ORIGINAL RESEARCH ARTICLE

Liver fibrosis score predicts mortality in heart failure patients with preserved ejection fraction

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Abstract

Aims Heart failure with preserved ejection fraction (HFpEF) has several pathophysiological aspects, including stiffness and/or congestion of multiple organs. Poor prognosis is expected in heart failure patients with liver stiffness, which has recently been assessed by non-alcoholic fatty liver disease fibrosis score (NFS; based on aspartate aminotransferase to alanine aminotransferase ratio, platelet counts, and albumin). We aimed to investigate the impact of NFS on prognosis of HFpEF patients, with consideration for the peripheral collagen markers such as procollagen type III peptide (PIIIP), type IV collagen 7S, and hyaluronic acid.

Methods and results We performed a prospective observational study. Consecutive 492 hospitalized HFpEF patients were divided into four groups based on their NFS: first–fourth quartiles (*n* = 123). The fourth quartile group had the highest levels of PIIIP, type IV collagen 7S, hyaluronic acid, and B-type natriuretic peptide ($P<0.001$ each). In addition, there were significant positive correlations between PIIIP, type IV collagen 7S, hyaluronic acid, B-type natriuretic peptide, and NFS ($P < 0.001$ each). In the follow-up period (mean 1107 days), 93 deaths occurred. All-cause mortality increased in all four quartiles (8.1%, 12.2%, 23.6%, and 31.7%, $P < 0.001$). In the multivariable Cox proportional hazard analysis, NFS was an independent predictor of all-cause mortality in the HFpEF patients.

Conclusions NFS, a novel indicator of liver fibrosis, correlates with circulating systemic markers of fibrosis and congestion and is associated with higher all-cause mortality in HFpEF patients. NFS can be calculated simply and may be a useful tool to assess liver stiffness and prognosis in HFpEF patients.

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a common and increasing public health problem.[1–3] It has several pathophysiological aspects including cardiac hypertrophy and interstitial fibrosis[1–5] and/or impaired functional reserve of multiple organs, such as lungs, vessels, skeletal muscle, kidney, and liver.[1,2,6] The abdominal compartment (e.g. liver, splanchnic vasculature, and gut) has recently been focused to contribute significantly to deranged cardiac as well as renal function in HF patients.[1,7] Congestive hepatopathy[8,9] due to HF causes functional abnormalities

of the liver,[10] and increased liver stiffness, measured by transient elastography, indicates higher mortality.[11–15] Liver dysfunction, such as the elevation of serum bilirubin, alkaline phosphatase, gamma-glutamyl transferase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), is frequent in HF related to reduced arterial perfusion and passive congestion and is associated with disease severity and prognosis.[7,9] In many HFpEF patients, fluid retention is less apparent in the periphery but occurs in the abdominal cavity.[1] Liver congestion due to increased central venous pressure might directly contribute to a state of impaired natriuresis.[7] Liver congestion may be mutually associated with

liver stiffness, resulting in fibrosis (e.g. nutmeg liver), and adverse prognosis.[8–10] In addition, elevated central venous pressure and right atrial pressure may contribute to cholestatic abnormalities and impairment of hepatocyte function and liver reserve in HF patients.[8–10]

On the other hand, not only previous imaging tests,[11–15] but also a simple score to evaluate liver fibrosis is desirable and required in HF patients. Recently, in patients with chronic liver failure, non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS) has begun to be used to assess liver fibrosis based on simple laboratory testing (age, body mass index, presence of diabetes, AST to ALT ratio, platelet counts, and albumin) in patients with NAFLD.[16–18] We hypothesized that NFS, which is measured simply and quickly, indicates liver congestion and fibrosis, and impaired functional reserve of the liver, and is associated with adverse prognosis in HFpEF patients.

Therefore, the aims of the present study were to verify the value of NFS as an assessment tool for liver fibrosis and higher mortality in patients with HFpEF, and its underlying clinical and pathophysiological background [e.g. echocardiographic and haemodynamic parameters, systemic peripheral collagen markers such as procollagen type III peptide (PIIIP), type IV collagen 7S, and hyaluronic acid, which are established biochemical markers of liver fibrosis].[19,20]

Methods

Subjects and study protocol

This was a prospective observational study that enrolled consecutive symptomatic HF patients hospitalized for treatment of decompensated HFpEF and discharged from the Fukushima Medical University Hospital between 2009 and 2014. Symptomatic HF was defined based on the Framingham criteria,[21] and left ventricular ejection fraction (LVEF) was more than 50%.[22] Blood samples and echocardiography were obtained at hospital discharge. All the patients underwent testing of hepatitis B surface antigen and hepatitis C antibodies, and their medical histories were checked for chronic liver disease (cirrhosis, hepatic tumours, bile duct disease, etc.). Patients with distinct liver diseases, severe valvular disease, acute coronary syndrome, advanced cancer, and/or undergoing dialysis were excluded. The patient flow is described in *Figure 1*. Liver fibrosis was estimated by NFS [$-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ body mass index (kg/m^2) $+ 1.13 \times$ diabetes mellitus (if presence, given 1) $+ 0.95 \times$ AST (U/L) to ALT (U/L) ratio $- 0.013 \times$ platelet count (10^{-9}/L) $- 0.66 \times$ albumin (mg/L)].[16–18] These patients were divided into four groups based on NFS: first (NFS < -1.13, $n = 123$), second ($-1.13 \leq$ NFS < 0.20, $n = 123$), third ($0.20 \leq$ NFS < 1.56, $n = 123$), and fourth quartiles ($1.56 \leq$ NFS, $n = 123$).[16–18]

Figure 1 Patient flowchart.
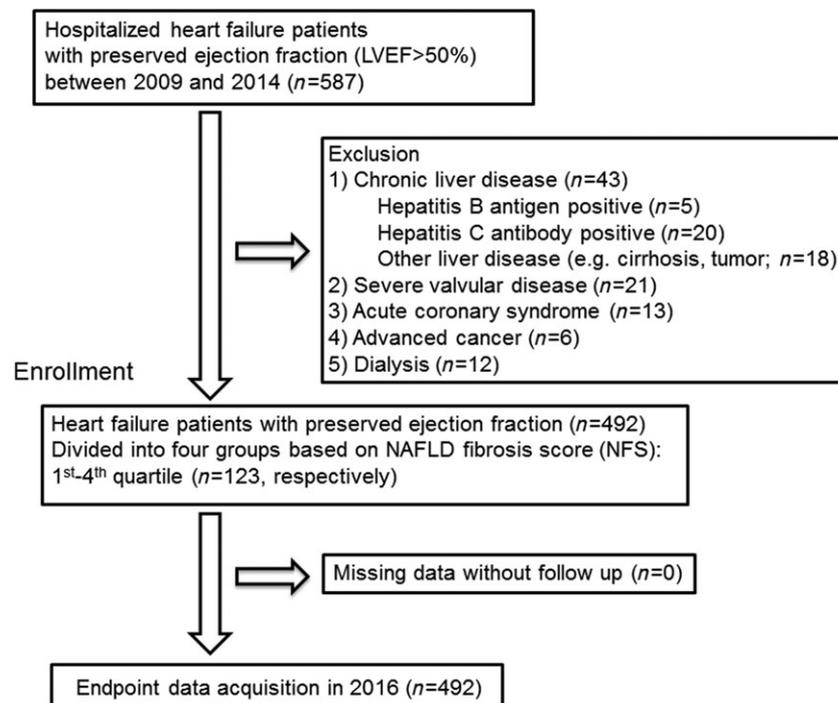
Diabetes was defined as recent use of insulin or antidiabetic drugs, a fasting blood glucose value of $\geq$126 mg/dL, and/or a haemoglobin A1c value of $\geq$6.5%. Hypertension was defined as recent use of antihypertensive drugs or systolic blood pressure of $\geq$140 mmHg and/or diastolic blood pressure of $\geq$90 mmHg. Dyslipidaemia was defined as recent use of cholesterol-lowering drugs, a triglyceride value of $\geq$150 mg/dL, a low-density lipoprotein cholesterol value of $\geq$140 mg/dL, and/or a high-density lipoprotein cholesterol value of <40 mg/dL. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2, measured by the Modification of Diet in Renal d as haemoglobin levels of <12.0 g/dL in females and <13.0 g/dL in males.[22] Atrial fibrillation was identified by an electrocardiogram performed during hospitalization and/or medical records including past history.

We compared the clinical features and results from laboratory tests and echocardiography among the four groups. All patients were followed up until 2016 for all-cause mortality as the primary outcome of our study (*Figure 1*). Cardiac death was adjudicated by independent experienced cardiologists and included death due to worsened HF in accordance with the Framingham criteria,[21] ventricular fibrillation documented by electrocardiogram or other implantable devices, and acute coronary syndrome. Non-cardiac death included death due to respiratory failure, renal failure, liver failure, infection, sepsis, stroke, cancer, or digestive haemorrhage. Status and date of death were obtained from the patients' medical records or their referring cardiologists. Survival time was calculated from the date of hospitalization until the date of death or last follow-up. Those who administered the survey were blind to the analyses, and written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of Fukushima Medical University. The investigation conforms to the principles outlined in the Declaration of Helsinki, and reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines.[23]

Measurement of procollagen type III peptide, type IV collagen 7S, and hyaluronic acid

The level of serum PIIIP was measured by immunoradiometric assay (RIA-gnost PIIIP c.t., CISbio Bioassays, Codolet, France). Serum type IV collagen 7S was measured by radioimmunoassay (type IV collagen 7S kit, SCETI MEDICAL LABO K.K., Tokyo, Japan). Serum hyaluronic acid was measured by latex agglutination-turbidimetric immunoassay (LPIA Ace HA., LSI Medience Co., Tokyo, Japan). These assays were blindly performed by a laboratory company (LSI Medience Co., Tokyo, Japan).

Echocardiography

Echocardiography was performed blindly by an experienced echocardiographer using the standard techniques.[22] Echocardiographic parameters included left ventricular dimension, LVEF, left atrial volume, the ratio of early transmitral flow velocity to mitral annular velocity (mitral valve E/e'), dimension and area of right ventricle and atrial, right ventricular fractional area change, inferior vena cava diameter, systolic pulmonary artery pressure (SPAP), tissue Doppler-derived tricuspid lateral annular systolic velocity (tricuspid valve S'), and the ratio of the peak transtricuspid velocity during early diastole to the peak tricuspid valve annular velocity during early diastole (tricuspid valve E/e').[24] The LVEF was calculated using Simpson's method. The right ventricular fractional area change, defined as (end diastolic area − end systolic area)/end diastolic area × 100, was a measure of right ventricular systolic function.[24] SPAP was calculated by adding the right atrial pressure (estimated by the diameter and collapsibility of the inferior vena cava) to the systolic trans tricuspid pressure gradient. Tricuspid valve E/e' was calculated by transtricuspid Doppler flow and tissue Doppler imaging.[24] All measurements were performed using ultrasound systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA).

Haemodynamic measurements

Right catheterizations were performed within 1 year prior to admission till discharge. All catheterizations were performed in a resting supine position under fluoroscopic guidance. Pulmonary capillary wedge pressure, mean pulmonary artery pressure, mean right atrial pressure, and cardiac output were measured using a 7F Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA).[25] We used the thermodilution method for the measurement of cardiac output.

Statistical analysis

Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data are log transformed (e.g. BNP, C-reactive protein, and hyaluronic acid). Categorical variables are expressed as numbers and percentages. The χ^2 test was used for comparisons of categorical variables. We used the analysis of variance followed by Tukey's post hoc test. Multivariable regression analysis was used to determine each element of NFS related to the score. Correlations between NFS and markers of liver fibrosis and haemodynamic parameters (e.g. PIIIP, type IV collagen 7S, hyaluronic acid, BNP, cardiac index, pulmonary capillary wedge pressure, mean pulmonary artery pressure, and right atrial pressure) were assessed using Pearson's correlation

analysis. The Kaplan–Meier method was used for presenting the all-cause mortality, and the log-rank test was used for initial comparisons. Univariable and multivariable Cox proportional hazard analyses were used to analyse predictors of all-cause mortality to adjust confounding factors. Hazard ratio and 95% confidence interval are presented. To minimize potential confounding, including those that are generally known risk factors for mortality and are not included in NFS elements, we considered the following clinical factors: NFS; sex; presence of New York Heart Association class III or IV; ischaemic aetiology; atrial fibrillation; chronic kidney disease; anaemia; BNP; hyponatraemia (<135 mEq/L); and usage of renin–angiotensin–aldosterone system inhibitors, β-blockers, and diuretics. Among these factors, those that independently predicted mortality with a value of $P < 0.05$ were selected in the final adjusted model. We constructed two models: in the first, we analysed NFS as a categorical variable model (fourth, third, second vs. first quartile), and in the second, we analysed NFS as a continuous variable model. A value of $P < 0.05$ was considered statistically significant for all comparisons. These analyses were performed using a statistical software package (SPSS ver. 21.0, IBM, Armonk, NY, USA).

Results

In the multiple regression analysis to determine NFS, the elements of the score were as follows: platelet count,

$\beta = -0.571$, $P < 0.001$; age, $\beta = 0.362$, $P < 0.001$; diabetes, $\beta = 0.279$, $P < 0.001$; AST/ALT ratio, $\beta = 0.253$, $P < 0.001$; albumin, $\beta = -0.223$, $P < 0.001$; and body mass index, $\beta = 0.185$, $P < 0.001$. In addition, there were significant positive correlations between NFS and systemic fibrosis markers and central venous pressure (PIIIP, $R = 0.429$, $P < 0.001$; type IV collagen 7S, $R = 0.343$, $P < 0.001$; hyaluronic acid, $R = 0.376$, $P < 0.001$; BNP, $R = 0.283$, $P < 0.001$; and right atrial pressure, $R = 0.216$, $P = 0.038$). In contrast, there were no significant correlations between NFS and cardiac index, pulmonary capillary wedge pressure, and mean pulmonary artery pressure.

The clinical features of the present study's subjects are summarized in *Table 1*. The fourth quartile group had a higher prevalence of ischaemic aetiology, diabetes, atrial fibrillation, chronic kidney disease, and anaemia, as well as higher usage of renin–angiotensin–aldosterone system inhibitors and diuretics. Subjects in the fourth quartile group also had a higher mean age and tended to have a higher body mass index. Comparisons of the laboratory data and echocardiographic and haemodynamic parameters among the four groups are shown in *Table 2*. The fourth quartile group had the lowest platelet count, as well as the lowest levels of albumin and cholinesterase. In addition, the fourth quartile group had the highest levels of BNP, C-reactive protein, PIIIP, type IV collagen 7S, and hyaluronic acid. In contrast, total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, and sodium did not differ significantly among the four groups. With regard to the

Table 1 Comparisons of clinical features among non-alcoholic fatty liver disease fibrosis score quartiles ($N = 492$)

	First quartile, NAFLD fibrosis < -1.13 ($n = 123$)	Second quartile, $-1.13 \leq$ NAFLD fibrosis < 0.20 ($n = 123$)	Third quartile, $0.20 \leq$ NAFLD fibrosis < 1.56 ($n = 123$)	Fourth quartile, $1.56 \leq$ NAFLD fibrosis ($n = 123$)	*P*-value
NAFLD fibrosis score	-2.28 ± 1.24††	-0.47 ± 0.39**††	0.87 ± 0.38**††	2.82 ± 1.31**	<0.001
Age (years)	59.5 ± 15.8††	69.7 ± 12.2**††	73.3 ± 10.7**	76.5 ± 9.9**	<0.001
Male gender (*n*, %)	59 (48.0)	59 (48.0)	61 (49.6)	66 (53.7)	0.786
Body mass index (kg/cm²)	23.4 ± 4.1	22.8 ± 4.3	23.4 ± 4.2	24.3 ± 4.3	0.061
NYHA class III or IV (*n*, %)	1 (0.8)	2 (1.6)	5 (4.1)	5 (4.1)	0.258
Ischaemic aetiology (*n*, %)	9 (7.3)	9 (7.3)	25 (20.3)	32 (26.0)	<0.001
Co-morbidity					
Hypertension (*n*, %)	81 (65.9)	103 (83.7)	108 (87.8)	100 (81.3)	<0.001
Diabetes (*n*, %)	12 (9.8)	31 (25.2)	53 (43.1)	73 (59.3)	<0.001
Dyslipidaemia (*n*, %)	97 (78.9)	90 (73.2)	94 (76.4)	95 (77.2)	0.759
Atrial fibrillation (*n*, %)	35 (28.5)	53 (43.1)	52 (42.3)	60 (48.8)	0.010
CKD (*n*, %)	30 (24.4)	58 (47.2)	83 (67.5)	84 (68.3)	<0.001
Anaemia (*n*, %)	48 (39.0)	61 (49.6)	80 (65.0)	94 (76.4)	<0.001
Medications					
RAS inhibitors (*n*, %)	69 (56.1)	89 (72.4)	91 (74.0)	95 (77.2)	0.001
β-blockers (*n*, %)	77 (62.6)	78 (63.4)	83 (67.5)	80 (65.0)	0.862
Diuretics (*n*, %)	64 (52.0)	77 (62.6)	76 (61.8)	94 (76.4)	0.001

CKD, chronic kidney disease; NAFLD, non-alcoholic fatty liver disease; NYHA, New York Heart Association; RAS, renin–angiotensin–aldosterone system.
*$P < 0.05$ vs. the first quartile.
**$P < 0.01$ vs. the first quartile.
†$P < 0.05$ vs. the fourth quartile.
††$P < 0.01$ vs. the fourth quartile.

Table 2 Laboratory, echocardiographic, and haemodynamic data

	First quartile (n = 123)	Second quartile (n = 123)	Third quartile (n = 123)	Fourth quartile (n = 123)	P-value
Laboratory data					
Platelet count (×10^3/μL)	254.7 ± 110.4††	192.3 ± 49.5**††	167.6 ± 50.7**	151.8 ± 54.9**	<0.001
Log BNP	2.0 ± 0.6†	2.3 ± 0.5*†	2.4 ± 0.5*†	2.5 ± 0.5*	<0.001
Log C-reactive protein	−0.8 ± 0.7	−0.6 ± 0.7†	−0.5 ± 0.8	−0.4 ± 0.8**	0.001
Albumin (g/dL)	4.0 ± 0.5††	3.7 ± 0.6**††	3.6 ± 0.5**††	3.2 ± 0.6**	<0.001
Total bilirubin (mg/dL)	0.9 ± 0.4	0.9 ± 0.4	0.9 ± 0.5	0.9 ± 0.5	0.965
Direct bilirubin (mg/dL)	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.2	0.113
AST (U/L)	35.0 ± 6.4	32.3 ± 6.9	61.7 ± 17.2	91.5 ± 44.0	0.175
ALT (U/L)	34.6 ± 5.4	35.7 ± 5.6	46.2 ± 17.9	46.2 ± 16.9	0.302
ALP (U/L)	244.0 ± 126.2	256.1 ± 151.0	269.4 ± 111.9	263.8 ± 106.0	0.569
γ-GTP (U/L)	49.7 ± 4.7	69.9 ± 11.4	57.6 ± 5.9	48.0 ± 6.7	0.166
Cholinesterase (U/L)	315.0 ± 78.5††	279.7 ± 85.0†††	249.4 ± 65.2**††	205.9 ± 75.1**††	<0.001
Sodium (mEq/L)	139.3 ± 3.2	139.4 ± 3.1	138.6 ± 4.4	138.6 ± 4.4	0.225
PIIIP (U/mL)	0.6 ± 0.3††	0.7 ± 0.4†	0.8 ± 0.4**	0.9 ± 0.3**	<0.001
Type IV collagen 7S (ng/mL)	4.3 ± 1.5††	4.8 ± 1.7*††	5.2 ± 2.2**†	6.1 ± 2.4**	<0.001
Log hyaluronic acid	1.6 ± 0.3††	1.8 ± 0.4*††	1.9 ± 0.5**††	2.1 ± 0.5**	<0.001
Echocardiographic data					
Interventricular septal wall thickness (mm)	11.7 ± 3.5	11.8 ± 3.4	11.4 ± 2.6	11.4 ± 2.1	0.672
LV end-diastolic diameter (mm)	45.2 ± 8.6	47.5 ± 9.3	46.1 ± 10.2	47.5 ± 8.5	0.175
LV end-systolic diameter (mm)	29.8 ± 7.3	30.1 ± 8.8	30.7 ± 9.5	31.2 ± 7.8	0.221
LV posterior wall (mm)	11.3 ± 2.6	11.3 ± 2.3	11.6 ± 2.2	11.1 ± 1.9	0.660
LVEF (%)	63.1 ± 9.5	61.8 ± 9.5	61.7 ± 8.9	60.9 ± 8.8	0.217
Left atrial volume (mL)	72.9 ± 70.4†	89.3 ± 64.0	88.0 ± 60.0	92.7 ± 58.0*	0.043
Mitral valve E/e′	13.8 ± 8.7	15.3 ± 9.9	14.5 ± 8.6	16.8 ± 9.7	0.204
RV area-diastolic (mL)	17.5 ± 7.5	17.6 ± 7.4	16.5 ± 6.0	17.0 ± 7.1	0.829
RV area-systolic (mL)	10.7 ± 5.8	10.7 ± 5.6	9.5 ± 4.3	10.1 ± 5.1	0.611
RV-FAC (%)	43.2 ± 17.0	41.8 ± 13.4	43.9 ± 15.2	43.6 ± 13.6	0.885
Right atrial diameter long (mm)	50.5 ± 9.5††	54.2 ± 11.6*	55.4 ± 13.4*	56.9 ± 14.6**	0.027
Right atrial diameter short (mm)	36.5 ± 9.0	36.7 ± 9.5	38.1 ± 10.9	35.6 ± 10.8	0.664
Right atrial end systolic area (cm^2)	17.1 ± 7.2††	18.9 ± 9.6	19.4 ± 10.8*	20.6 ± 11.3**	0.033
SPAP (mmHg)	36.3 ± 23.3	33.2 ± 18.8	31.9 ± 16.7	32.9 ± 16.3	0.478
Tricuspid valve S′ (cm/s)	9.4 ± 3.7	9.7 ± 3.8	8.9 ± 3.5	9.9 ± 3.5	0.796
Tricuspid valve E/e′	5.5 ± 3.3	4.3 ± 2.9	6.3 ± 4.6	5.1 ± 2.3	0.188
Inferior vena cava (mm)	14.1 ± 4.0††	14.3 ± 3.9†	15.1 ± 5.3	16.3 ± 5.7**	0.006
Haemodynamic data (n = 290)					
Cardiac output (L/min)	4.6 ± 2.0	4.5 ± 1.6	4.1 ± 1.1	4.5 ± 1.5	0.212
Cardiac index (L/min/m^2)	2.9 ± 1.2	2.8 ± 0.9	2.7 ± 0.7	2.9 ± 0.9	0.521
Pulmonary capillary wedge pressure (mmHg)	13.1 ± 7.1	13.5 ± 7.2	13.6 ± 6.8	13.7 ± 7.3	0.959
Mean pulmonary artery pressure (mmHg)	24.1 ± 15.0	23.6 ± 11.1	23.5 ± 10.0	22.4 ± 9.0	0.217
Right atrial pressure (mmHg)	6.8 ± 3.8††	6.9 ± 4.4†	7.6 ± 5.3*	8.6 ± 5.0**	0.031

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LV, left ventricular; LVEF, left ventricular ejection fraction; PIIIP, procollagen type III peptide; RV, right ventricular; RV-FAC, right-ventricular fractional area change; SPAP, systolic pulmonary artery pressure.
*$P < 0.05$ vs. the first quantile.
**$P < 0.01$ vs. the first quartile.
$^†P < 0.05$ vs. the fourth quartile.
$^{††}P < 0.01$ vs. the fourth quartile.

echocardiographic parameters, although left and right ventricular systolic function, left ventricular dimension, and SPAP did not differ among the four groups, left atrial volume, right atrial area, and inferior vena cava diameter were larger in the fourth quartile than in the first quartile. Among the haemodynamic parameters (n = 290), right atrial pressure was higher in the fourth quartile than in the first to third quartiles. In contrast, cardiac index, pulmonary capillary wedge pressure, and mean pulmonary artery pressure did not differ among the four groups.

During the follow-up period (mean 1096 days), there were 33 cardiac deaths, including 17 due to worsening HF, 13 due to ventricular fibrillation, and 3 due to acute coronary syndrome, and 60 non-cardiac deaths (respiratory failure and/or pneumonia, n = 17; infection/sepsis, n = 13; stroke, n = 11; renal failure/liver failure/multiple organ failure, n = 9; digestive haemorrhage, n = 3; aneurysm, n = 2; and other causes, n = 5). As shown in *Figure 2*, all-cause mortality increased in all four quartiles (P < 0.001).

The Cox proportional hazard model was used to examine the prognostic value of the NFS in HFpEF patients (*Table 3*). In the multivariable Cox proportional hazard analysis, a high NFS score was determined to be an independent predictor of all-cause mortality in HFpEF patients after adjusting for other confounding factors (*Table 3*).
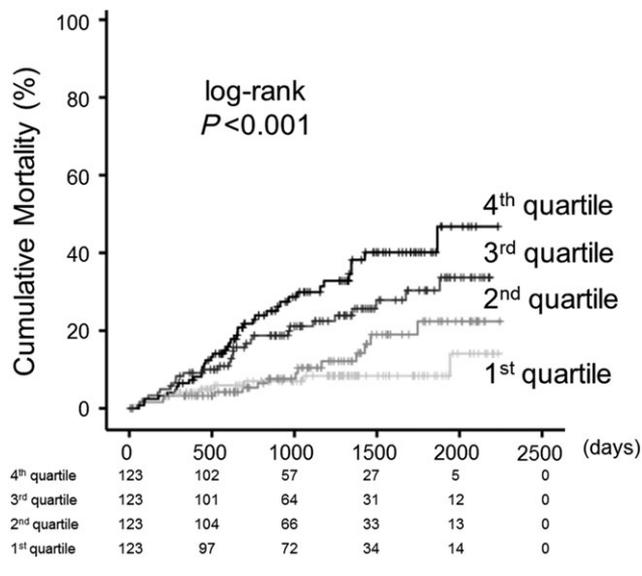
Discussion

The present study is the first to present that NFS, a marker of liver fibrosis, was correlated with central venous pressure (right atrial pressure, inferior vena cava diameter, right atrial area, left atrial volume, and BNP) and circulating markers of systemic fibrosis (PIIIP, type IV collagen 7S, and hyaluronic acid) and is associated with higher mortality in HFpEF patients. In contrast, higher NFS was not associated with left ventricular hypertrophy and impaired right and left ventricular systolic function and lower cardiac index in HFpEF patients.

HF sometimes consists of not only congestion but also reduced arterial flow called hypoxic hepatopathy. Hypoxia causes centrilobular necrosis in the liver and leads to the elevation of transaminase.[26] Increased central venous pressure causes hepatocyte atrophy and perisinusoidal oedema in the liver.[8,10] Sinusoidal damage leads to impaired clearance of

aspartate aminotransaminase.[27] Portal hypertension and liver fibrosis cause a reduced platelet count and protein synthesis.[7,9] Increased pressure within the hepatic sinusoid favours bile duct damage by disrupting endothelial cells and the interhepatocyctic tight junctions that separate the extravascular space from the bile canaliculus. Further, stagnant flow favours thrombosis within sinusoids, hepatic venules, and portal tracts, thereby contributing to liver fibrosis.[9,28] Centrilobular liver cell necrosis can extend to peripheral areas if HF persists and worsens and is followed by the deposition and spread of connective tissue bridging one central vein to another, ultimately leading to liver cirrhosis.[9] Concordant with these findings, increased central venous pressure and atrial volume overload, rather than decreased cardiac output or increased pulmonary artery pressure, were assumed in high-NFS groups in the current HFpEF patients.

Systemic fibrosis, fibrogenesis, and collagen turnover may be one plausible link between HFpEF and NAFLD.[5,16,19,29–32] Extracellular matrix alterations, which contain synthesis and degradation of collagen, occur not only in the myocardium but also in the arterial wall, kidneys, lungs, and liver in systemic disease (e.g. HF and chronic liver disease).[29,30] Collagen-dependent ventricular stiffness is increased in HFpEF.[1–5] The cardiac extracellular matrix is predominantly composed of fibrillar collagen type I (85%) and type III (11%).[29] Myocardial fibrosis occurs when synthesis of fibrillary collagen types I and III predominates over unchanges or decreased degradation.[32] An excess of highly cross-linked thick collagen type I fibres to the detriment of poorly cross-linked thin collagen type III fibres is typical of adverse fibrosis.[32] On the other hand, type IV collagens are relatively specifically observed in the liver and partially observed in the basement membrane of the myocytes, in the perivascular, and in the pericellular space in the heart.[29] Unlike type I and type III collagens, which are processed by proteolysis, type IV collagen is deposited intact in the matrix and the serum component of type IV collagen reflects matrix degradation.[20]

Circulating markers of plausible systemic fibrosis and collagen turnover, such as procollagen type III collagen

Table 3 Cox proportional hazard model of all-cause mortality in heart failure with preserved ejection fraction

All-cause mortality ($n = 93/492$)	Hazard ratio	95% confidence interval	P-value
Non-alcoholic fatty liver disease fibrosis score: categorical variable model			
Fourth vs. first quartile unadjusted	4.354	2.172–8.729	<0.001
Fourth vs. first quartile adjusted[a]	2.784	1.343–5.775	0.006
Third vs. first quartile unadjusted	2.992	1.458–6.139	0.003
Third vs. first quartile adjusted[a]	2.014	1.005–4.246	0.046
Second vs. first quartile unadjusted	1.533	0.689–3.412	0.296
Second vs. first quartile adjusted[a]	1.235	0.550–2.774	0.609
Non-alcoholic fatty liver disease fibrosis score: continuous variable model			
Unadjusted model	1.285	1.176–1.404	<0.001
Adjusted model[a]	1.132	1.020–1.256	0.020

[a]Adjusted for sex, New York Heart Association class III or IV, ischaemic aetiology, atrial fibrillation, chronic kidney disease, anaemia, BNP, hyponatraemia, renin–angiotensin–aldosterone system inhibitors, β-blockers, and diuretics.

aminoterminal peptide as metabolites of PIIIP,[33–36] type IV collagen,[36,37] carboxy-terminal telopeptide of collagen type I,[33,35] and growth differentiation factor 15,[38] are associated with cardiac remodelling and adverse prognosis in HF patients.[33–35,38] Elevated circulating levels of type III collagen is associated with increased aortic fibrosis and stiffness,[39] increased myocardial collagen types I and III,[33] systolic and diastolic dysfunction of right and left ventricles in hypertensive patients,[35,40] and diastolic dysfunction in HFpEF patients[39,41,42] and is partly associated with adverse prognosis in HFpEF patients.[34] On the other hand, it has been recently reported that type IV collagen 7S, which is a relatively specific fibrosis marker in the liver, is correlated with pulmonary capillary wedge pressure and right ventricular and atrial pressure, but not with cardiac index,[37] and associated with higher 1 year incidence of death or HF hospitalization in patients with HF.[37] Concordant with these findings, in the present study, there were significant associations between type IV collagen 7S, PIIIP, and hyaluronic acid, which are established markers of liver fibrosis,[16,17,19,20,43,44] and the NFS. We assumed that higher NFS may indicate higher central venous pressure with resultant liver fibrosis (type IV collagen 7S, hyaluronic acid, and PIIIP) and impaired liver functional reserve and partly reflected by cardiac fibrosis (PIIIP) in HFpEF patients. The NFS[16–18] can be used as an alternative marker for the measurement of liver fibrosis and/or reserve. This score can be calculated only by parameters measured in daily medical care. These parameters, such as AST, ALT, albumin, and platelet count, can be measured quickly even in outpatient clinics, by emergency medical services and more with point-of-care testing.

HFpEF and NAFLD may share other common pathophysiologies,[1,2,45–47] namely elevated renin–angiotensin–aldosterone system, oxidative stress and inflammation, insulin resistance, impaired adiponectin, increased visceral fat, and increased systemic organ fibrosis associated with collagen turnover. Hence, NFS may suggest severity of pathophysiology of HFpEF, as well as NAFLD.

Study strengths and limitations

Our study has several strengths. For instance, the present study is the first to show the association of high NFS with high all-cause mortality in HF patients, taking into consideration echocardiographic and haemodynamic parameters and peripheral collagen markers. In addition, HF diagnoses were made, and detailed causes of death were determined by our experienced cardiologists. Furthermore, there were no patients who dropped out.

The current study also has several limitations. First, as a prospective cohort study of a single centre with a relatively small number of patients, the study may be somewhat underpowered. Second, it remains unclear whether NFS only reflects liver fibrosis and/or congestion, with these together resulting in liver stiffness. Although HF patients with distinct liver disease were excluded, we cannot completely deny the presence of any liver disease. The relationship between NFS and other evaluations of fibrosis, such as liver biopsy, which is not generally performed in HF patients, or imaging (e.g. computed tomography) should be assessed in further studies. Third, time of catheterization is not simultaneous with evaluation of NFS at all. Hence, changes of haemodynamics did not necessarily reflect NFS. Fourth, we have used only variables on hospitalization in this study, without taking into consideration changes in medical parameters and post-discharge treatment. Fifth, although we used multivariable Cox proportional hazard regression analyses, the effects of differences in clinical background among the four groups may not have been completely adjusted. Therefore, the present results should be viewed as preliminary, and further studies with a larger population are needed.

Conclusions

NFS, a novel indicator of liver fibrosis, is correlated with central venous pressure and peripheral collagen markers and is associated with higher mortality in the present HFpEF patients. NFS can be calculated simply and may be a useful tool to assess liver fibrosis and prognosis in HFpEF patients.

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Conflict of interest

None declared.

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