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SHORT COMMUNICATION

Association of liver fibrosis risk scores with clinical outcomes in patients with heart failure with preserved ejection fraction: findings from TOPCAT

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Abstract

Aims Non-alcoholic fatty liver disease leads to progressive liver fibrosis and appears to be a frequent co-morbid disease in heart failure with preserved ejection fraction (HFpEF). It is well known that liver fibrosis severity predicts future liver-related morbidity and mortality, but its impact on outcomes in patients with HFpEF remains unknown. This analysis aimed to describe the prevalence of liver fibrosis, as assessed using surrogate biomarkers, in patients with HFpEF and the association of such biomarkers in predicting clinical outcomes in these patients.

Methods and results Patients with HFpEF from TOPCAT Americas were included in the analysis. The non-alcoholic fatty liver disease fibrosis score (NFS) and fibrosis-4 (FIB-4) scores were calculated using a combination of clinical characteristics and laboratory parameters. Risk of advanced fibrosis was classified as low, intermediate, and high. For the 1423 with sufficient data, we used Cox regression analysis to test the association between the risk of fibrosis severity and the combined primary endpoint of all cardiovascular death, aborted cardiac arrest, and hospitalization for heart failure. Advanced fibrosis, as determined by high fibrosis scores, was present in 37.57% by the NFS and 8.02% by the FIB-4. Higher risk of advanced hepatic fibrosis was associated with older age. In unadjusted models, the risk of advanced fibrosis was associated with the primary cardiovascular outcome [NFS high vs. low, hazard ratio (HR) 1.709 (95% confidence interval, CI 1.238–2.358, $P = 0.0011$) and FIB-4 high vs. low, HR 1.561 (95% CI 1.139–2.140, $P = 0.0056$)]. After multivariable adjustment, this association was diminished [NFS high vs. low, HR 1.349 (95% CI 0.938–1.939, $P = 0.1064$) and FIB-4 high vs. low, HR 1.415 (95% CI 0.995–2.010, $P = 0.0531$)].

Conclusions Our study suggests that advanced liver fibrosis, as estimated by fibrosis risk scores, may not be uncommon in patients with HFpEF, and there appears to be a limited independent association between liver fibrosis risk scores and clinical outcomes related to heart failure events.

Keywords Heart failure with preserved ejection fraction; Liver fibrosis

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Background

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease, which encompasses non-alcoholic fatty liver and non-alcoholic steatohepatitis. Non-alcoholic steatohepatitis promotes progressive liver fibrosis and thus can cause cirrhosis. In patients with NAFLD, advanced liver fibrosis as measured by validated scoring systems is linked to worse clinical outcomes including all-cause mortality,[1] and cardiovascular disease is one of the leading causes of mortality.[2] The prevalence of NAFLD in heart failure with preserved ejection fraction (HFpEF) is high (>25%) based on several small observational

studies.[3,4] Both HFpEF and NAFLD are characterized by metabolic dysregulation. Accumulating evidence suggests that NAFLD, independent of other established risk factors for heart failure, is associated with HFpEF/diastolic dysfunction[5–7] and, further, that liver disease could precede HFpEF onset.[8] NAFLD has also been shown to be associated with change in myocardial structure and function over time, although obesity appears to account for much of this association.[9]

Despite this known overlap in pathology, liver disease is often not assessed in HFpEF clinical practice and clinical trials. Therefore, the prevalence and implications of liver disease in a contemporary cohort of HFpEF are unclear. This analysis aimed to address these gaps in knowledge by describing the prevalence of liver fibrosis, as assessed using surrogate biomarkers, and the association of such biomarkers in predicting clinical outcomes in patients with HFpEF from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial.

Aims and methods

Study population

TOPCAT examined the effects of spironolactone compared with placebo and remains one of the largest HFpEF clinical trials to date.[10] Patients from TOPCAT (excluding Eastern European countries) were included in this analysis. Of note, liver disease was not captured as a predefined variable at baseline in TOPCAT, and aspartate transaminase (AST) and alanine transaminase (ALT) >3× upper level of normal was an exclusion criterion for the trial.

Assessment of liver fibrosis

The diagnosis of liver disease relies on clinical exam, laboratory values, and/or liver biopsy. Validated scoring systems may be used to estimate degree of fibrosis non-invasively once a diagnosis of liver disease has been made. Both the NAFLD fibrosis score (NFS) and fibrosis-4 (FIB-4) (developed in chronic hepatitis C but used in a variety of liver diseases) are validated, non-invasive scoring systems that stratify the risk for hepatic fibrosis based on commonly measured laboratory tests.[1] We applied these scores to a HFpEF population that is inherently at greater risk for chronic liver disease (and specifically NAFLD) but whose liver disease status was not documented in the TOPCAT data collection. Liver/fibrosis scores for this analysis were calculated using the following formulas:

- *Non-alcoholic fatty liver disease fibrosis score*: $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ body mass index (kg/m^2) $+ 1.13 \times$ diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet ($\times 10^9$/L) $- 0.66 \times$ albumin (g/dL). NFS < -1.455 = Group 1, correlates with histological fibrosis stage F0–F2, negative predictive value of 88–93% for advanced fibrosis. NFS $-1.455 - 0.675$ = Group 2, indeterminate score. NFS > 0.675 = Group 3, correlates with F3–F4, positive predictive value of 82–90% for advanced fibrosis.
- *Fibrosis-4*: (age [years] × AST [U/L])/(platelet [$\times 10^9$/L] × √ALT[U/L]). FIB-4 < 1.45 = Group 1, negative predictive value of 90% for advanced liver fibrosis (Ishak Stages 4–6). FIB-4 1.45–3.25 = Group 2, intermediate score. FIB-4 > 3.25 = Group 3, positive predictive value of 65% for advanced liver fibrosis.

Statistical analyses

Unadjusted and adjusted Cox regression models were developed to determine the association between fibrosis risk score and clinical outcomes by comparing groups within each risk category. The primary endpoint was a combined endpoint of all cardiovascular death, aborted cardiac arrest, secondary endpoints of all-cause hospitalization, and hospitalization for heart failure. Secondary endpoint was hospitalization for heart failure. Adjusted models included the following covariables: sex, race, New York Heart Association class, smoking, previous hospitalization for heart failure, systolic blood pressure, sodium (mmol/L), blood urea nitrogen (mg/dL), prior cardiovascular disease, and spironolactone assignment. Adjustment variables were determined a priori based on the associated risk with HFpEF and NAFLD. Baseline variables that were collinear with the components of the NFS/FIB-4 score were not considered as adjustment variables. Statistical comparison between baseline groups was made with the Jonckheere–Terpstra test. The two-sided level of statistical significance was set at $P < 0.05$ for all analyses. Statistical analysis was performed using R, Version 3.6.0. (R Foundation for Statistical Computing, Vienna, Austria).

Results

Based on the NFS, 11.19% of the TOPCAT Americas cohort were low risk for advanced fibrosis (NFS Group 1) and 37.57% were high risk (NFS Group 3); fibrosis severity was indeterminate in 51.25% (NFS Group 2). According to the FIB-4 algorithm, 42.61% were low risk for advanced fibrosis (FIB-4 Group 1), 49.36% were intermediate risk (FIB-4 Group 2), and 8.02% were high risk (FIB-4 Group 3). Regardless of the algorithm used to stage fibrosis, patients with high risk for advanced fibrosis were older (mean 72 years old in NFS Group 3 vs. 68 years old in NFS Group 1 and mean 77 years old in FIB-4 Group 3 vs. 68 years old in FIB-4 Group 1). Patients with high risk for advanced fibrosis by NFS were

Table 1 Patient characteristics by NFS and FIB-4 groups

	NFS[a]				FIB-4[b]			
Group	1 (n = 184)	2 (n = 843)	3 (n = 618)	P-value	1 (n = 701)	2 (n = 812)	3 (n = 132)	P-value
Age (years)	68.26 ± 9.65	72.17 ± 9.73	71.93 ± 9.43	0.0206	67.66 ± 9.54	74.30 ± 8.63	76.48 ± 8.69	<0.0001
Female sex (0)	111 (60.33%)	449 (53.26%)	272 (44.01%)	<0.0001	378 (53.92%)	406 (50.00%)	48 (36.36%)	<0.0001
Race								
Caucasian	154 (83.70%)	674 (79.95%)	464 (75.08%)	0.0040	531 (75.75%)	656 (80.79%)	105 (79.55%)	0.0293
Black	19 (10.33%)	134 (15.90%)	126 (20.39%)	0.0008	137 (19.54%)	124 (15.27%)	18 (13.64%)	0.0149
Body mass index (kg/m^2)	28.41 ± 6.20	31.86 ± 6.64	38.00 ± 8.45	<0.0001	35.57 ± 8.55	32.63 ± 7.45	31.37 ± 7.51	<0.0001
Systolic blood pressure (mmHg)	124.57 ± 15.50	127.37 ± 15.78	128.30 ± 16.13	0.0211	128.11 ± 16.28	127.45 ± 15.49	123.39 ± 15.99	0.0155
Heart rate (b.p.m.)	67.78 ± 12.94	67.68 ± 12.29	68.52 ± 12.59	0.3646	69.76 ± 12.59	67.36 ± 12.38	68.05 ± 12.34	0.1087
Sodium (mmol/L)	138.95 ± 3.78	139.77 ± 2.97	139.77 ± 3.06	0.1190	139.46 ± 3.34	139.75 ± 2.90	140.35 ± 2.99	0.0063
AST (U/L)	24.93 ± 12.57	24.80 ± 11.75	26.04 ± 14.19	0.0997	20.09 ± 7.75	27.15 ± 10.51	41.36 ± 25.12	<0.0001
ALT (U/L)	29.18 ± 21.03	25.86 ± 14.03	22.87 ± 12.49	<0.0001	25.14 ± 15.41	25.16 ± 14.01	24.55 ± 13.57	0.6758
Glomerular filtration rate (mL/min/1.73 m^2)	67.58 ± 22.59	64.59 ± 21.65	63.04 ± 20.99	0.0137	65.99 ± 22.54	63.18 ± 20.62	62.75 ± 21.28	0.0175
Current smoking, N (%)	18 (9.78%)	49 (5.81%)	38 (6.16%)	0.3176	53 (7.57%)	39 (4.80%)	13 (9.85%)	0.5702
Diabetes mellitus, N (%)	27 (14.67%)	254 (30.13%)	445 (72.01%)	<0.0001	359 (51.21%)	318 (39.16%)	49 (37.12%)	<0.0001
Atrial fibrillation, N (%)	62 (33.70%)	367 (43.53%)	276 (44.66%)	0.0504	239 (34.09%)	393 (48.40%)	73 (55.30%)	<0.0001
Prior hospitalization for heart failure, N (%)	111 (60.33%)	460 (54.57%)	387 (62.62%)	0.0373	454 (64.76%)	439 (54.06%)	65 (49.24%)	<0.0001
NYHA Classes III and IV, N (%)	46 (25.14%)	267 (31.71%)	266 (43.04%)	<0.0001	245 (35.05%)	289 (35.59%)	45 (34.09%)	0.9720
Beta-blocker, N (%)	136 (73.91%)	664 (78.86%)	486 (78.64%)	0.4056	577 (82.43%)	626 (77.09%)	90 (68.18%)	0.0002
ACEi/ARB, N (%)	137 (74.46%)	646 (76.72%)	510 (82.52%)	0.0025	556 (79.43%)	633 (77.96%)	97 (73.48%)	0.1898
Diuretics, N (%)	151 (82.07%)	745 (88.48%)	574 (92.88%)	<0.0001	632 (90.29%)	722 (88.92%)	116 (87.88%)	0.2944

ACEi, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; NYHA, New York Heart Association.
From a total of 1645 trial patients, 1423 patients had the required data for our adjusted analysis.
[a]Non-alcoholic fatty liver disease fibrosis score (NFS)—groups as defined in Aims and methods section.
[b]Fibrosis-4 (FIB-4)—groups as defined in Aims and methods section.

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more obese (mean body mass index 38 kg/m^2 in NFS Group 3 vs. 28 kg/m^2 in NFS Group 1) but were less obese by the FIB-4 scoring system (33 kg/m^2 in FIB-4 Group 3 vs. 36 kg/m^2 in FIB-4 Group 1). Activity level (metabolic equivalents/week) down-trended in patients with increased risk for fibrosis (mean 8.87 in NFS Group 3 vs. 11.5 in NFS Group 1 and mean 8.74 in FIB-4 Group 3 vs. 9.92 in FIB-4 Group 1) (*Table 1*).

In the unadjusted model, degree of fibrosis risk according to NFS demonstrated a significant association with the primary combined cardiovascular outcome [Group 3 vs. Group 1, hazard ratio (HR) 1.709 (95% confidence interval,

Figure 1 (A) Kaplan–Meier curves for primary outcome split into non-alcoholic fatty liver disease fibrosis score (NFS) groups and (B) Kaplan–Meier curves for primary outcome split by fibrosis-4 (FIB-4) Groups 1–3.

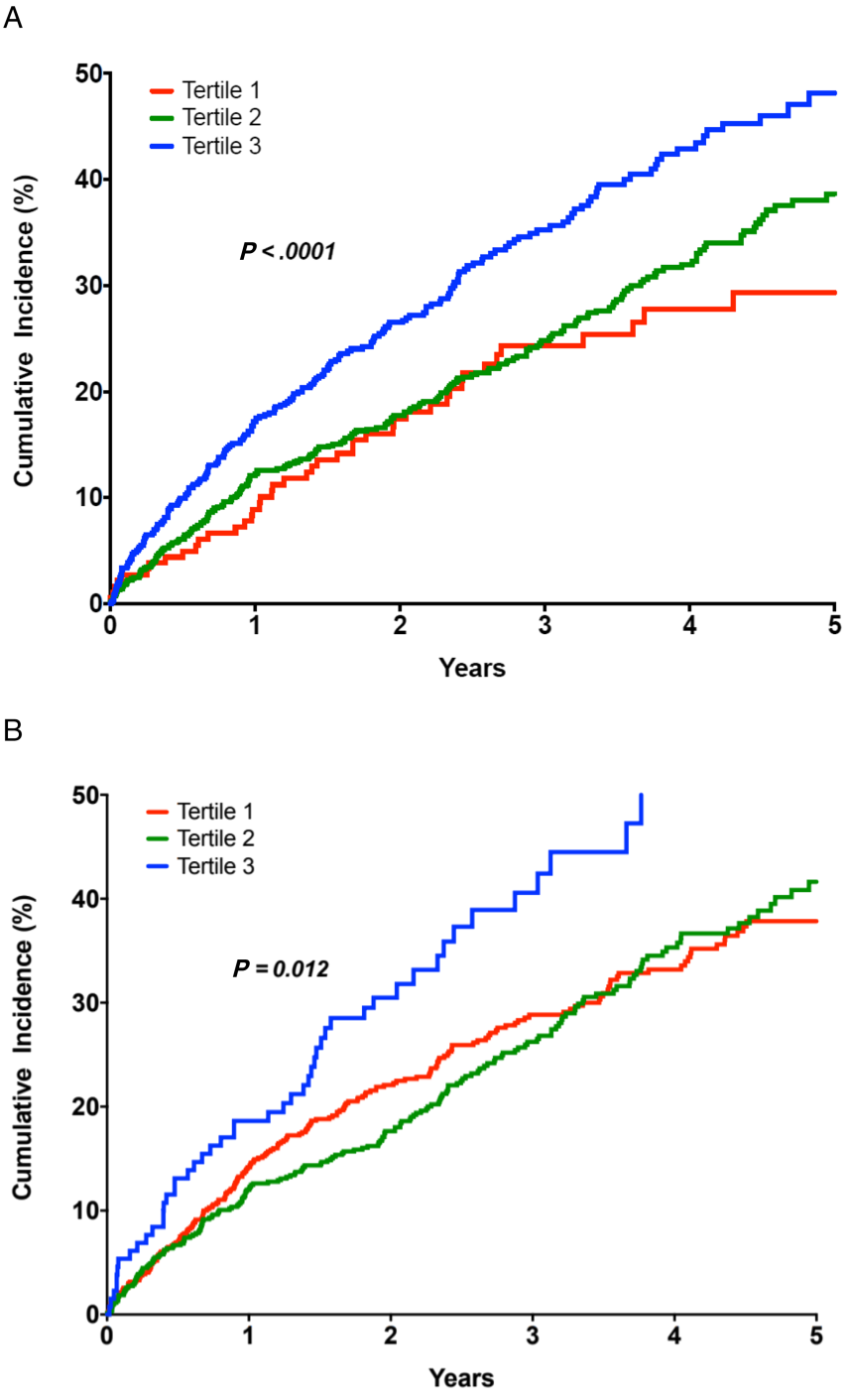

Table 2 Unadjusted and adjusted hazard ratios/95% confidence intervals describing association between liver disease and primary outcome, and secondary outcomes such as all-cause hospitalization and hospitalization for heart failure

Primary outcome: combination of all-cardiovascular death, aborted cardiac arrest, and hospitalization for heart failure						
	Unadjusted			Adjusted[a]		
Model/metric	HR	95% CI	*P*-value	HR	95% CI	*P*-value
NFS Group 2[b]	1.162	0.844–1.600	0.3566	1.091	0.764–1.558	0.6303
NFS Group 3[b]	1.709	1.238–2.358	0.0011	1.349	0.938–1.939	0.1064
FIB-4 Group 2[c]	0.987	0.818–1.190	0.8882	0.942	0.771–1.149	0.5539
FIB-4 Group 3[c]	1.561	1.139–2.140	0.0056	1.415	0.995–2.010	0.0531
All-cause hospitalization						
	Unadjusted			Adjusted[a]		
Model/metric	HR	95% CI	*P*-value	HR	95% CI	*P*-value
NFS Group 2[b]	1.319	1.056–1.647	0.0147	1.095	0.861–1.394	0.4582
NFS Group 3[b]	1.533	1.221–1.925	0.0002	1.127	0.878–1.394	0.3490
FIB-4 Group 2[c]	1.021	0.896–1.164	0.7500	0.990	0.861–1.138	0.8870
FIB-4 Group 3[c]	1.149	0.903–1.461	0.2584	1.177	0.907–1.526	0.2203
Hospitalization for heart failure						
	Unadjusted			Adjusted[a]		
Model/metric	HR	95% CI	*P*-value	HR	95% CI	*P*-value
NFS Group 2[b]	0.980	0.796–1.206	0.8479	1.098	0.859–1.403	0.4560
NFS Group 3[b]	1.411	1.142–1.744	0.0014	1.349	0.965–1.596	0.0918
FIB-4 Group 2[c]	0.856	0.751–0.976	0.0204	0.968	0.837–1.120	0.6630
FIB-4 Group 3[c]	1.144	0.881–1.485	0.3125	1.469	1.096–1.970	0.0101

CI, confidence interval; HR, hazard ratio.
[a]Covariables for adjusted model: sex, race, New York Heart Association (NYHA) class, smoking, systolic blood pressure, sodium (mmol/L), blood urea nitrogen (mg/dL), prior cardiovascular disease, previous hospitalization for heart failure, and use of spironolactone.
[b]Non-alcoholic fatty liver disease fibrosis score (NFS)—reference: NFS Group 1.
[c]Fibrosis-4 (FIB-4)—reference: FIB-4 Group 1.

CI 1.238–2.358, *P* = 0.0011)] (*Figure 1* & Table *2*). After adjustment, this association was diminished [Group 3 vs. Group 1, HR 1.349 (95% CI 0.938–1.939, *P* = 0.1064)]. Similarly, in an unadjusted model, degree of fibrosis risk according to FIB-4 demonstrated a significant association with the primary cardiovascular outcome [Group 3 vs. Group 1, HR 1.561 (95% CI 1.139–2.140, *P* = 0.0056)]. After adjustment, this association also became non-significant [Group 3 vs. Group 1, HR 1.415 (95% CI 0.995–2.010, *P* = 0.0531)]. In an adjusted model, risk for advanced fibrosis was not associated with a significant increase in all-cause hospitalization either by NFS [Group 3 vs. Group 1, HR 1.127 (95% CI 0.878–1.446, *P* = 0.3490)] or FIB-4 [Group 3 vs. Group 1, HR 1.177 (95% CI 0.907–1.526, *P* = 0.2203)]. However, FIB-4 was independently associated with hospitalization for HF [Group 3 vs. Group 1, HR 1.469 (95% CI 1.096–1.970, *P* = 0.0101)].

Discussion

Heart failure with preserved ejection fraction is a heterogeneous disease, and to date, therapies seeking to improve the neurohormonal balance or cardiovascular performance have failed to improve clinical outcomes. There are many contributing factors to HFpEF pathophysiology, and as a result, HFpEF is composed of several phenotypes.[11,12] As with NAFLD, metabolic disturbances are increasingly regarded as contributors to HFpEF incidence. However, there is good rationale to suspect that HFpEF is not merely associated with NAFLD but rather a potential consequence of NAFLD.[5,6,9,12] Despite the association of HFpEF and NAFLD, the screening for NAFLD in HFpEF patients is infrequently pursued, and thus, the diagnosis of NAFLD is rarely made. In a large contemporary HFpEF cohort with NAFLD risk factors including obesity and diabetes, we found a high prevalence (ranging 8–38%) of risk for advanced liver fibrosis as measured by scoring systems. This finding underscores the importance of considering NAFLD, which may be masquerading as congestive hepatopathy, in HFpEF patients with mild–moderate elevations in AST/ALT.

Neither the NFS nor the FIB-4 score correlated with the combined cardiovascular outcome measure after adjustment for potential confounders. However, a high FIB-4 score remained significantly associated with hospitalization for heart failure, even after multivariable adjustment. Further, unadjusted models did demonstrate significant associations, suggesting some overlap between liver disease and

co-morbidities regarding their effect on outcomes. For instance, obesity (included in NFS, and not in FIB-4) appears to be a critical link in the pathological process of myocardial remodelling in heart failure.[9] Additionally, the relationship between fibrosis score and outcomes may have been diluted by the heterogeneous phenotypes in TOPCAT, some of which may not have been genuine HFpEF including a group of younger patients with milder symptoms and markers of lung disease, although some of these patients were enrolled in Eastern Europe and were excluded from this analysis.[12]

This study was a *post hoc* trial analysis and, therefore, carries the inherent limitations of this type of study including inability to infer direct causality. Further, elevated aminotransferases in the setting of heart failure-associated congestion may be a confounder in this analysis, although this is partly mitigated by the use of multiple components to each score, the exclusion of patients with markedly elevated aminotransferases, and by the use of AST/ALT ratios in the scores as opposed to absolute levels.[13] Further, prior work has demonstrated that most patients in TOPCAT were relatively volume contracted as opposed to volume expanded, which should minimize this potential limitation. Lastly, and most importantly, in this trial (and most heart failure studies), there was no recorded 'gold standard' of chronic liver disease diagnosis by imaging or biopsy to confirm the presence of chronic liver disease or stage fibrosis severity. Therefore, there may be a subset of patients in the 'advanced' liver fibrosis risk categories by our analysis that do not truly have intrinsic liver disease but rather have significant co-morbidities that overlap with features of liver disease; the neutral results of the adjusted models support this theory.

In conclusion, this study indicates that there may be a high prevalence of liver fibrosis in a large, contemporary HFpEF population along with a limited association between the risk for advanced liver fibrosis and clinical outcomes, mostly restricted to heart failure related events. Further research —namely, the inclusion of 'gold standard' liver disease instruments such as liver imaging and/or biopsy in HFpEF—is necessary to better understand the complex interplay between chronic liver disease and HFpEF and determine whether there are any clear causal interactions.

Conflict of interest

M.F. was supported by a Mario Family Award and Translating Duke Health Award and has received consulting fees from AstraZeneca, Axon Therapies, CVRx, Daxor, Edwards Lifesciences, Galvani, NXT Biomedical, and Respicardia.

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