


Liver fibrosis scores and atrial fibrillation incidence in heart failure with preserved ejection fraction

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Abstract

Aim Non-alcoholic fatty liver disease (NAFLD)-related advanced liver fibrosis (Stage 3 or 4) was reported to be linked to worse prognosis in patients with heart failure with preserved ejection fraction (HFpEF). This study aims to assess the relationship between liver fibrosis scores and new-onset atrial fibrillation (AF) incidence in patients with HFpEF in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial.

Methods and results Baseline liver fibrosis levels, assessed by NAFLD fibrosis score (NFS) or Fibrosis-4 index (FIB-4), with AF incidence were expressed as hazard ratios (HRs) using the Cox proportional hazard model. The risk for advanced fibrosis was estimated to be 21.5% (447/2072) as assessed by FIB-4 (>3.25) and 4.2% (88/2072) as assessed by NFS (>0.676) in HFpEF patients without baseline AF. After a median follow-up of 3.11 years, 106 new-onset AF cases occurred. In multivariate analysis, elevated NFS [NFS = −1.455–0.676: HR 2.44, 95% confidence interval (CI) 1.27–4.68; NFS > 0.676: HR 3.36, 95% CI 1.27–6.80; per 1 unit increase: HR 1.15, 95% CI 1.01–1.32], not FIB-4 (FIB-4 = 1.45–3.25: HR 1.02, 95% CI 0.67–1.55; FIB-4 > 3.25: HR 1.69, 95% CI 0.76–3.79; per 1 unit increase: HR 1.13, 95% CI 0.93–1.37), was associated with increased AF incidence. The NFS (C-index 0.662), not FIB-4 (C-index 0.531), had a moderate predictive ability in predicting incident AF.

Conclusions Among patients with HFpEF, the risk of advanced liver fibrosis is associated with an increased incidence of new-onset AF and may be a novel predictor for new-onset AF. Additional studies are needed to confirm our results.

Keywords Heart failure; Liver fibrosis; FIB-4; NFS; Risk prediction; Atrial fibrillation

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Introduction

Chronic liver diseases, such as non-alcoholic fatty liver disease (NAFLD), are common in patients with heart failure with preserved ejection fraction (HFpEF) due to shared risk factors (alcohol abuse, drugs, inflammation, autoimmunity, infections), as well as complex cardiohepatic interactions.¹ Advanced liver fibrosis (Stage 3 or 4) is the primary pathology of many chronic liver diseases and was detected in 32% of patients with chronic heart failure via the gold standard of biopsies.² Regarding HFpEF, the prevalence of advanced liver

fibrosis is in the range 37.5–53% based on several cohorts^{3–6} assessed by the NAFLD fibrosis score (NFS) or Fibrosis-4 index (FIB-4) score, simple non-invasive tools developed to distinguish the severity of liver fibrosis in liver diseases.^{7–9} Furthermore, accumulating evidence suggests that liver fibrosis is independent of other established risk factors for heart failure^{10,11} and significantly contributes to heart failure progression, cardiovascular events, and all-cause death in patients with HFpEF.^{1,4}

Atrial fibrillation (AF) is one of the most common comorbidities in HFpEF, presenting in approximately one-third of

patients. There is a close link between HFpEF and AF, and each condition independently contributes to poor outcomes—the so-called vicious twins. Therefore, identifying the potential risk factors for AF in HFpEF is clinically important for preventing AF and thus improving prognosis, especially in stroke. Evidence from epidemiological studies has shown a positive association between advanced liver fibrosis and the risk of AF in patients with NAFLD or Type 2 diabetes.^{12,13}

Additionally, advanced liver fibrosis is not uncommon in patients with HFpEF. Given this background, we are curious as to whether liver fibrosis contributes to the increased incidence of new-onset AF in patients with HFpEF. Based on the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, we conducted a second analysis to investigate the relationship between liver fibrosis assessed by NFS and FIB-4 scores and incident AF in patients with HFpEF.

Methods

The study population was from TOPCAT, an international, multicentre randomized, double-blinded, placebo-controlled trial that assessed the effect of spironolactone on clinical outcomes in patients with HFpEF compared with placebo.¹⁴ TOPCAT complied with the Declaration of Helsinki and received ethical approval. All patients signed informed consent before randomization. All relevant data were obtained from the National Heart, Lung, and Blood Institute.

Liver fibrosis was assessed by NFS and FIB-4 scores. NFS and FIB-4 scores were computed using the following formulas:

$$\text{FIB-4} = \frac{\text{age [years]} \times \text{AST (aspartate aminotransferase) [U/L]}}{(\text{platelet} [\times 10^9/\text{L}] \times \sqrt{\text{ALT (alanine aminotransferase) [U/L]}})}$$

$$\begin{aligned} \text{NFS} = & -1.675 + 0.037 \times \text{age [years]} + 0.094 \\ & \times \text{bodymassindex [kg/m}^2\text{]} + 1.13 \\ & \times \text{diabetes (yes = 1, no = 0)} + \frac{0.99 \times \text{AST [U/L]}}{\text{ALT [U/L]}} \\ & - 0.013 \times \text{platelet [10}^9\text{/L]} - 0.66 \times \text{albumin [g/dL]} \end{aligned}$$

AF post-randomization was determined by a follow-up electrocardiogram (ECG), event questionnaire, and review of relevant medical records every 4 months during the first year of the study and every 6 months thereafter. AF occurrence was adjudicated by the clinical endpoint committee. The Cox proportional hazard model with and without multivariable adjustment was used to examine the associations [expressed as hazard ratios (HRs) and 95% confidence intervals (CIs)] of NFS or FIB-4 scores with the incidence of AF. The selected variables were from a backward stepwise method and additional clinically relevant factors. We evaluated the discriminatory ability of the NFS or FIB-4 for predicting AF using the C-index. For internal model and score validation, we used the *k*-fold in

10-fold cross-validation with 200 repetitions. Subgroup analysis stratified by prespecified variables in the main TOPCAT: sex (male vs. female), region (the Americas vs. non-Americas), and treatment arm (spironolactone vs. placebo).

Sensitivity analysis was conducted by (i) recalculating the estimated effect by a competing risk model (death was defined as a competent event) and (ii) excluding patients with concomitant use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and use of any beta-blocker. All statistical analyses were performed with Stata software (version 16.0) and R software (version 4.1.2). A two-sided *P*-value <0.05 was considered statistically significant. Full details of the methods are presented in the Supporting Information.

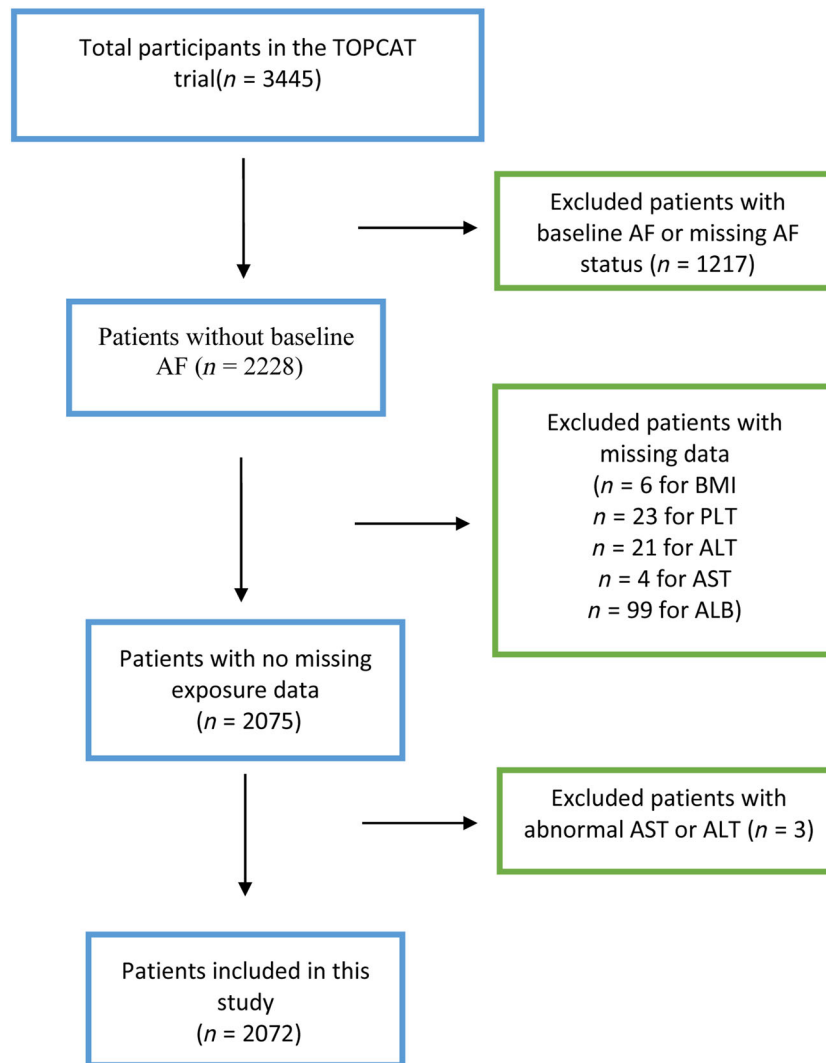
Results

Baseline characteristics and prevalence of liver fibrosis score in heart failure with preserved ejection fraction

As shown in *Figure 1*, after exclusion of 1217 HFpEF patients with baseline AF or missing AF status and missing individuals for calculating FIB-4 or NFS scores [$n = 6$ for body mass index (BMI), $n = 23$ for platelet (PLT), $n = 21$ for alanine aminotransferase (ALT), $n = 4$ for aspartate aminotransferase (AST), $n = 99$ for albumin (ALB)], abnormal AST or ALT values were observed ($n = 3$). Finally, we included a studied population of 2072 without baseline AF, with 930 (44.9%) men and 1814 White participants (89.2%). The median \pm interquartile range (IQR) values in all patients were 67 (60.0, 74.0) years for age, 30.6 (27.1, 35.4) kg/m² for BMI, and 68 (61–75) bpm for heart rate. The median BNP ($n = 744$) and N-terminal pro BNP (NT-proBNP; $n = 564$) concentrations were 248 (IQR 144, 438) and 828 (IQR 456, 1668) pg/mL, respectively.

The characteristics of participants across the NFS and FIB-4 groups are shown in *Table 1*. The median liver fibrosis scores in the overall cohort were -0.50 (IQR $-1.48, 0.51$) and 1.42 (IQR $1.07, 1.93$) as assessed by NFS and FIB-4, respectively. Overall, the prevalence of a high risk for advanced liver fibrosis was estimated to be higher by NFS than by FIB-4. The low, moderate, and high risk rates for liver fibrosis scores were 25.7, 52.8, and 21.6%, respectively, as assessed by NFS and 51.5, 44.3, and 4.2%, respectively, as assessed by FIB-4. There was a significant difference in the baseline characteristics across risk for liver fibrosis groups, such as age, heart function, BMI, smoking history, and ALT and ALB levels. Only a small proportion of patients provided echocardiographic data at baseline. The echocardiographic data at baseline across the NFS and FIB-4 groups are presented in Supporting Information, *Tables S1* and *S2*.

Figure 1 Flow chart of study selection of liver fibrosis scores from the TOPCAT trial. AF, atrial fibrillation; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; PLT, platelet; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial.



New-onset atrial fibrillation during follow-up

During a median follow-up of 3.11 years among 6893 person-years, 106 new-onset AF cases were detected. The baseline characteristics with and without AF incidence post-randomization are shown in *Table 2*. The patients with AF incidence had a larger mitral regurgitation (MR) jet area, higher left atrial area, higher MR jet area-to-left atrial area ratio, lower Peak A wave velocity, and lower left atrial volume index. There were no significant differences in the remaining echocardiographic parameters across the two studied groups (see Supporting Information, *Table S3*).

The risk of AF incidence gradually increased across the risk of liver fibrosis score strata. According to NFS, AF incidence per 100 person-years ranged from 0.58 at scores <-1.455

to 2.25 at scores >0.676 . The rate of person-years across the FIB-4 group was higher, ranging from 1.33 per 100 person-years at a FIB-4 of <1.45 points to 2.55 per 100 person-years at a score of >3.25 .

Association between NFS and FIB-4 levels and new-onset atrial fibrillation in heart failure with preserved ejection fraction

Crude associations of the individual components of the NFS and FIB-4 with new-onset AF incidence are presented in *Table 3*. Diabetes, age, ALT, and AST were positively associated with AF incidence, and platelets were inversely related to AF incidence, whereas no significant association was observed for ALB and BMI.

Table 1 Baseline characteristics stratified by Fibrosis-4 index and non-alcoholic fatty liver disease fibrosis score groups

	Overall (n = 2072)	NFS < -1.455 (n = 532)	NFS = -1.455-0.676 (n = 1,093)	NFS > 0.676 (n = 447)	FIB-4 < 1.45 (n = 1,067)	FIB-4 = 1.45-3.25 (n = 917)	FIB-4 > 3.25 (n = 88)
Demographic							
Age (years)	67.0 (60.0, 74.0)	62.0 (56.0, 69.0)	69.0 (61.0, 75.0)	70.0 (62.0, 77.0)*	63.0 (57.0, 70.0)	70.0 (63.0, 77.0)	73.0 (66.0, 80.0)*
Sex, male	930 (44.9)	229 (43.0)	479 (43.8)	222 (49.7)	458 (42.9)	424 (46.2)	48 (54.5)
Race, White	1814 (87.5)	506 (95.1)	961 (87.9)	347 (77.6)*	926 (86.8)	812 (88.5)	76 (86.4)
Current smoking	261 (12.6)	98 (18.4)	128 (11.7)	35 (7.8)*	153 (14.3)	95 (10.4)	13 (14.8)*
Ever smoking	695 (33.5)	136 (25.6)	363 (33.2)	196 (43.8)*	348 (32.6)	316 (34.5)	31 (35.2)
Never smoking	1116 (53.9)	298 (56.0)	602 (55.1)	216 (48.3)*	566 (53.0)	506 (55.2)	44 (50.0)
BMI, kg/m ²	30.6 (27.1, 35.4)	27.8 (25.0, 31.1)	30.4 (27.1, 34.5)	37.0 (32.3, 43.0)*	41.0 (27.4, 36.5)	30.1 (26.7, 34.6)	30.8 (27.6, 34.5)*
Heart rate, bpm	68 (61, 75)	68 (62, 69)	69 (61, 75)	70 (62, 77)*	68 (62, 75)	68 (60, 74)	64.5 (60, 74)
SBP, mmHg	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (118, 136)
DBP, mmHg	80 (70, 84)	80.0 (75, 85)	80 (70, 85)	71 (62, 80)*	80 (70, 85)	80 (70, 83)	70 (60, 80)
NYHA III or IV class	604 (29.2)	118 (22.2)	296 (27.1)	190 (42.5)*	282 (26.5)	299 (32.6)	23 (26.1)*
Chronic health conditions, n%							
Peripheral vascular disease	193 (9.3)	31 (5.8)	92 (8.4)	70 (15.7)*	92 (8.6)	91 (9.9)	10 (11.4)
COPD	219 (10.6)	41 (7.7)	109 (10.0)	69 (15.4)*	114 (10.7)	99 (10.8)	6 (6.8)
Hypertension	1905 (91.9)	486 (91.4)	998 (91.3)	421 (94.2)	993 (93.1)	833 (90.8)	79 (89.8)
Diabetes mellitus	698 (33.7)	44 (8.3)	322 (29.5)	332 (74.3)*	379 (35.5)	290 (31.6)	29 (33.0)
Previous MI	579 (27.9)	158 (29.7)	312 (28.5)	109 (24.4)	298 (27.9)	258 (28.1)	23 (26.1)
Previous stroke	133 (6.4)	24 (4.5)	73 (6.7)	36 (8.1)	73 (6.8)	56 (6.1)	4 (4.5)
CABG	259 (12.5)	47 (8.8)	127 (11.6)	85 (19.0)*	113 (10.6)	132 (14.4)	14 (15.9)*
PCI	313 (15.1)	57 (10.7)	158 (14.5)	98 (21.9)*	151 (14.2)	149 (16.2)	13 (14.8)
Thyroid disease	260 (12.5)	56 (10.5)	135 (12.4)	69 (15.4)	135 (12.7)	115 (12.5)	10 (11.4)
Dyslipidaemia	1206 (58.2)	264 (49.6)	625 (57.2)	317 (70.9)*	613 (57.5)	535 (58.3)	58 (65.9)
C2HEST score	2.0 (1.0, 3.0)	1.0 (1.0, 2.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)*	1.0 (1.0, 2.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)*
Measurements							
eGFR, mL/min × 1.73 m ²	67.0 (55.4, 80.6)	71.5 (60.7, 84.3)	66.0 (55.5, 79.5)	63.1 (49.8, 77.2)*	69.7 (57.0, 83.8)	64.8 (53.9, 77.5)	59.4 (64.8, 77.5)*
White blood cell count, 10 ³ /mL	6.7 (5.6, 7.9)	6.8 (5.6, 7.9)	6.5 (5.5, 7.8)	6.9 (5.8, 8.2)*	7.0 (5.8, 8.4)	6.4 (5.4, 7.5)	6.3 (5.0, 7.2)*
Haemoglobin, g/dL	13.1 (12.2, 14.3)	13.5 (12.6, 14.6)	13.2 (12.3, 14.3)	12.7 (11.6, 13.9)*	13.2 (12.2, 14.3)	13.1 (12.2, 14.2)	13.0 (11.5, 14.3)
Platelet (K/μL)	228 (196, 265)	268 (236, 310)	220 (196, 254)	195 (162, 229)*	252 (221, 290)	207 (180, 235)	157.5 (128.3, 192)*
AST, U/L	23.0 (18.0, 29.0)	22.0 (17.43, 29.0)	23.0 (18.0, 29.0)	23.0 (18.0, 30.0)	20.0 (16.0, 24.0)	26.0 (21.0, 33.0)	39.0 (30.0, 52.6)*
ALT, U/L	21.9 (15.8, 31.0)	25.0 (18.0, 34.0)	21.0 (15.0, 30.0)	19.0 (14.0, 28.0)*	22.4 (16.0, 31.0)	21.0 (15.0, 30.0)	21.3 (14.0, 30.0)*
ALP, U/L	90.0 (67.0, 126.0)	95.0 (69.0, 135.7)	89.0 (66.0, 125.5)	87.0 (67.0, 120.0)*	90.0 (68.0, 127.0)	88.0 (66.0, 124.5)	103.0 (64.0 (135.7)
ALB, g/dL	4.1 (3.8, 4.4)	4.4 (4.1, 4.8)	4.1 (3.8, 4.4)	3.9 (3.5, 4.1)*	4.1 (3.8, 4.5)	4.1 (3.8, 4.4)	4.1 (3.7, 4.4)*
BNP ^a	227.0 (133.0, 427.5)	214.0 (132.0, 426.0)	203.0 (132.0, 424.0)	244.5 (139.0, 432.8)	198.0 (121.0, 410.0)	236.0 (142.0, 433.5)	242.5 (156.3, 428.8)
NT-pro BNP ^a	646.0 (386.0, 1462.0)	571.5 (191.0, 1492.0)	680.0 (406.75, 1327.8)	660.0 (386.0, 1630.0)	604.0 (284.0, 1354.0)	715.5 (432.8, 1616.5)	591.0 (232.0, 1585.0)

M (IQR) for non-normally distributed data, M ± SD for normally distributed data, and n (%) for categorical variables. Calculations of Fibrosis-4 and NFS are described in the Methods section. Calculation of C2HEST can be found in our previous article.¹⁵

ALB, albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4 index; MI, myocardial infarction; NFS, non-alcoholic fatty liver disease fibrosis score; NT-pro BNP, N-terminal proBNP; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

^aBNP or NT-pro BNP values were available in 442 or 351 patients, respectively.
*P < 0.05.

Table 2 Baseline characteristics of heart failure with preserved ejection fraction patients with and without incident atrial fibrillation during follow-up

	Without incident AF (n = 1951)	With incident AF (n = 121)	p
Demographic			
Age (years)	66.0 (59.0, 74.0)	74.0 (65.5, 79.5)	<0.001*
Sex, male	866 (44.4)	64 (52.9)	0.068
Race, White	1714 (87.9)	100 (82.6)	0.092
Current smoking	254 (13.0)	7 (5.8)	0.020*
Ever smoking	637 (32.6)	58 (47.9)	0.001*
Never smoking	1060 (54.3)	56 (46.3)	0.085
BMI (kg/m ²)	30.5 (27.0, 35.3)	32.7 (27.9, 37.8)	0.027*
Heart rate (bpm)	68 (62, 75)	64 (60, 74)	0.005*
SBP (mmHg)	130 (120, 140)	131 (120, 140)	0.748
DBP (mmHg)	80 (70, 85)	73 (63, 80)	<0.001*
NYHA class (III or IV)	561 (28.8)	43 (35.5)	0.113
Chronic health conditions			
Peripheral vascular disease	171 (8.8)	22 (18.2)	0.001*
COPD	202 (10.4)	17 (14.0)	0.199
Hypertension	1794 (92.0)	111 (91.7)	0.932
Diabetes mellitus	643 (33.0)	55 (45.5)	0.005*
Congestive heart failure	1451 (74.4)	75 (62.0)	0.003*
Previous MI	542 (27.8)	37 (30.6)	0.506
Previous stroke	122 (6.3)	11 (9.1)	0.217
CABG	236 (12.1)	23 (19.0)	0.026*
PCI	285 (14.6)	28 (23.1)	0.011*
Thyroid disease	242 (12.4)	18 (14.9)	0.426
Dyslipidaemia	1122 (57.5)	84 (69.4)	0.010*
C2HEST score	2.0 (1.0, 2.0)	3.0 (1.0, 3.0)	<0.001*
Measurements			
eGFR (mL/min × 1.73 m ²)	67.3 (55.7, 80.9)	62.5 (51.4, 75.7)	0.013*
White blood cell count (k/μL)	6.7 (5.6, 7.9)	6.9 (5.9, 8.5)	0.053
Haemoglobin (g/dL)	13.2 (12.2, 14.3)	13.1 (12.1, 14.1)	0.601
Platelet (k/μL)	228.0 (197.0, 265.0)	215.0 (178.5, 263.0)	0.053
AST (U/L)	23.0 (18.0, 29.0)	22.0 (17.0, 27.0)	0.141
ALT (U/L)	22.0 (15.8, 31.0)	20.0 (16.0, 27.0)	0.263
ALP (U/L)	90.0 (67.0, 126.0)	92.0 (71.0, 139.5)	0.323
ALB (g/dL)	4.1 (3.8, 4.5)	4.0 (3.7, 4.3)	0.053

M (IQR) for non-normally distributed data, M ± SD for normally distributed data, and n (%) for categorical variables.

AF, atrial fibrillation; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; NYHA, New York Heart Association; SBP, systolic blood pressure.

*P < 0.05.

Table 3 The univariate Cox regression analyses between the components of Fibrosis-4 index and non-alcoholic fatty liver disease fibrosis score and atrial fibrillation incidence

	HR (95% CI)
Diabetes	1.91 (1.28, 2.85)*
BMI, kg/m ²	1.024 (0.997, 1.051)
Age, 10 years	1.31 (1.26, 1.37)*
ALT, 10 U/L	0.95 (0.92, 0.98)*
AST, 10 U/L	0.90 (0.87, 0.93)*
ALB, g/dL	1.05 (0.98, 1.11)
Platelet, 10/mm ³	0.987 (0.981, 0.993)*

ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HR, hazard ratio.

*P < 0.05.

The K-M curve showed that AF incidence significantly increased with increasing NFS scores (P < 0.001); however, it was not significant according to FIB-4 scores (P = 0.26) (Figure 2). In the Cox regression, the AF incidence was ele-

vated with NFS groups (NFS = -1.455-0.676: HR 2.44, 95% CI 1.27-4.68; NFS > 0.676: HR 3.36, 95% CI 1.27-6.80) in all adjusted models, whereas it was not significant according to FIB-4 (FIB-4 = 1.45-3.25: HR 1.02, 95% CI 0.67-1.55; FIB-4 > 3.25: HR 1.69, 95% CI 0.76-3.79) (Table 4).

When NFS and FIB-4 were analysed as continuous variables, each point increase in the NFS was associated with a 15% increase in AF incidence (HR 1.15, 95% CI 1.01-1.32) after full adjustments; nevertheless, the association was not significant according to FIB-4 (HR 1.13, 95% CI 0.93-1.37) (Table 4).

Discriminatory capacity of non-alcoholic fatty liver disease fibrosis score and Fibrosis-4 index

The discriminatory performances of the liver fibrosis scores for predicting incident AF in patients with HFpEF were expressed as the C-indices. As shown in Figure 3, NFS (C-index

Figure 2 Kaplan–Meier curves for AF incidence across NFS and FIB-4 groups in patients with heart failure with preserved ejection fraction. NFS, non-alcoholic fatty liver disease fibrosis score; FIB-4, Fibrosis-4 index; AF, atrial fibrillation. Calculations of FIB-4 and NFS are described in the Methods section.

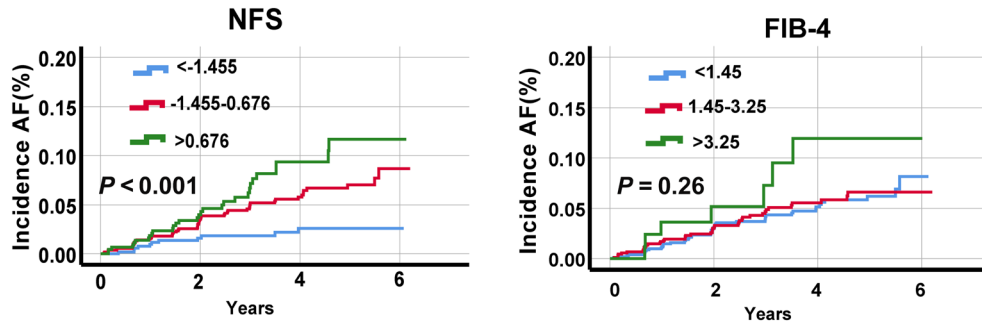


Table 4 Unadjusted and adjusted hazard ratio/95% confidence interval of association between liver fibrosis scores and atrial fibrillation incidence

Fibrosis scores	Cases (%)	Person-years	Incidence rate, per 100 person-years	Crude HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
NFS^b						
Per 1 unit increase	97 (4.7)	6893	1.41	1.20 (1.05, 1.36)*	1.19 (1.04, 1.36)	1.15 (1.01, 1.32)*
NFS < -1.455	11 (2.1)	1892	0.58	Ref	Ref	Ref
NFS = -1.455–0.676	56 (5.1)	3665	1.53	2.62 (1.37, 5.01)*	2.61 (1.37, 4.99)*	2.44 (1.27, 4.68)*
NFS > 0.676	30 (6.7)	1336	2.25	3.80 (1.90, 7.59)*	3.75 (1.88, 7.49)*	3.36 (1.27, 6.80)*
<i>P</i> for trend				<0.001*	<0.001*	0.001*
FIB-4^a						
Per 1 unit increase	97 (4.7)	6893	1.41	1.13 (0.94, 1.36)	1.12 (0.94, 1.35)	1.13 (0.93, 1.37)
FIB-4 < 1.45	48 (4.5)	3596	1.33	Ref	Ref	Ref
FIB-4 = 1.45–3.25	42 (4.6)	3023	1.39	1.04 (0.69, 1.57)	1.03 (0.68, 1.56)	1.02 (0.67, 1.55)
FIB-4 > 3.25	7 (8.0)	274	2.55	1.91 (0.86, 4.21)	1.86 (0.84, 4.12)	1.69 (0.76, 3.79)
<i>P</i> for trend				0.314	0.344	0.433

Model 1 was adjusted for sex.

^aModel 2 was adjusted for Model 1 + treatment arm, diabetes mellitus, smoking or ever smoking, body mass index, heart rate, estimated glomerular filtration rate, hypertension, thyroid, coronary artery bypass graft surgery, and percutaneous coronary intervention.

^bModel 2 was adjusted for Model 1 + treatment arm, smoking or ever smoking, heart rate, estimated glomerular filtration rate, hypertension, thyroid, coronary artery bypass graft surgery, and percutaneous coronary intervention.

**P* < 0.05.

0.662, 95% CI 0.608–0.716, sensitivity 81.8%, specificity 48.1%), not FIB-4 (C-index 0.531, 95% CI 0.471–0.593, sensitivity 27.1%, specificity 78.2%), had moderate performance in predicting incident AF. The performance of NFS and FIB-4 after internal validation showed a mean C-index of 0.660 (IQR 0.604, 0.721) or 0.528 (IQR 0.429, 0.590).

gender (females vs. males) and region (Americas vs. Russia/Georgia), but an expected interaction for the treatment arm (spironolactone vs. placebo) was found (*P* = 0.01). According to FIB-4, there were no interactions in all subgroups (all *P* > 0.05).

Sensitivity and subgroup analyses

As presented in the Supporting Information, *Tables S4* and *S5*, the sensitivity analyses confirmed the results by using a competing risk regression model, excluding the Russian/Georgian population and patients who were treated with ACEIs/ARBs and beta-blockers.

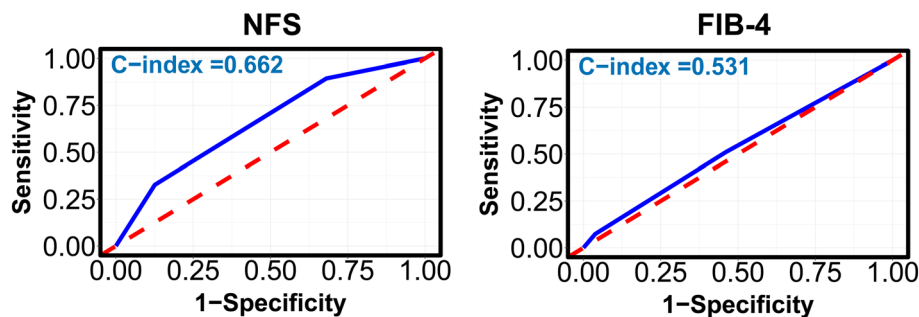
The subgroup analyses for incident AF are described in Supporting Information, *Tables S6–S8*. There were no significant interactions between NFS and subgroups based on

Discussion

Major findings

This *post hoc* analysis from TOPCAT demonstrated that in patients with HFpEF, an elevated NFS score rather than FIB-4 was significantly associated with incident AF. The subgroup and sensitivity analyses confirmed results. Moreover, NFS has a moderate predictive ability for predicting AF occurrence. Overall, these findings suggested that among patients

Figure 3 The receiver operating characteristic curves for predicting atrial fibrillation incidence in patients with heart failure with preserved ejection fraction, assessed by NFS and FIB-4 scores. NFS, non-alcoholic fatty liver disease fibrosis score; FIB-4, Fibrosis-4 index. The C-statistic of the NFS and FIB-4 score was calculated as category variables using a crude Cox regression model.



with HFpEF, advanced liver fibrosis was associated with increased new-onset AF incidence and may be a novel predictor of new-onset AF. To the best of our knowledge, this is the first study to assess the relationship between FIB-4 or NFS and the incidence of AF in patients with HFpEF.

Heart failure and liver diseases often coexist and independently contribute to poor outcomes.¹⁶ Advanced liver fibrosis is the primary determinant of progression to cirrhosis and liver failure. In a small-cohort ($N = 183$) study by Miller *et al.*⁵ including baseline AF, the prevalence of advanced liver fibrosis reached 48.6% as assessed by NFS (>0.676). As previously reported, the prevalence of advanced liver fibrosis was 37.65% in TOPCAT Americans, including baseline AF. In our study, advanced liver fibrosis was 21.5% in the overall population and increased to 29.3% in Americans. The results from Peters *et al.*⁴ also showed that patients with higher NFS or FIB-4 scores were more likely to have AF at baseline. These results suggest that HFpEF patients with AF probably have a greater incidence of hepatic fibrosis.

Recent evidence showed that liver fibrosis scores were significant predictors of cardiovascular events in HFpEF.^{17–19} However, in the context of FIB-4, our results seemed inconsistent with previous studies. Our results showed that the association between FIB-4 and incident AF among patients with HFpEF was not significant. Notably, the diagnostic performance of NFS and FIB-4 for liver fibrosis was comparable in patients with NAFLD.^{20,21} However, the presence of advanced liver fibrosis assessed by FIB-4 (4.2%) was much lower than that assessed by NFS (21.5%) in the present study. This inconsistency was interesting. To date, neither NFS nor FIB-4 has been validated in HFpEF patients. However, a recent study by Miller *et al.*⁵ suggested that compared with FIB-4, NFS might be a more sensitive indicator in liver fibrosis in HFpEF, which might explain this inconsistency. Another important point to discuss here is the ability of liver fibrosis scores to exclude advanced fibrosis rather than detect significant/advanced fibrosis.^{22,23} That is, FIB-4 or NFS scores have a higher negative predictive value but lower positive predictive value. In light of this evidence, the presence of advanced fibrosis in

many patients might be underestimated, including HFpEF. More data with other measures of imaging or biopsy are needed to assess the prevalence and prognosis of liver fibrosis in HFpEF.

NFS or FIB-4 has been shown to predict death in the general population and clinical outcomes in patients without liver-related diseases, including heart failure.^{4,19,24,25} We showed that NFS has a moderate predictive ability for AF incidence in HFpEF. However, it should be emphasized that the aim of this study was not to elaborate a predictive model for new-onset AF but to point out the role of advanced liver fibrosis on AF in HFpEF.

Our results supported the emerging concept of phenogroups of patients with HFpEF with distinct clinical characteristics and long-term outcomes. A phenomapping analysis of the TOPCAT study identified a phenogroup that demonstrated a high prevalence of obesity, diabetes, chronic kidney disease, elevated renin levels, high pro-inflammatory biomarkers, concentric left ventricular (LV) hypertrophy, and liver fibrosis.²⁶ Consistently, Salah *et al.* also proposed the novel term ‘advanced liver disease/cirrhosis HFpEF’,¹⁶ representing the disease trajectory among HFpEF. Heart failure and AF commonly coexist, and patients with AF have worse outcomes.²⁷ Based on our results, we also supposed an increased incidence of AF with advanced liver fibrosis, which reinforced the concept of ‘advanced liver disease/cirrhosis HFpEF’.¹⁶ The expected interaction of NFS for the response to spironolactone randomized therapy can also be mirrored by the heterogeneity in the clinical profiles among HFpEF patients.

Potential mechanisms

The mechanisms underlying the relationship between advanced liver fibrosis and incident AF in patients with HFpEF remain incompletely elucidated. Cardiac autonomic dysfunction has been suggested as a possible mechanism. Several studies have demonstrated that a dysfunctional autonomic

nervous system could play a significant role in the initiation and perpetuation of AF.^{28,29} NAFLD and advanced liver disease have proven to be independent risk factors for autonomic dysfunction.³⁰ In addition, advanced liver fibrosis can also lead to increased levels of neuropeptides that have been shown to be associated with the development of AF.³¹ Moreover, vagal-mediated AF is thought to be caused by vasoactive intestinal peptide.^{32,33} Another potential mechanism behind the elevated risk of AF in the setting of advanced liver fibrosis is the abnormal pathway of fibrosis. Systemic fibrosis, fibrogenesis, and collagen conversion may be a possible link between HFpEF and NAFLD.^{34–36} Elevated levels of galectin-3 were observed in patients with liver disease.^{37,38} Galectin-3 is implicated in fibrosis of both the liver and heart and is associated with an increased incidence of AF.^{39,40} Transforming growth factor beta⁴¹ and connective tissue growth factor⁴² may also be potential mediators that share the common pathway of fibrosis. Therefore, we assumed that in HFpEF patients, higher liver fibrosis scores may be indicators of higher central venous pressure with resultant liver fibrosis and impaired liver functional reserve and partly reflected by cardiac fibrosis, resulting in a higher incidence of AF.

Comparison with previous studies

Several studies showed that liver fibrosis scores were associated with worse outcomes in HFpEF.^{17–19} In addition, a prospective study of 492 patients with HFpEF reported that NFS was associated with atrial pressure and left atrial volume and the risk of all-cause mortality.³ Our study reinforced these results, further showing that elevated NFS was significantly associated with incident AF and had a moderate predictive ability in predicting incident AF among patients with HFpEF.

Clinical implications

HFpEF is a heterogeneous disease that contains considerable phenotypic diversity and has no obvious effective treatment.^{43,44} Considering that AF is very common in HFpEF and contributes to a poor prognosis, it is crucial for clinicians to develop strategies to reduce the incidence of AF in HFpEF. Several risk scoring models for predicting incident AF have been established^{15,45}; however, they lack excellent predictive performance in HFpEF.¹⁵ Our findings provide important information, and liver fibrosis might be a new component in risk scores for AF in HFpEF.

Our findings suggest that advanced liver fibrosis was associated with increased new-onset AF incidence and may be a predictor for new-onset AF in patients with HFpEF. However, our study should not be interpreted as emphasizing the im-

portance of liver biopsy in predicting the outcomes in HFpEF. Clinicians could incorporate liver fibrosis score assessment into their AF risk scoring models to prevent incident AF and predict the progression of HFpEF. On the other hand, physicians should be vigilant of the changes in transaminase and platelets, which might indicate changes in liver fibrosis, especially when using medications that affect liver function, such as statins, amiodarone, and warfarin.

Strength and limitations

Previous reports demonstrated that advanced liver fibrosis was associated with poor prognosis in patients with heart failure.^{3,18,19,46} Our analysis extended these studies and has several important strengths. This is the first study to explore the association between liver fibrosis scores and incident AF in patients with HFpEF.

The present study has several limitations. First, it should be emphasized that the liver fibrosis level assessed in the present study is based on scoring systems. Although the diagnostic accuracy of FIB-4 and NFS has been tested in patients with certain liver diseases, such as NAFLD or hepatitis B virus infection, our results might be explained as exploratory before the diagnostic performance of NFS or FIB-4 in liver fibrosis in heart failure is well validated. Second, this is a retrospective study, and we cannot infer direct causality. Measured and unmeasured confounding may influence our results. Third, our population was based on a clinical trial, and most patients were White, which may not be completely representative of real-world patients; thus, it may limit the generalizability of our findings. Fourth, we evaluated the NFS and FIB-4 at baseline; changes in the NFS and FIB-4 during hospitalization or after discharge remain unclear. Lastly, the current evidence suggests that FIB-4 and NFS do not perform accurately in some populations (e.g. age < 35 years, morbidly obese adults), and further studies are needed to clarify the role of these scores in HFpEF.

Conclusion

Among patients with HFpEF, advanced liver fibrosis is associated with increased new-onset AF incidence and may be a novel predictor of new-onset AF. Additional studies are needed to confirm our results.

Conflict of interest

None declared.

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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. Baseline echocardiographic characteristics stratified by NFS groups.

Table S2. Baseline echocardiographic characteristics stratified by Fibrosis-4.

Table S3. Baseline echocardiographic characteristics stratified by AF incident post-randomization.

Table S4. The Fibrosis scores and the risk of incident AF in the competing risk regression model.

Table S5. Association between Fibrosis scores and Atrial fibrillation in patients without concomitant use of ACE inhibitors or ARBs, or without concomitant use of any β -blocker, NFS and FIB-4 were analyzed as continuous variables.

Table S6. Unadjusted and adjusted hazard ratios/95% confidence intervals describing association between Fibrosis scores and Atrial fibrillation in Americas cohort and non-Americas cohort, analyzed as continuous variables.

Table S7. Unadjusted and adjusted hazard ratios/95% confidence intervals describing association between Fibrosis scores and Atrial fibrillation in male and female, analyzed as continuous variables.

Table S8. Unadjusted and adjusted hazard ratios/95% confidence intervals describing association between Fibrosis scores and Atrial fibrillation in patients using spironolactone or placebo, analyzed as continuous variables.

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