack of consensus when considering these candidates.[28] We previously reported that LB results have discordance with explanted livers in patients who underwent combined heart-liver transplants, reflecting the heterogeneity of CH, and suggesting that LB in this population must be interpreted with caution.[9,18,29] This finding has also been reported in Fontan patients where the liver is exposed to chronically elevated pressures.[30] As such, there have been efforts to develop clinical risk scores to assist in evaluating the reversibility of liver damage, including Farr et al combined biopsy fibrosis stage with MELD-XI and reported higher scores were predictive of 1-year post-HT mortality.[6] Others have focused on the Fontan patient population[31,32] and, notably, found the VAST score to be predictive of fibrosis.[26] Similarly, we found markers of elevated right-sided pressure, like those seen in Fontan patients, were associated with advanced fibrosis. Additionally, we found lower LDL to be independently associated with advanced fibrosis, consistent with previous reporting that LDL is predictive of both survival in heart failure[33] and cirrhosis.[34]

Numerous risk scores have been validated in inflammatory hepatopathies; however, these results have not translated to the CH population. We evaluated the King score, APRI, Lok index, FIB-4 Score, AAR, and MELD-XI scores and similarly found poor performance in predicting fibrosis. Likewise, we found that the factor most strongly

Table 4 Evaluation of Predictive Score for Advanced Fibrosis in Synthetic Dataset

	AUROC	Sensitivity	Specificity	Percent liver biopsies required
Simulation 1: Using optimal cutpoint identified for each bootstrap				
Score: *Severe TR + Heavy Alcohol Use + LDL*	0.71 (0.63-0.80)	48% (33%-76%)	93% (78%-99%)	10% (4%-25%)
US only	0.50 (0.43-0.58)	41% (22%-100%)	73% (0%-81%)	23% (18%-28%)
Simulation 2: Using cutpoint of –4 for all bootstraps				
Score: *Severe TR + Heavy Alcohol Use + LDL*	0.69 (0.59-0.78)	44% (26%-62%)	93% (90%-96%)	11% (7%-14%)
US only	0.50 (0.43-0.58)	41% (22%-100%)	73% (0%-82%)	23% (18%-28%)

Abbreviations: AUCOC, area under receiver operating characteristic curve; LDL, low-density lipoprotein; TR, tricuspid regurgitation; US, ultrasound of liver parenchyma.

Numbers represent median of all 1000 bootstraps with 95% confidence intervals in parenthesis.

associated with performance of LB, a nodular liver parenchyma by ultrasound, was itself poorly predictive of advanced fibrosis.

The factors which were included in the proposed risk score are suggestive of different mechanisms of liver injury. First, history of heavy alcohol use is consistent with a direct toxic insult to the liver. Next, severe tricuspid regurgitation is reflective of hepatic pressure overload. It may be that the combination of multiple insults, not solely a congestive process, result in irreversible liver damage. LDL, the third factor included in the model, is reflective of liver function. Our ability to combine additional factors reflective of hepatic congestive, toxicity, and/or function was limited by the small population.

In pursuing LB, patients are exposed to potential complications. Transjugular liver biopsies have a reported major complication rate of 0.59%.[19] While not considered specifically in previous studies, many HT candidates are on systemic anticoagulation for comorbid cardiac conditions or mechanical circulatory devices which confers an increased risk of bleeding or may preclude an LB altogether. These concerns highlight that the score-based approach demonstrated in this study may be of clinical utility.

Despite the challenges, accurate assessment of fibrosis stage in HT candidates is critical. Liver fibrosis stage impacts candidacy and contributes to decision making about which patients are declined for HT, eligible for lone HT, or require CHLT. LB, despite the challenges, remains the gold standard and helps clinicians evaluate for alternative, non-CH, etiologies of liver disease, including nonalcoholic steatohepatitis or alcohol. In the past, those patients determined to require CHLT have experienced longer wait times and higher waitlist mortality compared to lone HT candidates,[35,36] though recent allocation changes may impact these trends.[37] These adverse outcomes suggest another possible use for the score-based approach demonstrated in this study, as patients with high scores, suggesting advanced fibrosis, may warrant increased priority for HT. Finally, hepatic fibrosis may be potentially reversible once normal cardiac function is restored which further clouds pre-HT evaluation. The limitations inherent to biopsy in a heterogenous process, such as CH, suggest more comprehensive, multifactorial evaluation of liver disease is sorely needed.

This study has several limitations. The population of interest, end-stage heart failure patients with significant liver disease, is unique and thus very small. Thus, the study is limited by small size and retrospective design. Our analysis of post-HT survival is limited by the number of patients with advanced fibrosis who underwent HT alone, as most patients found to have advanced fibrosis underwent CHLT. Further, while we relied on the most frequently utilized biopsy grading scale in CH, there is no universally accepting staging system. Despite potential challenges with interpreting the LB, this test remains the gold standard, as no other evaluation strategy has proven consistent in this understudied population, and we relied on the LB to validate our risk score development. Additionally, the small number of patients necessitated grouping fibrosis stages (1 and 2, 3 and 4) for statistical analysis which may obscure between group differences for individual fibrosis stages. From a statistical standpoint, the small number of candidates with advanced fibrosis limited the number of variables that could be assessed in a multivariable model, requiring us to use a simulation-based approach. Given the narrow population of interest, there is no immediately available external cohort for risk score validation. Additional studies utilizing other cohorts will be needed to validate this proposed score. Finally, medications prior to transplant were not collected which may have influenced pre-HT laboratory studies.

Conclusions

In conclusion, we show that a score based on 3 noninvasive factors reduced the need for LB during the assessment of HT candidates with CH. We also found that LB fibrosis stage was not associated with post-HT survival and previously proposed clinical risk scores perform poorly in this population. Identification of novel strategies for the assessment of liver disease in this population stands to benefit the large group of patients whose transplant candidacy depends on the assessment of their liver disease.

Disclosure statement

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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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2023.100045.

References

1. Lemmer A, Van-Wagner LB, Ganger D. Assessment of advanced liver fibrosis and the risk for hepatic decompensation in patients with congestive hepatopathy. Hepatology (Baltimore, Md) 2018;68:1633-1641. https://doi.org/10.1002/hep.30048.
2. Ford RM, Book W, Spivey JR. Liver disease related to the heart. Transplant Rev (Orlando, Fla) 2015;29:33-7. https://doi.org/10.1016/j.trre.2014.11.003.
3. Møller S, Bernardi M. Interactions of the heart and the liver. Eur Heart J 2013;34:2804-11. https://doi.org/10.1093/eurheartj/eht246.
4. Samsky MD, Patel CB, DeWald TA, et al. Cardiohepatic interactions in heart failure: an overview and clinical implications. J Am Coll Cardiol 2013;61:2397-405. https://doi.org/10.1016/j.jacc.2013.03.042.
5. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant 2016;35:1-23. https://doi.org/10.1016/j.healun.2015.10.023.

6. Farr M, Mitchell J, Lippel M, et al. Combination of liver biopsy with MELD-XI scores for post-transplant outcome prediction in patients with advanced heart failure and suspected liver dysfunction. J Heart Lung Transplant 2015;34:873-82. https://doi.org/10.1016/j.healun.2014.12.009.
7. Lebray P, Varnous S, Pascale A, et al. Predictive value of liver damage for severe early complications and survival after heart transplantation: a retrospective analysis. Clin Res Hepatol Gastroenterol 2018;42:416-26. https://doi.org/10.1016/j.clinre.2018.03.006.
8. Hsu R-B, Chang C-I, Lin F-Y, et al. Heart transplantation in patients with liver cirrhosis. Eur J Cardio-Thorac Surg 2008;34:307-12. https://doi.org/10.1016/j.ejcts.2008.05.003.
9. Dhall D, Kim SA, Mc Phaul C, et al. Heterogeneity of fibrosis in liver biopsies of patients with heart failure undergoing heart transplant evaluation. Am J Surg Pathol 2018;42:1617-24. https://doi.org/10.1097/PAS.0000000000001163.
10. Bae JM, Jeon TY, Kim JS, et al. Fontan-associated liver disease: spectrum of US findings. Eur J Radiol 2016;85:850-6. https://doi.org/10.1016/j.ejrad.2016.02.002.
11. Wallihan DB, Podberesky DJ. Hepatic pathology after Fontan palliation: spectrum of imaging findings. Pediatr Radiol 2013;43:330-8. https://doi.org/10.1007/s00247-012-2531-y.
12. Chen B, Schreiber RA, Human DG, Potts JE, Guttman OR. Assessment of liver stiffness in pediatric fontan patients using transient elastography. Can J Gastroenterol Hepatol 2016;2016:7125193. https://doi.org/10.1155/2016/7125193.
13. Wu FM, Earing MG, Aboulhosn JA, et al. Predictive value of biomarkers of hepatic fibrosis in adult Fontan patients. J Heart Lung Transplant 2017;36:211-9. https://doi.org/10.1016/j.healun.2016.07.011.
14. Schachter JL, Patel M, Horton SR, Mike Devane A, Ewing A, Abrams GA. FibroSURE and elastography poorly predict the severity of liver fibrosis in Fontan-associated liver disease. Congenit Heart Dis 2018;13:764-70. https://doi.org/10.1111/chd.12650.
15. Deng H, Qi X, Guo X. Diagnostic accuracy of APRI, AAR, FIB-4, FI, King, Lok, Forns, and FibroIndex scores in predicting the presence of esophageal varices in liver cirrhosis. Medicine 2015;94:e1795. https://doi.org/10.1097/MD.0000000000001795.
16. Wang L, Feng Y, Ma X, et al. Diagnostic efficacy of noninvasive liver fibrosis indexes in predicting portal hypertension in patients with cirrhosis. PLoS ONE 2017;12:e0182969. https://doi.org/10.1371/journal.pone.0182969.
17. Louie CY, Pham MX, Daugherty TJ, Kambham N, Higgins JPT. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. Mod Pathol 2015;28:932-43. https://doi.org/10.1038/modpathol.2015.40.
18. Rushakoff JA, Kransdorf EP, Patel JK, Kobashigawa JA, Sundaram V, Guindi M. Heterogeneity of liver fibrosis in patients with congestive hepatopathy: a biopsy and explant comparison series. Ann Diagn Pathol 2022;56:151876. https://doi.org/10.1016/j.anndiagpath.2021.151876.
19. Dohan A, Guerrache Y, Dautry R, et al. Major complications due to transjugular liver biopsy: incidence, management and outcome. Diagn Interv Imaging 2015;96:571-7. https://doi.org/10.1016/j.diii.2015.02.006.
20. Cross TJ, Rizzi P, Berry PA, Bruce M, Portmann B, Harrison PM. King's Score: an accurate marker of cirrhosis in chronic hepatitis C. Eur J Gastroenterol Hepatol 2009;21:730-8. https://doi.org/10.1097/MEG.0b013e32830dfcb3.
21. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-26. https://doi.org/10.1053/jhep.2003.50346.
22. Lok AS, Ghany MG, Goodman ZD, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: results of the HALT-C cohort. Hepatology 2005;42:282-92. https://doi.org/10.1002/hep.20772.
23. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology 2007;46:32-6. https://doi.org/10.1002/hep.21669.
24. Nyblom H, Berggren U, Balldin J, Olsson R. High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. Alcohol Alcohol 2004;39:336-9. https://doi.org/10.1093/alcalc/agh074.
25. Wernly B, Lichtenauer M, Franz M, et al. Model for End-stage Liver Disease excluding INR (MELD-XI) score in critically ill patients: easily available and of prognostic relevance. PLoS One 2017;12:e0170987. https://doi.org/10.1371/journal.pone.0170987.
26. Elder RW, McCabe NM, Hebson C, et al. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. Int J Cardiol 2013;168:3764-9. https://doi.org/10.1016/j.ijcard.2013.06.008.
27. Goyal A, Dalia T, Ranka S, et al. Impact of biopsy proven liver fibrosis on patients undergoing evaluation and treatment for advanced heart failure surgical therapies. Am J Cardiol 2023;194:46-55. https://doi.org/10.1016/j.amjcard.2023.02.004.
28. Shingina A, Chadha R, Lim N, et al. Combined heart liver transplantation practices survey in north america: evaluation and organ listing practices. Liver Transpl 2023;29:591-7. https://doi.org/10.1097/LVT.0000000000000079. June.
29. Krings G, Can B, Ferrell L. Aberrant centrizonal features in chronic hepatic venous outflow obstruction: centrilobular mimicry of portal-based disease. Am J Surg Pathol 2014;38:205-14. https://doi.org/10.1097/PAS.0000000000000099.
30. Vaikunth SS, Higgins JP, Concepcion W, et al. Does liver biopsy accurately measure fibrosis in Fontan-associated liver disease? A comparison of liver biopsy pre-combined heart and liver transplant and liver explant post-transplant. Clin Transplant 2020;34:e14120. https://doi.org/10.1111/ctr.14120.
31. Assenza GE, Graham DA, Landzberg MJ, et al. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. Heart 2013;99:491-6. https://doi.org/10.1136/heartjnl-2012-303347.
32. Deo SV, Al-Kindi SG, Altarabsheh SE, et al. Model for end-stage liver disease excluding international normalized ratio (MELD-XI) score predicts heart transplant outcomes: evidence from the registry of the United Network for Organ Sharing. J Heart Lung Transplant 2016;35:222-7. https://doi.org/10.1016/j.healun.2015.10.008.
33. Rauchhaus M, Clark AL, Doehner W, et al. The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol 2003;42:1933-40. https://doi.org/10.1016/j.jacc.2003.07.016.
34. Janicko M, Veseliny E, Lesko D, Jarcuska P. Serum cholesterol is a significant and independent mortality predictor in liver cirrhosis patients. Ann Hepatol 2013;12:581-7.
35. Wolf JH, Sulewski ME, Cassuto JR, et al. Simultaneous thoracic and abdominal transplantation: can we justify two organs for one recipient? Am J Transplant 2013;13:1806-16. https://doi.org/10.1111/ajt.12291.
36. Schaffer JM, Chiu P, Singh SK, Oyer PE, Reitz BA, Mallidi HR. Heart and combined heart-kidney transplantation in patients with concomitant renal insufficiency and end-stage heart failure. Am J Transplant 2014;14:384-96. https://doi.org/10.1111/ajt.12522.
37. Iyengar A, Weingarten N, Herbst DA, et al. Waitlist trends in heart-liver transplantation with updated US Heart Allocation System. Ann Thorac Surg 2022;116:1270-5. https://doi.org/10.1016/j.athoracsur.2022.08.010.