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ORIGINAL RESEARCH

Characterizing Heart Failure With Preserved Ejection Fraction in End-Stage Liver Disease and Liver Transplant Outcomes

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ABSTRACT

BACKGROUND Heart failure with preserved ejection fraction (HFpEF) and its risk factors are increasingly recognized in patients with end-stage liver disease (ESLD).

OBJECTIVES The aim of this study was to characterize HFpEF and identify relevant risk factors in patients with ESLD. Additionally, the prognostic impact of high-probability HFpEF on post-liver transplantation (LT) mortality was investigated.

METHODS Patients with ESLD prospectively enrolled from the Asan LT Registry between 2008 and 2019 were divided into groups with low (scores of 0 and 1), intermediate (scores of 2-4), and high (scores of 5 and 6) probability using the Heart Failure Association–PEFF diagnostic score for HFpEF. Gradient-boosted modeling in machine learning was further used to appraise the apparent importance of risk factors. Finally, post-LT all-cause mortality was followed for 12.8 years (median 5.3 years); there were 498 deaths after LT.

RESULTS Among the 3,244 patients, 215 belonged to the high-probability group, commonly those with advanced age, female sex, anemia, dyslipidemia, renal dysfunction, and hypertension. The highest risk factors for the high-probability group, according to gradient-boosted modeling, were female sex, anemia, hypertension, dyslipidemia, and age >65 years. Among patients with Model for End-Stage Liver Disease scores of >30, those with high, intermediate, and low probability had cumulative overall survival rates of 71.6%, 82.2%, and 88.9% at 1 year and 54.8%, 72.1%, and 88.9% at 12 years after LT (log-rank $P = 0.026$), respectively.

CONCLUSIONS High-probability HFpEF was found in 6.6% of patients with ESLD with poorer long-term post-LT survival, especially those with advanced stages of liver disease. Therefore, identifying HFpEF using the Heart Failure Association–PEFF score and addressing modifiable risk factors can improve post-LT survival.
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Patients with end-stage liver disease (ESLD) are at high risk for developing heart failure (HF) after a stressful hemodynamic stimulus because of the possible coexistence of subclinical HF and cirrhotic cardiomyopathy (CCM).[1,2] The prevalence of HF with preserved ejection fraction (HFpEF) is 1.1% to 5.5% in the general population,[3] and this proportion is expected to increase over time with increased aging and cardiometabolic risk factors.[4,5] HFpEF evolves from a combination of risk factors, such as advanced age, female sex, obesity, hypertension, diabetes mellitus, anemia, and dyslipidemia.[4,6]

With the growing burden of nonalcoholic fatty liver disease (NAFLD), HFpEF risk factors are also growing in patients with ESLD. Therefore, 3 NAFLD-related HFpEF phenotypes were recently proposed: obstructive, metabolic, and advanced liver cirrhosis HFpEF.[7] However, the prevalence and impact of HFpEF have not been systematically investigated in a large ESLD cohort, although CCM, which predominantly reflects diastolic dysfunction, is generally the hallmark of ESLD.[8,9]

The diagnosis of HFpEF remains challenging in clinical practice; therefore, the Heart Failure Association (HFA)-PEFF scoring system has recently been proposed for diagnosing HFpEF by the European Society of Cardiology to facilitate the identification of patients with HFpEF.[6] In this study, we first made the clinical diagnosis of HFpEF in patients with ESLD by categorizing them into 3 risk groups using the HFA-PEFF scoring system: low, intermediate, and high probability.[6] Furthermore, we investigated which HFpEF clinical profiles and phenotypes were closely linked to the high-probability group in a large ESLD cohort comprising heterogeneous liver disease entities, severity, and risk factors. Additionally, we examined the prognostic implication of the high-probability group for predicting post-liver transplantation (LT) mortality and major adverse cardiovascular events (MACE) in the Asan LT Registry.

METHODS

STUDY POPULATION. Overall, we retrospectively evaluated 4,638 consecutive, prospectively registered patients who underwent LT from January 2008 to February 2019 in the Asan LT Registry (Asan Medical Center, Seoul, Korea). Among these, we excluded 1,394 patients for the following reasons: 207 aged <18 years, 205 who underwent retransplantation after the initial graft rejection, 62 with pre-existing chronic renal failure receiving renal replacement therapy, 191 with significant coronary artery disease (ie, coronary artery bypass graft surgery, percutaneous coronary intervention), 127 with acute fulminant liver failure, 125 with toxic hepatitis, 20 with valvular heart disease with greater than moderate regurgitation or stenosis or a history of valvular replacement surgery, 430 without diastolic echocardiographic parameters and tricuspid regurgitation velocity, 15 with incomplete perioperative data, and 12 with left ventricular ejection fraction (LVEF) <50%. Ultimately, 3,244 patients were included (Supplemental Figure 1).

DATA COLLECTION. Baseline demographic characteristics, laboratory, echocardiographic, and perioperative variables were collected from the fully computerized database extraction software (ABLE, Asan Biomedical Research). All laboratory variables and B-type natriuretic peptide (BNP) data were measured preoperatively and updated at the time of LT when variables were measured repeatedly. The study complied with the principles outlined in the Declaration of Helsinki. The study design and a waiver of the requirement to obtain informed consent from the participants were approved by the Institutional Review Board of the Asan Medical Center (2021-1074).

ECHOCARDIOGRAPHIC DATA AND BNP. All patients underwent routine preoperative 2-dimensional and Doppler echocardiography with tissue Doppler imaging, following the chamber quantification and tissue Doppler guidelines of the American Society of Echocardiography.[10] BNP (ADVIA Centaur, Bayer Diagnostics) concentration has been measured as part of our institution's routine pre-LT cardiac work-up since 2008 among all LT candidates, irrespective of HF signs and symptoms.[1,11]

HFA-PEFF SCORING. The HFA-PEFF score comprises functional (tissue Doppler e′, E/e′ ratio, tricuspid valve regurgitation velocity, and global longitudinal strain), morphologic (left ventricular hypertrophy, relative wall thickness, and left atrial volume), and echocardiographic parameters, as well as serum natriuretic peptide.[6] Within each domain, a major criterion scores 2 points and a minor criterion 1 point. Among the echocardiographic parameters, we did not include global longitudinal strain and left atrial volume index, which were not routinely measured in the institution's echocardiography laboratory. However, despite this limitation, the European Society of Cardiology states that the HFA-PEFF score can be

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CCM = cirrhotic cardiomyopathy

ESLD = end-stage liver disease

GFR = glomerular filtration rate

HF = heart failure

HFA = Heart Failure Association

HFpEF = heart failure with preserved ejection fraction

LT = liver transplantation

LVEF = left ventricular ejection fraction

MACE = major adverse cardiovascular event(s)

MELD = Model for End-Stage Liver Disease

NAFLD = nonalcoholic fatty liver disease

TABLE 1 Baseline Characteristics of Patients With End-Stage Liver Disease According to HFA-PEFF Score

	All Patients (N = 3,244)	HFA-PEFF Score		P Value
		Low and Intermediate (n = 3,029, 93.4%)	High (n = 215, 6.6%)	
Baseline characteristics				
Age, y	54 (48-59)	53 (48-58)	57 (51-63)	<0.001
Age >65 y	165 (5.1)	139 (4.6)	26 (12.1)	<0.001
Female	829 (25.6)	110 (16.7)	115 (53.5)	<0.001
BMI, kg/m^2	24.2 (22.0-26.4)	24.2 (22.0-26.5)	24.0 (21.2-26.3)	0.105
Obesity	201 (6.2)	183 (6.0)	18 (8.4)	0.221
MELD score	14 (9-22)	13 (9-21)	22 (15-33)	<0.001
Hepatitis B virus	2,008 (62.0)	1,919 (63.5)	89 (41.6)	<0.001
Hepatitis C virus	217 (6.7)	206 (6.8)	11 (5.1)	0.421
Biliary disease	130 (4.0)	118 (3.9)	12 (5.6)	0.295
Alcoholic liver disease	744 (22.9)	683 (22.5)	61 (28.4)	0.060
Medical history				
Hypertension	530 (16.3)	478 (15.8)	52 (24.2)	0.002
Diabetes mellitus	749 (23.1)	690 (22.8)	59 (27.4)	0.138
Atrial fibrillation	34 (1.0)	32 (1.1)	2 (0.9)	1.000
Dyslipidemia	344 (10.6)	306 (10.1)	38 (17.7)	0.001
Smoking	321 (9.9)	305 (10.1)	16 (7.4)	0.259
Beta-blocker use	1,024 (31.6)	952 (31.4)	72 (33.5)	0.581
Variceal bleeding	721 (22.6)	669 (22.4)	52 (24.8)	0.486
Hepatic encephalopathy	514 (15.8)	449 (14.8)	65 (30.2)	<0.001
Intractable ascites	831 (26.0)	747 (25.0)	84 (40.0)	<0.001
Renal replacement therapy	195 (6.4)	12 (1.8)	30 (14.0)	<0.001
Laboratory variables				
Hemoglobin, g/dL	10.4 (8.9-12.3)	10.6 (9.1-12.4)	8.9 (7.9-10.1)	<0.001
Platelet count, per mm^3	59 (41-90)	60 (41-91)	52 (37-72)	<0.001
Prothrombin time (INR)	1.42 (1.20-1.81)	1.40 (1.20-1.77)	1.78 (1.41-2.26)	<0.001
Total bilirubin, mg/dL	2.0 (1.0-6.5)	1.9 (1.0-5.6)	6.5 (2.4-22.9)	<0.001
Albumin, g/dL	3.1 (2.7-3.5)	3.1 (2.7-3.5)	3.1 (2.7-3.5)	0.581
AST, IU/L	41 (28-64)	41 (28-63)	48 (34-74)	<0.001
ALT, IU/L	24 (16-38)	24 (16-38)	24 (15-38)	0.676
C-reactive protein, mg/dL	0.31 (0.10-1.04)	0.29 (0.10-0.97)	0.70 (0.30-1.8)	<0.001
Creatinine, mg/dL	0.79 (0.64-1.00)	0.79 (0.64-0.99)	0.80 (0.59-1.25)	0.683
GFR, mL/min/1.73 m^2	78 (60-90)	79 (60-90)	62 (51-90)	<0.001
BNP, pg/mL	49 (22-114)	44 (20-98)	177 (118-383)	<0.001
Echocardiographic measurements				
EDVI, mL/m^2	61.8 (52.6-72.6)	61.5 (52.5-72.3)	65.6 (53.8-78.7)	0.004
ESVI, mL/m^2	21.9 (18.1-26.1)	21.8 (18.2-26.0)	22.7 (18.0-27.3)	0.117
SVI, mL/m^2	39.7 (33.7-47.2)	39.5 (33.6-46.8)	43.2 (34.7-50.9)	0.001
LVEF, %	64.6 (61.7-67.3)	64.6 (61.7-67.2)	64.5 (61.9-67.7)	0.268
RWT	0.36 (0.32-0.39)	0.36 (0.32-0.39)	0.38 (0.34-0.44)	<0.001
LVMI, g/m^2	89.1 (76.8-102)	88.2 (76.6-100.9)	106.4 (95.3-122)	<0.001
e′, cm/s	7.6 (6.4-8.9)	7.7 (6.6-9.0)	6.2 (5.4-7.0)	<0.001
E/e′ ratio	9 (8-11)	9 (8-11)	13 (10-15)	<0.001
Peak TR velocity, m/s	2.4 (2.2-2.5)	2.4 (2.2-2.5)	2.6 (2.3-2.9)	<0.001

Values are median (IQR) or n (%).

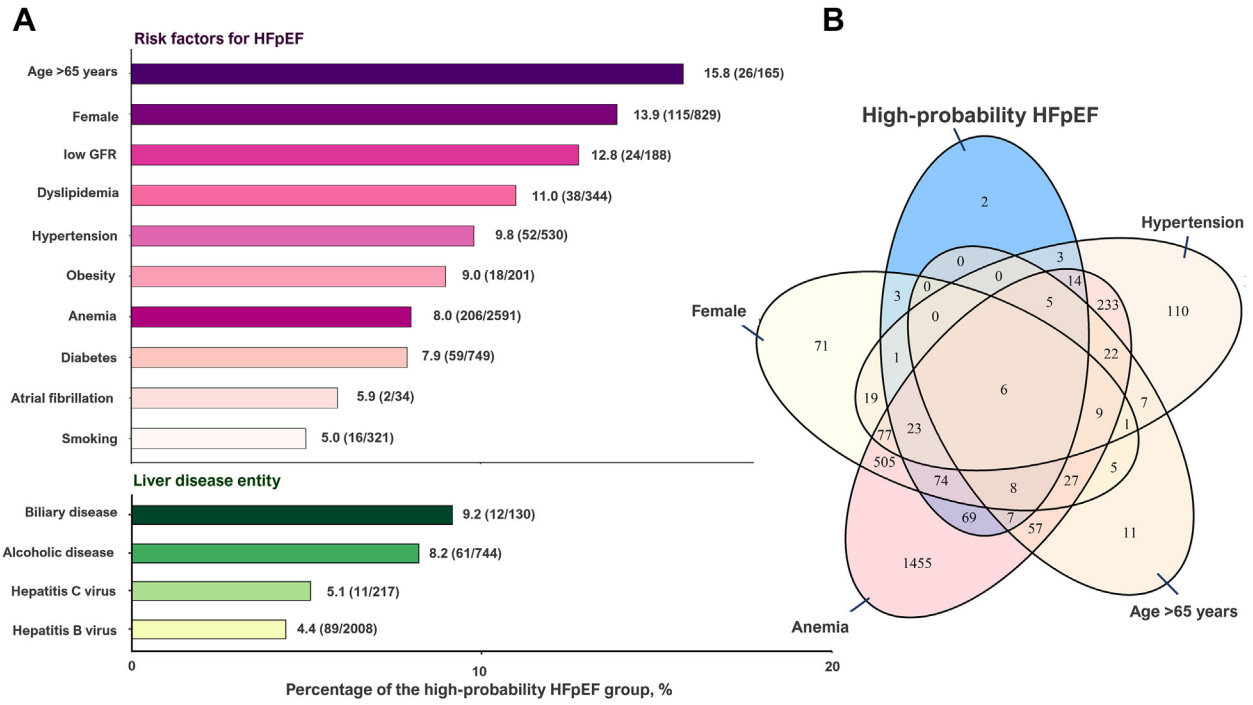
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BNP = B-type natriuretic peptide; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; GFR = glomerular filtration rate; HFA = Heart Failure Association; INR = international normalized ratio; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; MELD = Model for End-Stage Liver Disease; RWT = relative wall thickness; SVI = stroke volume index; TR = tricuspid regurgitation.

calculated even if not all parameters are obtained, which adds to the practical utility of this score.[6]

With required echocardiographic parameters and BNP, each patient's step 2 HFA-PEFF scores were categorized into 3 groups as follows: low (score of 0 or 1), intermediate (score of 2-4), and high probabilities (score of 5 or 6) (Supplemental Appendix).[6]

CLINICAL PROFILES AND HFpEF PHENOTYPES IN PATIENTS WITH ESLD. We constructed a multivariable model with 10 prespecified HFpEF risk factors on

FIGURE 1 Proportion and Venn Diagram of the Group With High Probability for HFpEF



(A) Bar graphs represent the percentages of patients in the high-probability group for each heart failure with preserved ejection fraction (HFpEF) risk factor. **(B)** Venn diagram of high-probability group of HFpEF **(light blue)** with hypertension, female sex, anemia, and age >65 years. GFR = glomerular filtration rate.

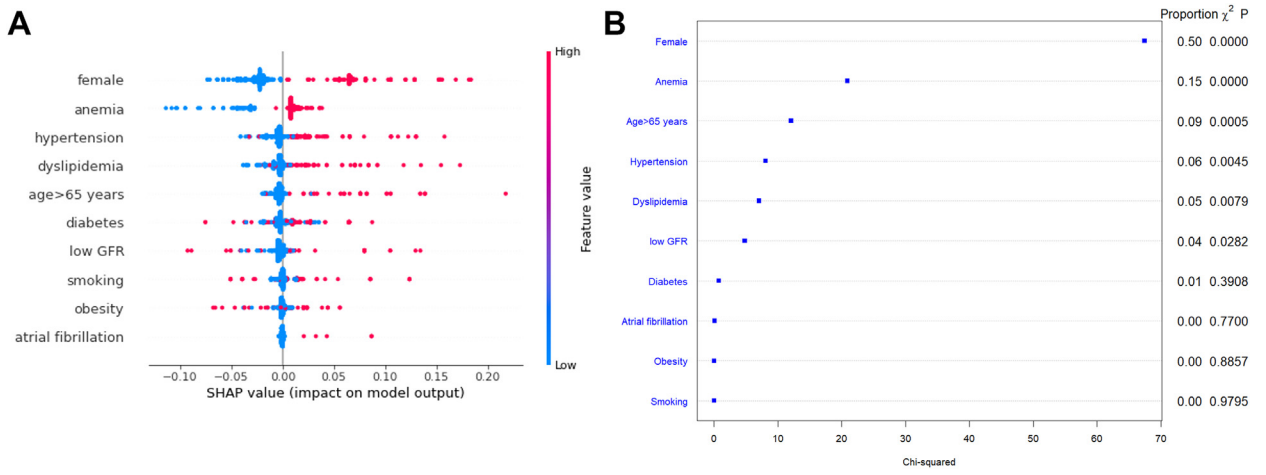
the basis of previous literature, including old age, female sex, obesity, diabetes, hypertension, low glomerular filtration rate (GFR), dyslipidemia, anemia, smoking, and atrial fibrillation, to identify significant clinical features and phenotypes for the high-probability group in patients with ESLD.[4,6]

Old age was defined as >65 years. Obesity was defined as a body mass index of ≥30 kg/m^2. Diabetes and hypertension were considered present when patients were already diagnosed and started on either antidiabetic or antihypertensive medications before LT candidacy. The use of diuretic agents for managing ascites or nonselective β-blockers to prevent variceal bleeding was not considered an indicator of hypertension, provided the patient was not diagnosed with hypertension before starting these drugs.[12] Dyslipidemia was defined as either a definite physician diagnosis or a ratio of low- to high-density lipoprotein of 3.5. Anemia was defined as hemoglobin levels <12.0 g/dL in women and <13.0 g/dL in men. Low GFR was defined as <30 mL/min/1.73 m^2. Liver disease severity was assessed using the Model for End-Stage Liver Disease (MELD). MELD score is calculated as: 3.78 ln[creatinine (mg/dL)] + 11.2 ln[bilirubin (mg/dL)] + 9.57 ln(international normalized ratio) + 6.43.

OUTCOMES AND FOLLOW-UP. Patient follow-up was initiated on the day of LT surgery, and censored data were followed up until September 2020 (ie, at least 1.6 years and up to 12.8 years after LT). All mortality data were regularly ascertained from the Asan Organ Transplantation Center. The primary outcome was cumulative all-cause mortality at 12 years. The secondary outcome was 1-year all-cause mortality and 30-day MACE. For the 1-year mortality rate, 100% of liver transplant recipients completed 1-year follow-up after LT. MACE was defined as the composite of post-LT cardiovascular mortality, atrial fibrillation, ventricular arrhythmia, ST-T-segment changes with chest tightness, myocardial infarction, pulmonary embolism, and stroke within 30 days after LT.

STATISTICAL ANALYSIS. Data are presented as numbers with proportions for categorical variables and as median (IQR) or mean ± SD for continuous variables. Differences in continuous variables between groups were examined using Student's *t*-test,

FIGURE 2 Clinical Profiles and Phenotypes Associated With High Probability for HFpEF



(A) The essential risk factors for high probability of developing HFpEF, assessed using the Shapley additive explanations (SHAP) score: the y-axis indicates the features in order of importance from top to bottom. On the x-axis, the SHAP value indicates the change in log odds. Gradient color indicates the original value for that variable, and each point represents a sample from the test set. **(B)** The relative contribution of variables to the risk for high-probability HFpEF ranked according to their chi-square values from the multivariate-adjusted model. Abbreviations as in Figure 1.

the Mann-Whitney rank-sum *U* test, and analysis of variance. For categorical variables, chi-square and Fisher exact tests were used, and the linear-by-linear chi-square test or the Armitage trend test was used to test for trends across ordered categories. Missing values of LVEF (n = 217), end-diastolic volume (n = 217), and BNP (n = 57) were filled with multiple imputation techniques using additive regression and bootstrapping.

Kaplan-Meier survival functions with log-rank tests, multivariate logistic analysis, and Cox proportional hazards models were performed to compare survival and MACE among patients in each HFA-PEFF grade category and to determine their adjusted HRs or ORs.

Clinical profile and high-probability HFA-PEFF phenotypes were evaluated with 10 risk factors using multivariable logistic analysis with backward elimination. Their ORs were adjusted according to the MELD liver disease severity score. We implemented an explainable artificial intelligence model to perform a feature-importance analysis to assess the apparent ranking of risk factors in ESLD. We used the extreme gradient boosting algorithm of gradient-boosted modeling, a decision tree-based ensemble model presenting Shapley additive explanations scores[13,14] with Python version 3.9 using the scikit-learn and shap packages. As an additional analysis, risk factors were ranked according to their chi-square values, corrected for the degrees of freedom allocated to that covariate in the model; hence, the relative contribution for each of the covariates can be compared on the same scale. Finally, partial effects were plotted to display the relationship between covariates and the log odds of the high HFA-PEFF score group.

To depict graphically and analyze nonlinear associations of high-probability HFpEF with MELD liver disease severity score on a continuous scale, restricted cubic spline analysis with 3 knots was used.

All statistical analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing), using the rms, Hmisc, survminer, moonBook, and Autoreg R packages, with a 2-sided significance level set at $P < 0.05$.

RESULTS

CLINICAL CHARACTERISTICS OF THE STUDY POPULATION.

Overall, 3,244 patients fulfilling the HFA-PEFF score criteria were analyzed; the median age was 54 years (IQR: 48-59 years; range: 18-76 years), and 74.4% were men. The primary causes of liver disease were hepatitis B (62%) or C (6.7%), virus-related liver disease, alcoholic liver disease (22.9%), and biliary disorders (4.0%). Patients with diabetes mellitus, hypertension, obesity, and age > 65 years numbered 749 (23.1%), 530 (16.3%), 201 (6.2%), and 165 (5.1%), respectively. The median MELD score was 14

(IQR: 9-22; range: 6-40), and most LT procedures were living-donor LT (86.4%). Baseline demographic, laboratory, and echocardiographic data are summarized in **Table 1** and Supplemental Table 1.

FREQUENCY AND CHARACTERISTICS OF PATIENTS WITH HIGH-PROBABILITY HFA-PEFF SCORES. On the basis of the HFA-PEFF scoring system, 215 (6.6%), 2,372 (73.1%), and 657 (20.3%) patients had high-, intermediate-, and low-probability HFA-PEFF scores, respectively. Patients in the high-probability group were older, had higher MELD scores and BNP levels, and had lower levels of hemoglobin and lower GFRs than those in the low-probability group. Also, they were often women with diabetes, hypertension, alcoholic liver disease, and/or dyslipidemia compared with patients in the low- and intermediate-probability groups. However, smoking history, atrial fibrillation, and obesity were not statistically different (**Table 1**, Supplemental Table 1). High-probability scores were found in 15.8% of those aged >65 years (26 of 165), 13.9% of female (115 of 829), 8.0% of those with anemia (206 of 2,591), 12.8% of those with low GFRs (24 of 188), 11.0% of those with dyslipidemia (11 of 344), 9.8% of those with hypertension (52 of 530), 9.0% of obese patients (18 of 201), and 7.9% of those with diabetes (59 of 749) (**Figure 1**). When categorized by liver disease entity, high-probability scores were found in 9.2% of patients with biliary disease (12 of 130), 8.2% of those with alcoholic liver disease (61 of 744), 5.1% of those with hepatitis C virus liver disease (11 of 217), and 4.4% of those with hepatitis B virus liver disease (89 of 2,008) (**Figure 1**).

CLINICAL PROFILES ASSOCIATED WITH HIGH-PROBABILITY HFA-PEFF SCORE. Among the 10 risk predictors, the apparently essential 5 risk factors for high-probability HFA-PEFF score assessed using the Shapley additive explanations score on gradient-boosted modeling analysis were female sex, anemia, hypertension, dyslipidemia, and age > 65 years (**Figure 2A**). Similar risk factors and their statistical significance are shown in **Figure 2B**, according to their relative contributions to high-probability HFA-PEFF scores, ranked by their chi-square values on the same scale from the multivariate-adjusted model. The significant factors for high-probability HFA-PEFF score were female sex, anemia, age >65 years, hypertension, dyslipidemia, and low GFR, but not obesity, diabetes mellitus, smoking, and atrial fibrillation (**Table 2**).

After adjusting for the liver disease MELD score severity in the multivariate logistic analysis with 10 risk factors, their partial effects and the log odds of the high HFA-PEFF score group are shown in Supplemental Figure 2.

TABLE 2 Clinical Features and High-Grade Heart Failure Association–PEFF Phenotypes

	Univariate Model		Multivariate Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female	3.73 (2.82-4.94)	<0.001	3.42 (2.56-4.56)	<0.001
Age >65 y	2.86 (1.83-4.46)	<0.001	2.30 (1.44-3.67)	<0.001
Anemia	6.18 (3.15-12.11)	<0.001	4.90 (2.48-9.70)	<0.001
Hypertension	1.70 (1.23-2.36)	0.001	1.66 (1.17-2.37)	0.004
Low GFR	2.20 (1.40-3.45)	<0.001	1.71 (1.06-2.75)	0.028
Dyslipidemia	1.91 (1.32-2.77)	<0.001	1.69 (1.15-2.50)	0.008
Diabetes	1.28 (0.94-1.75)	0.118		
Smoking history	0.72 (0.43-1.21)	0.214		
Obesity	1.42 (0.86-2.36)	0.173		
Atrial fibrillation	0.88 (0.21-3.69)	0.861		

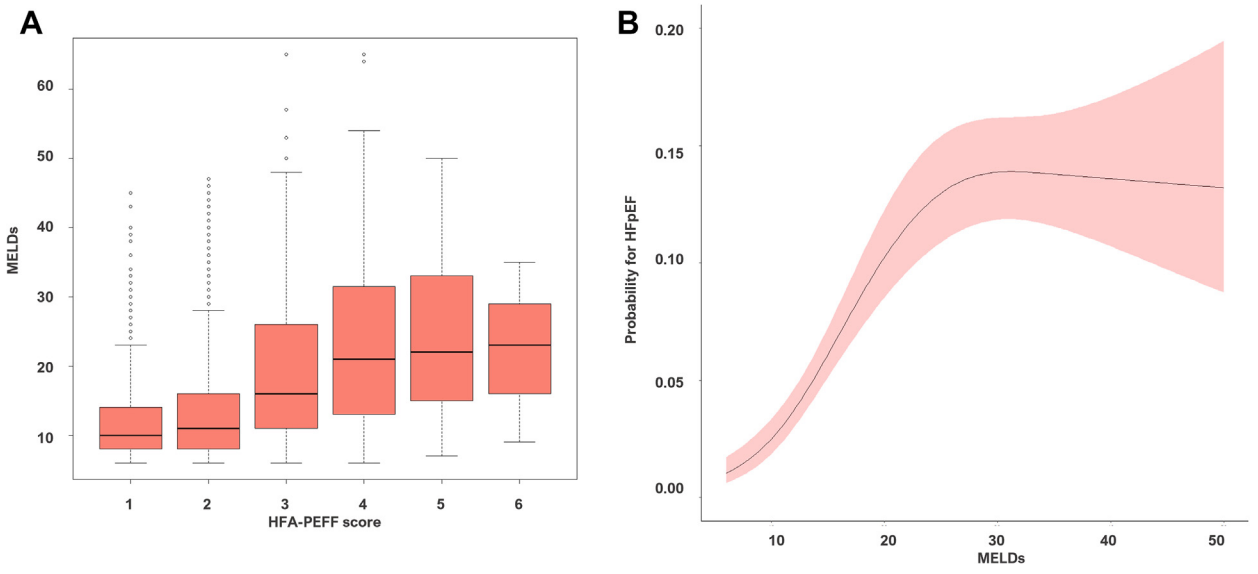
GFR = glomerular filtration rate.

ASSOCIATION OF LIVER DISEASE SEVERITY WITH HFA-PEFF SCORE. Patients in the high-probability HFpEF group had higher MELD scores compared with those in the low- and intermediate-probability HFpEF groups ($P < 0.001$) (**Table 1**). MELD scores showed a rising trend in relation to HFA-PEFF scores, reaching a limit when HFA-PEFF score exceeded 4 (**Figure 3A**). The trend was also observed in the cubic spline curve analysis of the relationship between liver disease severity and HFA-PEFF score (**Figure 3B**), indicating that worsening liver disease severity is associated with the occurrence of HFpEF.

IMPACT OF HFA-PEFF SCORE GROUP ON LT OUTCOMES. During a median follow-up duration of 5.3 years (IQR: 2.8-8.5 years) after LT, 498 patients (15.4%) died, of whom 238 (7.3%) died within 1 year, and 443 (13.7%) had MACE within 30 days. In Kaplan-Meier survival curve analysis stratified by HFA-PEFF category, patients belonging to the high-, intermediate-, and low-probability groups had survival rates of 72.1%, 82.4%, and 82.5% (log-rank $P < 0.001$) (**Figure 4A**) at 12 years and MACE rates of 27.4%, 13.9%, and 8.4%, respectively (**Table 2**). Particularly, in patients with advanced liver disease with MELD scores of >30 (n = 457), the HFA-PEFF score classification revealed greater survival rate differences of 54.8%, 72.1%, and 88.9% at 12 years (log-rank $P = 0.026$) (**Figure 4B**) and MACE rates of 35.8%, 21.8%, and 16.7%, respectively ($P = 0.009$) (**Table 3**).

In the Cox proportional hazard model, the high-probability group (vs the intermediate- and low-probability groups) showed adjusted HRs of 1.46 (95% CI: 1.08-1.98) for overall mortality rate at 12 years, 1.70 (95% CI: 1.18-2.44) for 1-year mortality, and 1.91 (95% CI: 1.37-2.68) for 30-day MACE (**Table 3**).

FIGURE 3 Association of Liver Disease Severity With HFA-PEFF Score



(A) Boxplot shows median and IQR, and whiskers represent 95% CIs. **(B)** The cubic spline curve between Model for End-Stage Liver Disease score (MELDs) and Heart Failure Association (HFA)-PEFF score, indicating that worsening liver disease severity is associated with the occurrence of heart failure with ejection fraction (HFpEF).

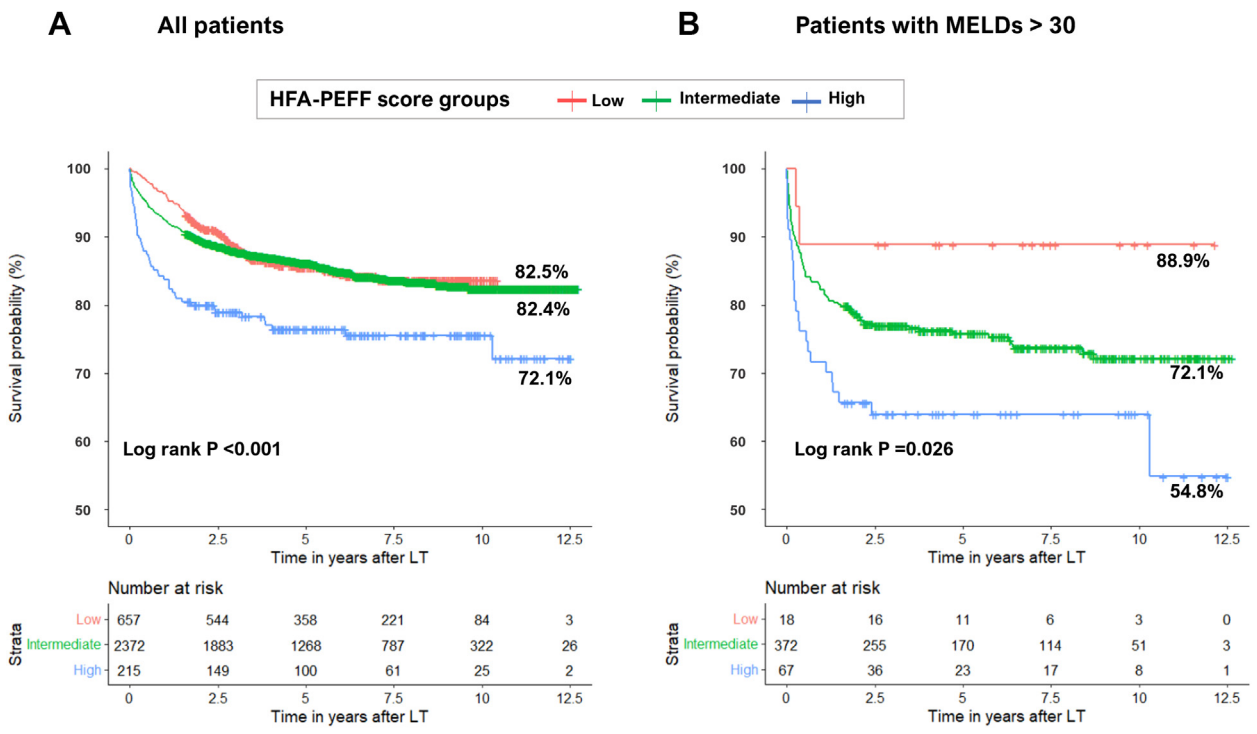
DISCUSSION

We made the clinical diagnosis of HFpEF in patients with ESLD using the HFA-PEFF scoring system, a recently validated method for the accurate diagnosis of HFpEF.[15] Overall, 6.6% of patients with ESLD were classified in the high-probability group of HFpEF and demonstrated a 46% (adjusted HR: 1.46; 95% CI: 1.08-1.98) increased risk for all-cause mortality during the follow-up period compared with those in the low- and intermediate-probability HFpEF groups ($P = 0.013$) (**Table 3**). Furthermore, in patients with advanced liver disease with MELD scores of >30, the post-LT cumulative survival rate at 12 years was significantly lower (54.8%) in the high-probability group than in the low-probability group (88.9%) (**Central Illustration**). Therefore, our findings suggest that diagnosis of HFpEF using the HFA-PEFF score has prognostic implications for predicting the increased risk for short- and long-term all-cause mortality and morbidity in patients with ESLD.

Of the 10 well-known HFpEF risk factors, the high-probability group in patients with ESLD was associated with female sex, anemia, hypertension, dyslipidemia, and age >65 years. This finding suggests that known risk factors for HFpEF in the general population are also relevant for developing HFpEF among patients with ESLD. Furthermore, the cubic spline curve analysis of the association between liver disease severity and HFA-PEFF score showed that as liver disease severity worsened, there was an increase in the likelihood of HFpEF. However, in contrast to the general population, obesity, diabetes, atrial fibrillation, and smoking were insignificant when adjusted for liver disease severity according to MELD score.

Ventriculoarterial coupling reflects the interaction between ventricular performance and effective arterial load. HFpEF arises from changes in ventriculoarterial coupling associated with aging, female sex, and hypertensive cardiac remodeling.[16] In a previous study we investigated alterations of ventriculoarterial coupling in patients with cirrhosis and concluded that patients with ESLD who have altered ventriculoarterial coupling have poor post-LT survival.[11] Women are more susceptible to HFpEF than men because they exhibit more concentric left ventricular remodeling and less ventricular dilatation in response to arterial hypertension.[17,18] In contrast, recent studies reported that after adjusting for age and other risk factors, the risk for HFpEF is similar in men and women.[19] However, our present study showed that female sex is a top influential factor for the high-probability group, even after adjusting for

FIGURE 4 Post-LT Kaplan-Meier Survival Curves



(A) Survival probability stratified by HFA-PEFF category in all patients (n = 3,244). **(B)** In patients with MELDs of >30 (n = 457), the HFA-PEFF score classification showed a more significant difference between survival rates. The post-liver transplantation (LT) cumulative survival rate at 12 years was significantly lower in the high-probability group than in the low-probability group. Abbreviations as in Figure 3.

age and other risk factors. Supposing that the vascular pathophysiology of atherosclerosis and vasodilation differs between women and men in patients with ESLD, our results are fascinating and suggest that women should be given special attention. However, further prospective randomized studies are needed to investigate the role of gender on HFpEF in patients with ESLD.

Regarding insignificant factors in patients with ESLD, a previous study among patients with revised CCM, in correspondence with our present study, showed no associations with diabetes mellitus, obesity, and smoking.[9] The mechanism is likely to be multifactorial and caused by highly prevalent hepatogenic glucose intolerance, the impact of the duration and severity of hepatogenic diabetes, cirrhotic sarcopenic obesity, and the disparity between smoking-induced atherosclerosis vs low vascular resistance induced by ESLD.

In the modern era, the importance of cardiovascular disease has been emphasized in the field of hepatology. It is now a leading cause of short- and long-term mortality after LT, ahead of graft rejection and infection. However, HF is difficult to diagnose in patients with ESLD, because they frequently have noncardiac dyspnea, fatigue, and hyperdynamic circulation.[1] In patients with ESLD, CCM is a well-known cardiomyopathy; however, the diagnostic criteria for CCM are predominantly a reflection of diastolic dysfunction.[8,20] There are few studies on CCM; however, a recent study with a small sample size (n = 210) reported that 30% of LT candidates who met the revised CCM criteria had an increased risk for MACE (HR: 1.93; $P = 0.04$) after LT, but the revised CCM did not affect post-LT mortality ($P = 0.56$).[9] Therefore, compared with our results, HFA-PEFF scoring is better than the revised CCM criteria for predicting survival after LT, possibly because HFA-PEFF scores do not include the E/A ratio but incorporate left ventricular mass and BNP instead.

There has been controversy in the field of HFpEF regarding the inclusion of selected patients with ESLD.[4] However, our study provides the basis that

TABLE 3 Relationship Between High HFA-PEFF Score and Post-Transplantation Outcomes

	HFA-PEFF Score			
	High (n = 215)	Intermediate (n = 2,372)	Low (n = 657)	Total (N = 3,244)
Median 5.3-y overall mortality	51 (23.7)	351 (14.8)	96 (14.6)	498 (15.4)
Crude HR (95% CI)	1.77 (1.33-2.37)			
Adjusted HR (95% CI)	1.46 (1.08-1.98)			
P value	0.013			
1-y mortality	35 (16.3)	179 (7.5)	24 (3.7)	238 (7.3)
Crude HR (95% CI)	2.60 (1.81-3.72)			
Adjusted HR (95% CI)	1.70 (1.18-2.44)			
P value	0.005			
30-d MACE	59 (27.4)	329 (13.9)	55 (8.4)	443 (13.7)
Crude OR (95% CI)	2.61 (1.90-3.58)			
Adjusted OR (95% CI)	1.91 (1.37-2.68)			
P value	<0.001			
Subgroup analysis: patients with MELD scores >30	(n = 67)	(n = 372)	(n = 18)	(n = 457)
Median 5.3-y overall mortality	25 (37.3)	94 (25.3)	2 (11.1)	121 (26.5)
Crude HR (95% CI)	1.70 (1.10-2.64)			
Adjusted HR (95% CI)	1.62 (1.03-2.56)			
P value	0.037			
1-y mortality	19 (28.4)	66 (17.7)	2 (11.1)	87 (19.0)
Crude HR (95% CI)	1.76 (1.06-2.93)			
Adjusted HR (95% CI)	1.68 (0.99-2.83)			
P value	0.053			
30-d MACE	24 (35.8)	81 (21.8)	3 (16.7)	108 (23.6)
Crude HR (95% CI)	2.03 (1.17-3.54)			
Adjusted HR (95% CI)	2.10 (1.20-3.67)			
P value	0.009			

Values are n (%). HRs and ORs were calculated to compare the relative risk of patients with high HFA-PEFF scores vs intermediate- and low-score groups, multivariate-adjusted for old age (>65 years), sex, MELD score, and type of donor (deceased or living).

HFA = Heart Failure Association; MACE = major adverse cardiovascular event(s); MELD = Model for End-Stage Liver Disease.

HFpEF might coexist or develop independently in patients with ESLD, regardless of liver disease. Previous studies also suggested that liver disease could precede HFpEF onset, and the risk factors and/or mechanisms for liver fibrosis may have greater overlap with those of HFpEF.[21,22] In a population-based study, VanWagner et al[23,24] demonstrated that patients with NAFLD had impaired left ventricular relaxation, higher left ventricular filling pressures, worse longitudinal strain, and lower LVEFs. In this regard, with the growing burden of NAFLD, 3 NAFLD-related HFpEF phenotypes have been proposed: 1) obstructive NAFLD/HFpEF, primarily linked to preload reserve failure; 2) metabolic NAFLD/HFpEF, connected to metabolic syndrome; and 3) advanced liver disease/cirrhosis HFpEF. Of these, the development of HFpEF in patients with advanced liver disease and cirrhosis may be caused by the formation of spontaneous portosystemic shunts and microshunts, which can lead to increased pulmonary flow and the presence of vasoactive factors in the splanchnic circulation, resulting in vasoconstriction, remodeling of the pulmonary vasculature, and the development of pulmonary hypertension. A study has shown that there is a significant contribution of precapillary factors to the development of pulmonary hypertension in patients with HFpEF.[25] Additionally, it has been observed that the formation of AV shunts may lead to dilatation of the right ventricle, deterioration in right ventricular function, and increased risk for death.[26] However, further prospective studies are necessary to establish whether any precise causal interactions exist between ESLD and HFpEF.

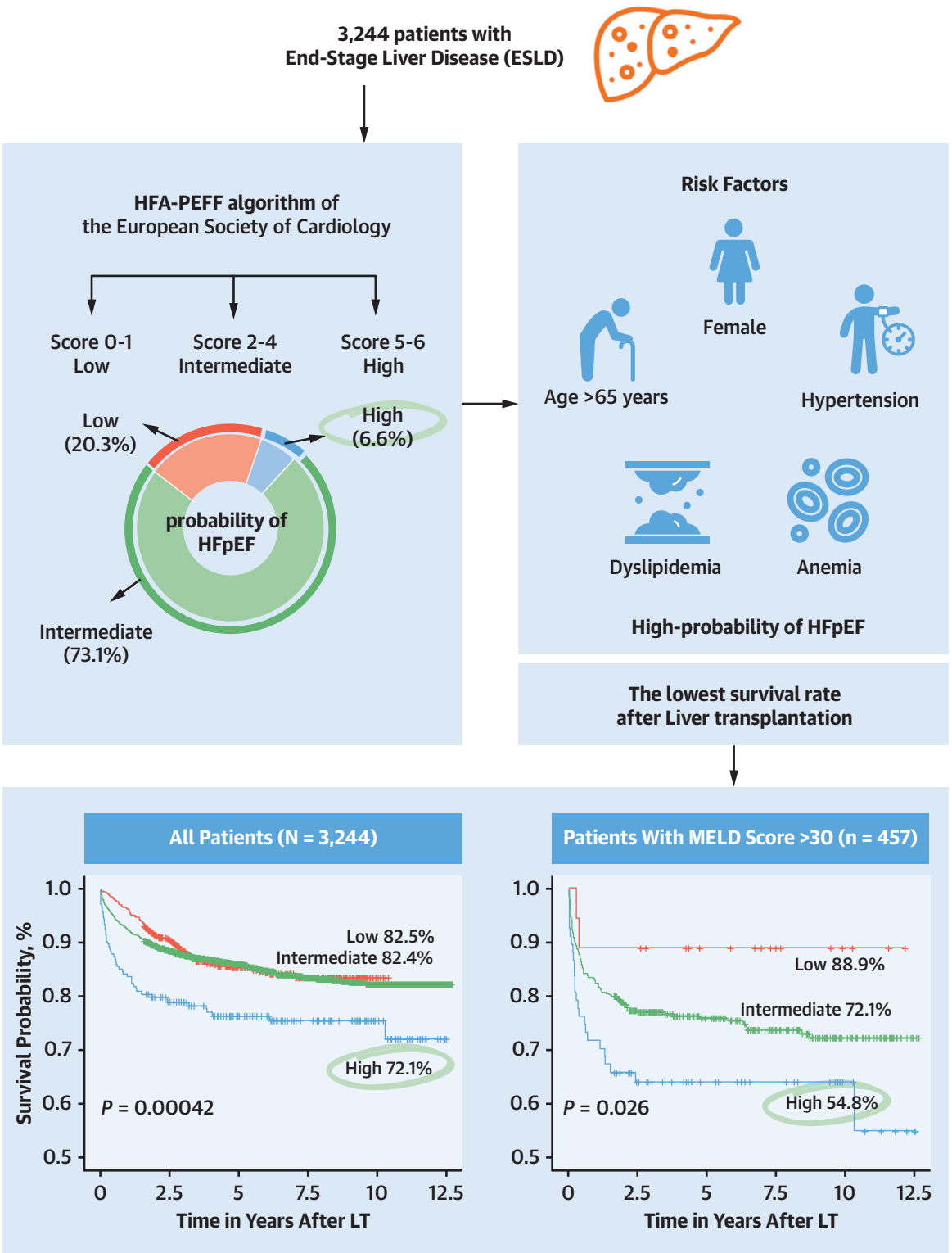
In this study, the intermediate-probability group, in which additional confirmatory invasive or stress testing would be needed, was determined to be 73.1% and considered relatively high. However, it should be noted that a recent study demonstrated that CCM can be found in up to 67% of patients when using different previous diagnostic criteria for CCM.[27] But concerns have been raised about the feasibility of stress or invasive testing in patients with ESLD, so further research using noninvasive methods to determine intrinsic diastolic properties is needed. Consequently, greater emphasis should be placed on identifying potential risk factors for HFpEF that may affect post-transplantation outcomes in this subgroup until a more advanced diagnostic tool is developed to confirm HFpEF.

Currently, there are no definitive therapeutic options for advanced diastolic dysfunction in patients with ESLD and CCM. Given the poor post-LT survival in patients with ESLD with high-probability HFpEF in the present study, novel HFpEF treatment strategies, such as mineralocorticoid receptor antagonists[4] or empagliflozin,[28] might optimize the pre-transplantation status of diastolic dysfunction and improve survival.

STUDY LIMITATIONS. First, the enrolled patients were from a single-center observational cohort; our data did not analyze NAFLD and nonalcoholic steatohepatitis separately because of the low rates of NAFLD and nonalcoholic steatohepatitis in our study cohort. Nevertheless, the high-probability HFpEF group among heterogenous patients with ESLD showed similar HFpEF clinical profiles and phenotypes.

Second, our study cohort was relatively young (median age 54 years), and patients aged >65 years

CENTRAL ILLUSTRATION **Prevalence and Risk Factors of HFpEF in End-Stage Liver Disease**



Shin W-J, et al. JACC: Asia. 2023;3(3):506–517.

Among patients with end-stage liver disease (n = 3,244), 6.6% had high probability of developing heart failure with preserved ejection fraction (HFpEF) and had worse post-liver transplantation (LT) survival outcomes. HFA = Heart Failure Association; MELD = Model for End-Stage Liver Disease.

accounted for only 5.1%, which was significant for the high-probability group. Supposing that participants with more advanced age were included, the old age rank might be altered.

Third, we did not evaluate the first step of the HFA-PEFF algorithm; however, in patients with ESLD, HF signs and symptoms are nonspecific, masked, and frequently confounded by ESLD comorbidities. In contrast, the diagnostic accuracy of applying only step 2 of the HFA-PEFF score has already been validated in large cohorts with high specificity (93%) and positive predictive value (98%) in diagnosing HFpEF.[15]

Fourth, we did not include pulmonary diseases such as chronic obstructive pulmonary disease in the multivariable logistic regression analysis, although it often coexists with HFpEF.[29] Further prospective research is thus necessary to understand the contribution of chronic obstructive pulmonary disease as a risk factor for HFpEF in the ESLD population.

CONCLUSIONS

A high-probability for developing HFpEF was found in 6.6% of patients with ESLD. Furthermore, they had prognostic implications for long- and short-term post-LT mortality rates and MACE and are closely linked to known HFpEF clinical profiles and phenotypes. Therefore, identifying patients with HFpEF with this score should be used to improve the pre-transplantation status of diastolic dysfunction and trigger specific therapeutic strategies to enhance survival outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: With the growing burden of NAFLD, HFpEF risk factors are also growing in patients with ESLD. With the application of the diagnostic HFA-PEFF score for HFpEF to an ESLD population, 6.6% of patients with ESLD were categorized as having a high probability for HFpEF. They had prognostic implications for long- and short-term post-LT mortality rates and are closely linked to known HFpEF clinical profiles and phenotypes.

TRANSLATIONAL OUTLOOK: In the population with ESLD, recognizing HFpEF is necessary for enhancing diastolic function prior to transplantation and optimizing outcomes by addressing modifiable risk factors.

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KEY WORDS cirrhotic cardiomyopathy, diastolic dysfunction, end-stage liver disease, heart failure with preserved ejection fraction, liver transplantation

APPENDIX For supplemental methods, a table, and figures, please see the online version of this paper.