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ORIGINAL ARTICLE

Comparison of liver fibrosis scores for predicting mortality and morbidity in heart failure with preserved ejection fraction

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Abstract

Aims Liver fibrosis scores (LFSs) are non-invasive and effective tools for estimating cardiovascular risks. To better understand the advantages and limitations of currently available LFSs, we determined to compare the predictive values of LFSs in heart failure with preserved ejection fraction (HFpEF) for primary composite outcome, atrial fibrillation (AF), and other clinical outcomes.

Methods and results This was a secondary analysis of the TOPCAT trial, and 3212 HFpEF patients were enrolled. Five LFSs, namely, non-alcoholic fatty liver disease fibrosis score (NFS), fibrosis-4 score (FIB-4), BARD, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, and Health Utilities Index (HUI) scores were adopted. Cox proportional hazard model and competing risk regression model were performed to assess the associations between LFSs and outcomes. The discriminatory power of each LFS was evaluated by calculating the area under the curves (AUCs). During a median follow-up of 3.3 years, a 1-point increase in the NFS [hazard ratio (HR) 1.10; 95% confidence interval (CI) 1.04–1.17], BARD (HR 1.19; 95% CI 1.10–1.30), and HUI (HR 1.44; 95% CI 1.09–1.89) scores was associated with an increased risk of primary outcome. Patients with high levels of NFS (HR 1.63; 95% CI 1.26–2.13), BARD (HR 1.64; 95% CI 1.25–2.15), AST/ALT ratio (HR 1.30; 95% CI 1.05–1.60), and HUI (HR 1.25; 95% CI 1.02–1.53) were at an increased risk of primary outcome. Subjects who developed AF were more likely to have high NFS (HR 2.21; 95% CI 1.13–4.32). High levels of NFS and HUI scores were a significant predictor of any hospitalization and hospitalization for heart failure. The AUCs for the NFS in predicting primary outcome (0.672; 95% CI 0.642–0.702) and incident of AF (0.678; 95% CI 0.622–0.734) were higher than other LFSs.

Conclusions In light of these findings, NFS appears to have superior predictive and prognostic utility compared with AST/ALT ratio, FIB-4, BARD, and HUI scores. Clinical trial registration: (https://clinicaltrials.gov). Unique identifier: NCT00094302.

Keywords Liver fibrosis score; Heart failure with preserved ejection fraction; Adverse outcomes

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Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) has become the most common type of HF, and its prevalence rises with age.[1,2] Previous studies have found a greater burden of non-cardiac comorbidities in patients with HFpEF, implying that the management of comorbidities may improve the prognosis in HFpEF patients.[3,4] Non-alcoholic fatty liver disease (NAFLD) has been recognized as the hepatic manifestation of metabolic syndrome, and it represents a wide spectrum of hepatic disorders.[5–7] NAFLD can burden the fibrosis of ventricles and precede the development of HFpEF.[8,9] As these two disorders share cardiometabolic risk factors, accumulating evidence indicates a close relationship between NAFLD and HFpEF, but the pathophysiological mechanisms to elucidate the relationship between NAFLD and HFpEF are still being evaluated.[10,11] The gold standard to determine liver fibrosis is liver biopsy, but it is an invasive approach with

acknowledged limitations. Consequently, non-invasive liver fibrosis scores (LFSs) composed of routine clinical and laboratory biomarkers have been identified in the investigation of NAFLD diagnosis and prognosis.[12] The commonly used scoring systems are the NAFLD fibrosis score (NFS), fibrosis-4 score (FIB-4), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, Health Utilities Index (HUI) score, and body mass index, AST/ALT ratio, and diabetes mellitus score (BARD) score.[12,13]

Recent studies suggested that LFSs were associated with mortality and hospital readmission in patients with HF.[14–18] A prospective observational study found that NFS was associated with circulating systemic markers of congestion and a higher risk of all-cause mortality in HFpEF patients.[15] FIB-4 index, calculated by age, AST, ALT, and platelet count, was a simple biomarker of severity of right ventricular dysfunction and was a useful tool for predicting incident HFpEF and major adverse cardiovascular events in HFpEF patients.[16,17] Advanced hepatic fibrosis evaluated by BARD score was an independent predictor of incident heart failure (HF) and was significantly associated with mortality in HF patients.[18] No data are available regarding the predictive value of BARD and HUI scores in HFpEF patients. The LFSs are the systems that calculated by different parameters, including demographics (age and body mass index), metabolic (diabetes), and biochemical (platelet, AST, ALT, albumin, and bilirubin) factors. It is possible that different LFSs reflect different mechanisms related to NAFLD pathogenesis and progression. Because the relationship between NAFLD and HFpEF is complex and undetermined, it is essential to understand the advantages and limitations of currently available LFSs to select the appropriate risk score for evaluating and managing NAFLD in patients with HFpEF. In this study, we aimed to explore the prognostic value of NFS, FIB-4, HUI, BARD, and AST/ALT ratio for primary composite outcome, atrial fibrillation (AF), and other clinical outcomes and compare the predictive performances of different LFSs in patients with HFpEF.

Methods

Study population

The TOPCAT was an international, multicentre, double-blinded, randomized clinical trial designed to evaluate the effect of spironolactone in patients with HFpEF.[19] The detailed design, baseline characteristics, and primary results of this trial have been previously reported.[19–21] The study conformed with the principles outlined in the Declaration of Helsinki and received ethical clearance. The TOPCAT study enrolled 3445 patients with symptomatic HF and a left ventricular ejection fraction of 45% or greater, 1767 (51%) from North and South America, and 1678 from Russia and Georgia.[20] Patients with an age of ≥50 years were included if they had at least one hospitalization for HF in the prior 12 months or if no qualifying hospitalization, a B-type natriuretic peptide in the previous 2 months ≥100 pg/mL or N-terminal pro-BNP ≥ 360 pg/mL.[19,21] Major exclusion criteria were life expectancy of less than 3 years, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or serum creatinine level ≥2.5 mg/dL, and known chronic hepatic disease (defined as ALT and AST levels >3.0 times the upper limit of the normal range). The dataset of the TOPCAT trial has been made publicly available at the National Heart, Lung, and Blood Institute and can be accessed via an approval proposal (BIOLINCC, https://biolincc.nhlbi.nih.gov/).

Liver fibrosis scores

Components of the five LFSs (NFS, FIB-4, HUI, BARD, and AST/ALT ratio) were identified in the TOPCAT database. Risk scores were calculated for all the eligible HFpEF cases. The originally described definitions for each LFS were shown in *Supporting information, Table S1*.[22–24] We excluded participants with missing components of the LFSs, yielding a final sample of 3212 individuals. Patients were categorized into three categories based on the previously cut-off points: low, intermediate, and high probability of liver fibrosis (the cut-offs of categorization: NFS, −1.455 and 0.675; BARD, 1 and 3; FIB-4, 1.3 and 2.67; HUI, 0.15 and 0.5; AST/ALT ratio, 0.8 and 1.0).

Study outcomes

Outcomes in the TOPCAT trial were centrally adjudicated by a clinical endpoint committee blinded to study group assignment, and the details of this process and definitions for each outcome examined have been described.[19,21] The primary outcome was a composite of cardiovascular death, aborted cardiac arrest, or hospitalization for management of HF.

Statistical analysis

Continuous variables were presented as mean ± standard deviation if they followed a normal distribution; otherwise, they were presented as medians and 25th to 75th percentiles. Categorical variables were presented as frequency (percentage). The intergroup differences were assessed using the chi-square test for categorical variables and analysis of variance (or Kruskal–Wallis test for non-normally distributed variables) for continuous variables. The cumulative incidence of clinical outcomes was evaluated using Kaplan–Meier curves with the log-rank test. Cox proportional hazard models and Fine and Gray's competing risk models were performed. Non-cardiovascular death was the competing risk in models

concerning primary outcome and cardiovascular death, and all-cause death was the competing risk for incident AF, HF hospitalization, and any hospitalization. The LFSs were separately analysed as continuous variables or categorical variables. In the multivariate model, gender, White race, heart rate, diastolic blood pressure (DBP), New York Heart Association class category, eGFR, previous myocardial infarction, previous stroke, chronic obstruction pulmonary disease (COPD), peripheral artery disease (PAD), dyslipidaemia, AF, diuretics, statin, beta-blocker, and anti-depressant drugs were used as adjustments. The time-dependent receiver operating characteristic curves (ROC) were conducted to assess the prognostic values of these five LFSs. Statistical analyses were performed with R version 4.1.1 (with packages compareGroups, survival, cmprsk, and time ROC), with a graphical user interface of GraphPad Prism 6.0. The *P* value of <0.05 was considered statistically significant.

Results

Baseline characteristics

We excluded participants with missing components of the LFSs yielding a final sample of 3212 individuals. The baseline clinical characteristics of 3212 HFpEF patients were summarized in *Table 1*. The median age of participants was

Table 1 Baseline characteristics of study patients

	Overall (n = 3212)	Non-primary endpoint (n = 2587)	Primary endpoint (n = 625)	P value
Randomization to spironolactone, *n*	1618 (50.4%)	1319 (51.0%)	299 (47.8%)	0.172
Age, years	69.0 (61.0–76.0)	68.0 (60.0–75.0)	71.0 (63.0–79.0)	<0.001
Male, *n* (%)	1539 (47.9%)	1191 (46.0%)	348 (55.7%)	<0.001
White race, *n* (%)	2859 (89.0%)	2352 (90.9%)	507 (81.1%)	<0.001
HR, beats/min	68 (61–76)	68.0 (61.0–75.0)	70.0 (62.0–78.0)	0.002
SBP, mmHg	130 (120–140)	130 (120–140)	130 (118–139)	0.025
DBP, mmHg	80 (70–80)	80.0 (70.0–82.0)	71.0 (62.0–80.0)	<0.001
BMI, kg/m^2	30.8 (27.1–35.6)	30.5 (27.1–35.1)	32.1 (27.6–38.2)	<0.001
Current smoking, *n* (%)	330 (10.3%)	270 (10.4%)	60 (9.60%)	0.586
NYHA functional class, *n* (%), III and IV	1052 (32.8%)	755 (29.2%)	297 (47.5%)	<0.001
Laboratory values				
EF, %	56 (51–61)	56.0 (51.0–61.0)	55.0 (50.0–61.0)	0.154
Serum creatine, mg/dL	1.04 (0.89–1.24)	1.01 (0.87–1.20)	1.20 (1.00–1.40)	<0.001
eGFR, mL (min × 1.73m^2)	65.5 (53.7–79.0)	66.8 (55.6–79.8)	58.7 (47.6–73.9)	<0.001
Platelet, k/uL	224.0 (190.0–264.0)	224 (192–262)	221 (181–271)	0.238
ALT, U/L	22.0 (16.0–31.0)	22.0 (16.0–31.8)	21.0 (15.0–30.0)	0.016
AST, U/L	23.0 (18.0–29.0)	23.0 (18.0–29.0)	22.0 (18.0–29.0)	0.060
Albumin, g/dL	4.10 (3.80–4.40)	4.10 (3.80–4.47)	3.90 (3.60–4.30)	<0.001
Comorbidities, *n* (%)				
Previous HF hospitalization	2305 (71.8%)	1855 (71.7%)	450 (72.0%)	0.922
Previous MI	819 (25.5%)	632 (24.4%)	187 (29.9%)	0.006
Previous stroke	239 (7.4%)	169 (6.5%)	70 (11.2%)	<0.001
COPD	382 (11.9%)	275 (10.6%)	107 (17.1%)	<0.001
Hypertension	2946 (91.7%)	2366 (91.5%)	580 (92.8%)	0.311
PAD	282 (8.8%)	190 (7.34%)	92 (14.7%)	<0.001
Dyslipidaemia	1920 (59.8%)	1474 (57.0%)	446 (71.4%)	<0.001
Atrial fibrillation	1166 (36.3%)	874 (33.8%)	292 (46.7%)	<0.001
Thyroid disease	513 (16.0%)	403 (15.6%)	110 (17.6%)	0.239
Diabetes mellitus	1036 (32.3%)	731 (28.3%)	305 (48.8%)	<0.001
Medications, *n* (%)				
Beta-blocker	2487 (77.4%)	1973 (76.3%)	514 (82.2%)	0.002
Calcium channel blocker	1204 (37.5%)	979 (37.9%)	225 (36.0%)	0.415
Diuretic	2653 (82.6%)	2093 (80.9%)	560 (89.6%)	<0.001
ACE-I or ARB	2699 (84.0%)	2187 (84.6%)	512 (81.9%)	0.118
Aspirin	2106 (65.6%)	1709 (66.1%)	397 (63.5%)	0.244
Statin	1673 (52.1%)	1286 (49.7%)	387 (61.9%)	<0.001
Anti-depressant drugs	248 (7.7%)	160 (6.19%)	88 (14.1%)	<0.001
Risk scores				
NFS	−0.38 (−1.41–0.64)	−0.53 (−1.48–0.46)	0.17 (−0.91–1.20)	<0.001
BARD	3.00 (2.00–3.00)	3.00 (2.00–3.00)	3.00 (2.00–4.00)	<0.001
FIB-4	1.50 (1.09–2.05	1.48 (1.09–2.01)	1.57 (1.10–2.22)	0.012
AST/ALT ratio	1.05 (0.81–1.35)	1.05 (0.79–1.35)	1.08 (0.85–1.35)	0.058
HUI	0.25 (0.09–0.54)	0.22 (0.08–0.51)	0.37 (0.12–0.69)	<0.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BRAD, body mass index, AST/ALT ratio, diabetes score; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular rate; HF, heart failure; HR, heart rate; MI, myocardial infarction; NFS, non-alcoholic fatty liver disease fibrosis score; NYHA, New York Heart Association; PAD, peripheral artery disease; SBP, systolic blood pressure.

69.0 years, in which 47.9% (n = 1539) were male. The median values of NFS, FIB-4, BARD, AST/ALT ratio, and HUI were −0.38, 1.50, 3.00, 1.05, and 0.25 points, respectively. Compared with those free of primary outcome, those developing primary outcome were older, more likely to be male, and had lower levels of DBP, eGFR, and albumin. Patients with incident primary outcome had a higher proportion of MI, stroke, COPD, PAD, dyslipidaemia, AF, and diabetes. Furthermore, patients who developed primary outcome had higher LFSs including NFS, FIB-4, BARD, and HUI scores. Baseline echocardiographic characteristics were presented in *Table S2*.

Association of liver fibrosis scores and adverse outcomes

During a mean follow-up of 3.3 years, a total of 625 (19.5%) primary composite outcome was observed, presenting 6.19 events per 100 person-years. Age- and sex-adjusted associations of the individual components in LFSs with adverse outcomes were presented in *Table S3*. Diabetes, age, and body mass index were independently associated with the increased risks of the primary outcome, HF hospitalization, any hospitalization, and all-cause death.

When patients were categorized into three risk strata, Kaplan–Meier analysis showed a graded incrzeased risk for primary outcome (log-rank $P < 0.05$, *Figure 1*). As shown in *Table 2*, the risk of primary endpoint was significantly increased in patients with high level of NFS (HR 3.08; 95% CI 2.42–3.93), FIB-4 (HR 1.50; 95% CI 1.18–1.92), BARD (HR 2.07; 95% CI 1.59–2.70), AST/ALT ratio (HR 1.31; 95% CI 1.07–1.61), and HUI (HR 2.01; 95% CI 1.66–2.44) score, when compared with those within the low groups. After adjustments for potential covariates, NFS (HR 1.63; 95% CI 1.26–2.13), BARD (HR 1.64; 95% CI 1.25–2.15), AST/ALT ratio (HR 1.30; 95% CI 1.05–1.60), and HUI (HR 1.25; 95% CI 1.02–1.53) scores remained independently associated with primary outcome. In the continuous analysis, after progressive adjustments for potential risk factors, a point increase in NFS (HR 1.10; 95% CI 1.04–1.17), BARD (HR 1.19; 95% CI 1.10–1.30) and HUI (HR 1.44; 95% CI 1.09–1.89) scores was independently associated with primary outcome.

Multivariate Cox analysis revealed that highest levels of NFS (HR 1.81; 95% CI 1.37–2.41) and FIB-4 (HR 1.70; 95% CI 1.30–2.22) were significantly associated with all-cause death (*Table S4*). When adjusted for potential risk factors, the risk for HF hospitalization was 1.93-fold, 1.96-fold, 1.33-fold, and 1.45-fold greater for the highest vs. lowest levels of NFS, BARD, HUI, and AST/ALT ratio (all P values < 0.05, *Table S5*). For cardiovascular death, multivariable-adjusted HRs for the highest vs. lowest scores were 1.34 (0.94–1.92) for NFS, 1.33 (0.93–1.91) for FIB-4, 1.28 (0.90–1.83) for BARD, 1.29 (0.97–1.72) for AST/ALT ratio, and 0.99 (0.74–1.32) for HUI scores (*Table S6*). The risk of any hospitalization was significantly increased in patients with high levels of NFS (HR 1.38; 95% CI 1.17–1.63) and HUI score (HR 1.20; 95% CI 1.05–1.37) (*Table S7*).

Association of liver fibrosis scores with atrial fibrillation risk

Convincing data indicated that there was a strong association between NAFLD and cardiac arrhythmias such as AF and ventricular arrhythmias.[25–27] The competing risk regression models were used to explore the association between LFSs

Figure 1 Kaplan–Meier curves for cumulative events of primary composite outcome during follow-up according to the liver fibrosis scores risk strata. (*A*) non-alcoholic fatty liver disease fibrosis score; (*B*) fibrosis-4 score; (*C*) diabetes mellitus score: (*D*) aspartate aminotransferase/alanine aminotransferase ratio; (*E*) Health Utilities Index.

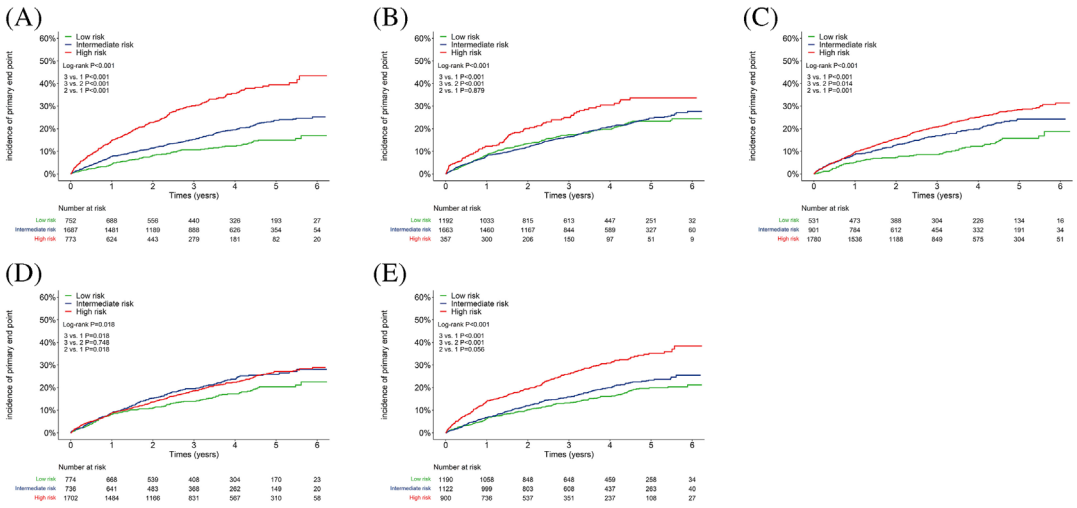


Table 2 Associations of the liver fibrosis scores with primary end point in patients with heart failure with preserved ejection fraction using competing risk regression models

Outcomes	Events	Person-years	Incidence rate, per 100 person-years	Unadjusted			Adjusted		
				HR	95% CI	*P* value	HR	95% CI	*P* value
NFS									
Overall[a]	625, 19.5%	10 095	6.19	1.26	1.18–1.34	<0.001	1.10	1.04–1.17	<0.001
Risk strata									
Low risk (*n* = 752)	90, 12.0%	2622	3.43	Ref.			Ref.		
Medium risk (*n* = 1687)	301, 17.8%	5461	5.51	1.56	1.24–1.98	<0.001	1.25	0.98–1.59	0.070
High risk (*n* = 773)	234, 30.3%	2012	11.63	3.08	2.42–3.93	<0.001	1.63	1.26–2.13	<0.001
FIB-4									
Overall[a]	625, 19.5%	10 095	6.19	1.12	1.05–1.18	<0.001	1.04	0.97–1.12	0.240
Risk strata									
Low risk (*n* = 1192)	221, 18.5%	3812	5.80	Ref.			Ref.		
Medium risk (*n* = 1663)	312, 18.8%	5299	5.89	1.01	0.85–1.20	0.930	0.96	0.80–1.15	0.660
High risk (*n* = 357)	92, 25.8%	985	9.34	1.50	1.18–1.92	0.001	1.12	0.85–1.48	0.420
BARD									
Overall[a]	625, 19.5%	10 095	6.19	1.37	1.26–1.50	<0.001	1.19	1.10–1.30	<0.001
Risk strata									
Low risk (*n* = 531)	63, 11.9%	1821	3.46	Ref.			Ref.		
Medium risk (*n* = 901)	165, 18.3%	2864	5.76	1.64	1.23–2.19	<0.001	1.42	1.06–1.91	0.020
High risk (*n* = 1780)	397, 22.3%	5410	7.34	2.07	1.59–2.70	<0.001	1.64	1.25–2.15	<0.001
AST/ALT ratio									
Overall[a]	625, 19.5%	10 095	6.19	1.05	0.954–1.16	0.300	1.04	0.93–1.17	0.520
Risk strata (*n* = 774)									
Low risk (*n* = 736)	124, 4.9%	2516	4.93	Ref.			Ref.		
Medium risk (*n* = 1702)	155, 21.1%	2300	6.74	1.37	1.08–1.73	0.010	1.32	1.03–1.69	0.027
High risk	346, 20.3%	5279	6.55	1.31	1.07–1.61	0.010	1.30	1.05–1.60	0.016
HUI									
Overall[a]	625, 19.5%	10 095	6.19	2.95	2.27–3.83	<0.001	1.44	1.09–1.89	0.020
Risk strata									
Low risk (*n* = 1190)	180, 15.1%	3934	4.58	Ref.			Ref.		
Medium risk (*n* = 1122)	206, 18.4%	3710	5.55	1.21	0.99–1.47	0.064	1.09	0.90–1.33	0.380
High risk (*n* = 900)	239, 26.6%	2451	9.75	2.01	1.66–2.44	<0.001	1.25	1.02–1.53	0.035

Abbreviations: AST/ALT, aspartate aminotransferase/alanine aminotransferase ratio; CI, confidence interval; FIB-4, fibrosis-4 score; HR, hazard ratio; HUI, Health Utilities Index; NFS, non-alcoholic fatty liver disease fibrosis score.
Variables for adjustment: gender, White race, heart rate, diastolic blood pressure, New York Heart Association class category, estimate glomerular filtration rate, previous myocardial infarction, previous stroke, chronic obstruction pulmonary disease, peripheral artery disease, dyslipidaemia, atrial fibrillation, diuretics, statin, beta-blocker, and anti-depressant drugs.
[a]Liver fibrosis scores were included as a continuous variable.

and incident AF. We included 2046 patients who were available for LFSs calculation and were without AF at baseline including a history of AF or AF confirmed on an electrocardiogram. Multivariate analysis demonstrated that a 1-point increase in the FIB-4 (HR 1.16; 95% CI 1.08–1.24) and HUI (HR 1.91; 95% CI 1.02–3.57) scores was independently associated with incident AF (*Table 3*). Compared with patients in low-risk stratum, those in the high-risk stratum of NFS (HR 2.21; 95% CI 1.13–4.32) showed an increased risk of incident AF (*Table 3*).

Discriminatory performance of the liver fibrosis scores

As shown in *Figure 2*, the time-dependent AUC for the NFS in predicting primary composite outcome (0.672; 95% CI 0.642–0.702) was higher than other studied LFSs, namely, FIB-4 (0.549; 95% CI 0.517–0.581), BARD (0.618; 95% CI 0.588–0.648), AST/ALT ratio (0.536; 95% CI 0.505–0.568), or HUI scores (0.609; 95% CI 0.577–0.640). The AUCs for the NFS, FIB-4, BARD, AST/ALT ratio, and HUI in predicting incident AF were 0.678 (95% CI 0.622–0.734), 0.538 (95% CI 0.475–0.601), 0.581 (95% CI 0.526–0.636), 0.489 (95% CI 0.432–0.546), and 0.625 (95% CI 0.563–0.688), respectively (*Figure 3*).

Discussion

In the retrospective analysis of the TOPCAT study, we explored the associations of five recommended liver fibrosis scoring systems with the adverse clinical outcomes and compared the prognostic performance of these five LFSs in HFpEF patients. With a large cohort of patients with HFpEF, this study demonstrated that higher levels of NFS and HUI scores were significantly associated with the risks of primary com-

Table 3 Associations of the liver fibrosis scores with incident atrial fibrillation in patients with heart failure with preserved ejection fraction using competing risk regression models

Outcomes	Events	Person-years	Incidence rate, per 100 person-years	Unadjusted			Adjusted		
				HR	95% CI	*P* value	HR	95% CI	*P* value
NFS									
Overall[a] (*n* = 2046)	119, 5.8%	6792	1.75	1.22	1.05–1.42	0.011	1.10	0.88–1.38	0.390
Risk strata									
Low risk (*n* = 527)	15, 2.8%	1873	0.80	Ref.			Ref.		
Medium risk (*n* = 1078)	64, 5.9%	3610	1.77	2.15	1.23–3.78	0.007	1.83	1.03–3.23	0.038
High risk (*n* = 441)	40, 9.1%	1309	3.05	3.48	1.92–6.30	<0.001	2.21	1.13–4.32	0.020
FIB-4									
Overall[a] (*n* = 2046)	119, 5.8%	6792	1.75	1.20	1.13–1.29	<0.001	1.16	1.08–1.24	<0.001
Risk strata									
Low risk (*n* = 840)	48, 5.7%	2837	1.69	Ref.			Ref.		
Medium risk (*n* = 1019)	52, 5.1%	3383	1.53	0.90	0.61–1.34	0.610	0.86	0.58–1.28	0.450
High risk (*n* = 187)	19, 1.02%	572	3.32	1.84	1.08–4.13	0.025	1.50	0.87–2.60	0.150
BARD									
Overall[a] (*n* = 2046)	119, 5.8%	6792	1.75	1.18	0.99–1.4	0.056	1.07	0.90–1.28	0.440
Risk strata									
Low risk (*n* = 331)	13, 3.9%	1177	1.10	Ref.			Ref.		
Medium risk (*n* = 596)	34, 5.7%	2012	1.69	1.51	0.80–2.85	0.210	1.36	0.71–2.58	0.350
High risk (*n* = 1119)	72, 6.4%	3603	2.00	1.75	0.97–3.15	0.061	1.48	0.81–2.70	0.210
AST/ALT ratio									
Overall[a] (*n* = 2046)	119, 5.8%	6792	1.75	1.09	0.76–1.58	0.63	1.11	0.84–1.46	0.480
Risk strata									
Low risk (*n* = 503)	30, 6.0%	1720	1.74	Ref.			Ref.		
Medium risk (*n* = 473)	26, 5.5%	1536	1.69	0.97	0.57–1.63	0.90	0.95	0.56–1.60	0.850
High risk (*n* = 1070)	63, 5.9%	3536	1.78	1.01	0.66–1.56	0.95	1.03	0.67–1.59	0.880
HUI									
Overall[a] (*n* = 2046)	119, 5.8%	6792	1.75	3.05	1.79–5.19	<0.001	1.91	1.02–3.57	0.043
Risk strata									
Low risk (*n* = 805)	33, 4.1%	2738	1.21	Ref.			Ref.		
Medium risk (*n* = 732)	42, 5.7%	2518	1.67	1.38	0.87–2.18	0.170	1.23	0.78–1.94	0.380
High risk (*n* = 509)	44, 8.6%	1536	2.86	2.25	1.43–3.54	<0.001	1.62	0.97–2.69	0.066

Abbreviations: AST/ALT, aspartate aminotransferase/alanine aminotransferase ratio; CI, confidence interval; FIB-4, fibrosis-4 score; HR, hazard ratio; HUI, Health Utilities Index; NFS, non-alcoholic fatty liver disease fibrosis score.
Variables for adjustment: gender, white race, heart rate, diastolic blood pressure, New York Heart Association class category, estimate glomerular filtration rate, previous myocardial infarction, previous stroke, chronic obstruction pulmonary disease, peripheral artery disease, dyslipidaemia, diuretics, statin, beta-blocker, and anti-depressant drugs.
[a]Liver fibrosis scores were included as a continuous variable.

posite outcome, any hospitalization, and HF hospitalization, even after adjusting for possible confounding factors. Intriguingly, we found that the patients with high-risk stratum of NFS had a significantly higher probability of developing AF and a 1-point increase in the FIB-4 and HUI was associated with an increased risk of incident AF. The study revealed that among the five LFSs, NFS might present a better prognostic value.

NAFLD is considered as an emerging risk factor for HFpEF and the prevalence of NAFLD in HFpEF could reach 25%.[8] NAFLD independently increases the risks of arrhythmia, atherosclerosis, and cardiomyopathy, which consequently lead to cardiovascular morbidity and mortality.[7] However, the current prognostic indicators may not comprehensively assess metabolic or hepatic parameters, LFSs might be used as a non-invasively accessible tool for identifying the high-risk population. Previous studies have shown that LFSs were associated with mortality in NAFLD and the general population, and some studies have evaluated the predictive value of LFSs for morbidity and mortality in HF patients.[14–18,28,29] Valbusa et al. observed a significant association between ultrasound-diagnosed NAFLD and increased risks of 1 year all-cause and cardiac re-hospitalization in elderly patients with acute HF.[28] A clinical study of 516 patients with chronic HF found that liver fibrosis evaluated by NFS was independently associated with composite cardiovascular events after adjustment for confounding factors.[29] HF patients with the highest quartile of NFS presented a significantly higher cardiovascular event rate than in those in the lower quartiles of NFS.[29] A prospective observational study reported that NFS was correlated with circulating systemic markers of congestion and a higher all-cause mortality in HFpEF patients.[15] A prior post-analysis of TOPCAT study, which excluded patients from Russia and George, observed significant association of high levels of NFS and FIB-4 with the risks of primary composite outcome, any hospitalization, and HF hospitalization in the univariate analysis. However, after adjustments for potential covariates, these associations were

Figure 2 Receiver operating characteristic (ROC) curves at 5 years for the LFSs in predicting (*A*) primary composite outcome, (*B*) HF hospitalization, (*C*) any hospitalization, (*D*) all-cause death, (*E*) cardiovascular death during follow-up. AUC, area under the curve; AST/ALT, aspartate aminotransferase/alanine aminotransferase ratio; FIB-4, fibrosis-4 score; HUI, Health Utilities Index; NFS, non-alcoholic fatty liver disease fibrosis score.

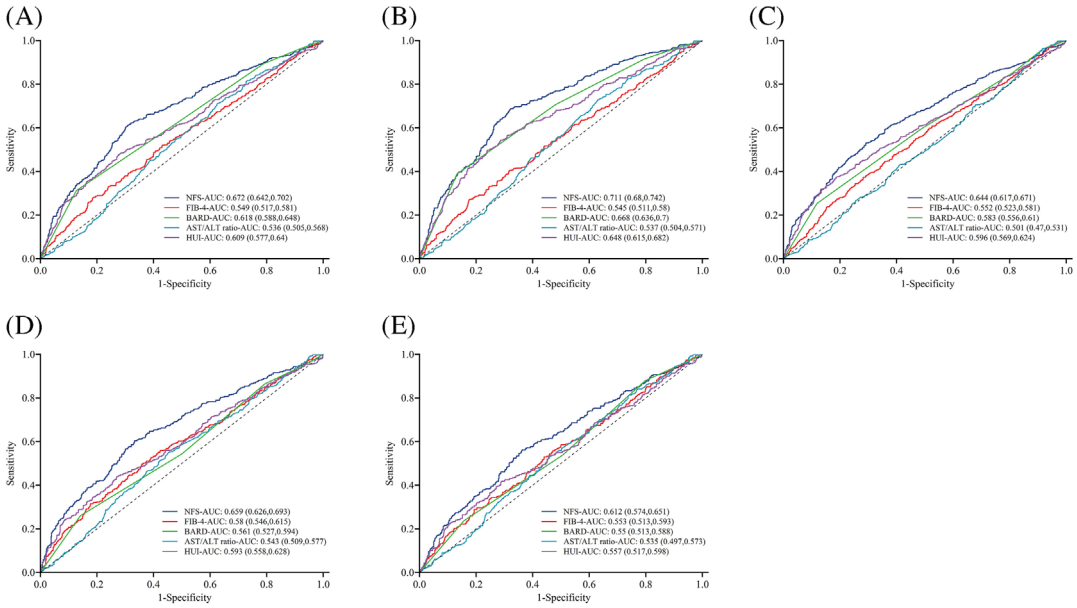
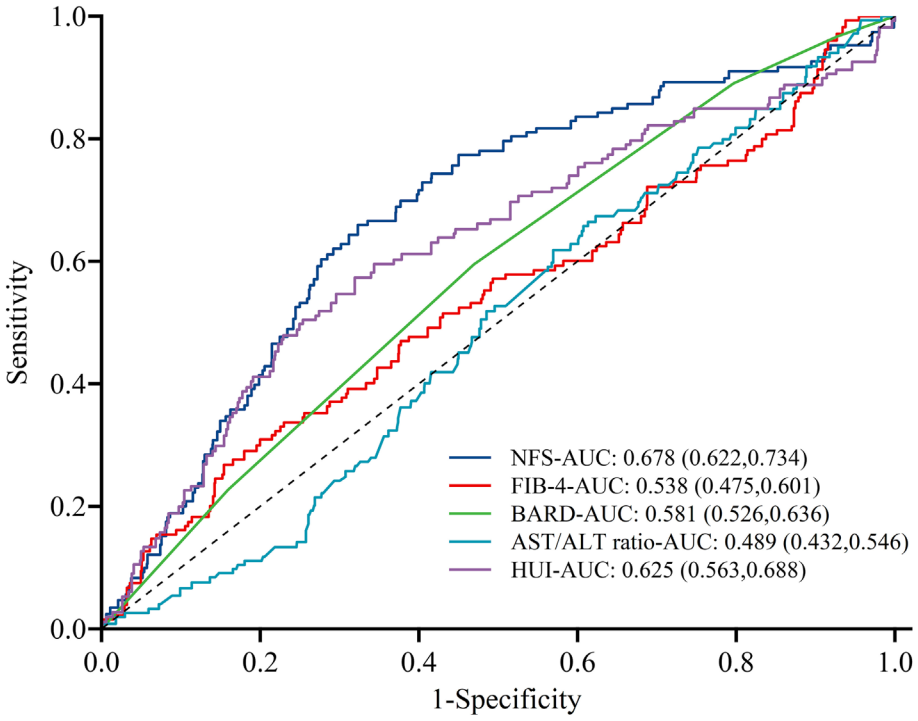


Figure 3 Receiver operating characteristic (ROC) curves at 5 years for the LFSs in predicting incident atrial fibrillation during follow-up. AUC, area under the curve; AST/ALT, aspartate aminotransferase/alanine aminotransferase ratio; FIB-4, fibrosis-4 score; HUI, Health Utilities Index; NFS, non-alcoholic fatty liver disease fibrosis score.



diminished.[10] In our study, Cox proportional hazard and competing risk regression models were performed. In the whole population of the TOPCAT study, after progressive adjustment for various cardiovascular risk factors, elevated NFS levels measured as continuous or dichotomous variables remained independently associated with primary composite outcome, any hospitalization, HF hospitalization, and all-cause death. Previous studies demonstrated that HUI score not only independently increased the risk of liver disease mortality but also increased mortality and morbidity among patients with coronary heart disease.[24] A recent study indicated that LFSs including HUI score were independent predictors of major adverse cardiac event, cardiovascular mortality, and all-cause mortality in patients with previous MI.[24] In our study, we found that high HUI score was associated with increased risks of primary composite outcome, any hospitalization, and HF hospitalization. In addition, we compared the predictive values of these five LFSs for adverse clinical outcomes in HFpEF patients, we found that NFS seemed to be a preferable tool for screening high-risk HFpEF patients.

Studies have suggested that NAFLD patients were at an increased risk of AF, whereas AF is associated with increased risks of morbidity and mortality.[25–27,30,31] This non-fortuitous association may involve a large number of factors, including cardiac anomalies, inflammation, and obesity.[7] Sinner et al. studied 3744 participants from the Framingham Heart Study Original and Offspring cohort; they observed an independent association between levels of liver enzymes and incident AF within 10 years follow-up.[25] Another Framingham Heart Study revealed that no significant association between NAFLD and incident AF was observed in age- and sex-adjusted or multivariable-adjusted models.[30] One study published by Targher et al. indicated that NAFLD increased the risk of incident AF in patients with type 2 diabetes.[31] Our study suggested that advanced liver fibrosis estimated by NFS, FIB-4, and HUI scores had the potential for predicting AF in HFpEF patients.

Strengths and limitations

In our study, we compared the prognostic value of LFSs in HFpEF patients and found that NFS, FIB-4, and HUI scores might predict incident AF in patients with HFpEF. Nevertheless, several limitations should be acknowledged in this study. The TOPCAT study did not record the liver status. Due to the nature of a retrospective analysis, the residual confounders from unmeasured factors (Hba1c, triglyceride, cholesterol, and diuretic dosage) might influence the validity of our findings. The absence of visual examination such as ultrasonography and liver biopsy in the present study did not allow to investigate the association between LFSs and liver fibrosis. We had not performed a second measurement of LFSs, so the effect of changes in LFSs on the outcome was still uncertain.

Conclusions

In a well-defined HFpEF cohort, we demonstrated that higher levels of NFS and HUI scores were associated with increased risks of primary composite outcome, any hospitalization, and HF hospitalization. We observed a strong gradient of elevated incident AF risk across increasing NFS categories and found that one-point increment of FIB-4 and HUI was related with an increased risk of incident AF. NFS might have better predictive ability for adverse outcomes in patients with HFpEF. These findings may support the notion that LFSs are useful tools for identifying and re-stratifying patients with HFpEF, and further studies are clinically warranted.

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Conflict of interest

All authors declare that they have no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. The algorithms for the liver fibrosis scores.
Table S2. Baseline echocardiographic characteristics of HFpEF patients.
Table S3. Associations of components of the LFSs with adverse outcomes in patients with HFpEF.

Table S4. Associations of the LFSs with all-cause death in patients with HFpEF.

Table S5. Associations of the LFSs with hospitalization for heart failure in patients with HFpEF using competing risk regression models.

Table S6. Associations of the LFSs with cardiovascular death in patients with HFpEF using competing risk regression models.

Table S7. Associations of the LFSs with any hospitalization in patients with HFpEF using competing risk regression models.

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