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ORIGINAL RESEARCH ARTICLE

Prognostic significance of liver stiffness assessed by fibrosis-4 index in patients with heart failure

Masafumi Takae, Koichiro Fujisue, Eiichiro Yamamoto*, Koichi Egashira, Takashi Komorita, Fumi Oike, Taiki Nishihara, Masahiro Yamamoto, Kyoko Hirakawa, Noriaki Tabata, Takanori Tokitsu, Kenshi Yamanaga, Daisuke Sueta, Shinsuke Hanatani, Taishi Nakamura, Hiroki Usuku, Satoshi Araki, Yuichiro Arima, Seiji Takashio, Satoru Suzuki, Koichi Kaikita, Kenichi Matsushita and Kenichi Tsujita

Department of Cardiovascular Medicine, Faculty of Life Sciences, Graduate School of Medical Science, Center for Metabolic Regulation of Healthy Aging (CMHA), Kumamoto University, Kumamoto, Japan

Abstract

Background Heart failure (HF)-related congestive hepatopathy is a well-recognized problem in management of HF. The fibrosis-4 (FIB4) index calculated by [age × aspartate aminotransferase (IU/L)/platelet count (10^9/L) × square root of alanine aminotransferase (IU/L)] is useful for evaluating liver stiffness. We aimed to investigate the impact of the FIB4 index on prognosis in patients with HF.

Methods and results Consecutive HF patients referred for hospitalization at Kumamoto University Hospital, Japan, were registered between 2006 and 2015. We observed cardiovascular outcomes in each type of HF [HF with reduced left ventricular ejection fraction (LVEF) (HFrEF), HF with mid-range LVEF (HFmrEF) and with preserved LVEF (HFpEF)] according to their FIB4 index; Group 1 (FIB4 index $<$1.3), Group 2 (FIB4 index: 1.3–2.67), and Group 3 (FIB4 index $>$2.67). This study enrolled 83 HFrEF patients, 117 HFmrEF patients, and 504 HFpEF patients. In HFpEF patients, the Kaplan–Meier curve revealed that Group 3 had a significantly higher rate of total cardiovascular events compared with the other two groups. By contrast, the occurrences of total cardiovascular events were not different among three groups in HFrEF and HFmrEF patients.
Multivariate Cox proportional hazard analysis with significant factors in univariate analysis identified that the FIB4 index as an independent and significant predictor for future total cardiovascular events in HFpEF patients (hazard ratio: 1.09, 95% confidence interval: 1.03–1.15, P = 0.001).

Conclusions The FIB4 index was a significant predictor for total cardiovascular events in HFpEF.

Keywords Heart failure; Prognosis; Fibrosis-4 index

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**Correspondence to: Eiichiro Yamamoto, Department of Cardiovascular Medicine, Faculty of Life Sciences, Graduate School of Medical Science, Center for Metabolic Regulation of Healthy Aging (CMHA), Kumamoto University, Kumamoto, Japan. Email: eyamamo@kumamoto-u.ac.jp*

Introduction

Chronic heart failure (HF) is now increasing and a leading cause of poor outcomes worldwide. Because cardiovascular events are the main cause of death in chronic HF patients, risk stratification for future cardiovascular events in these patients can provide valuable information in the clinical setting. Although several clinical factors such as aging, obesity, type 2 diabetes mellitus, and metabolic syndrome are associated with the risk and prognosis of HF, they are not sufficient for practical risk stratification. One possible reason is that the backgrounds of HF are complicated. The new European Society of Cardiology guideline suggests that patients with HF should be categorized as HF with preserved left ventricular (LV) ejection fraction (EF) (LVEF) (HFpEF) (EF $\geq$ 50%), HF with reduced LVEF (HFrEF) (EF $<$ 40%), and HF with mid-range LVEF (HFmrEF) (EF 40–49%).[1] Although HFpEF and HFrEF were reported to have different underlying causes, demographics, comorbidities, and responses to treatments, it remains still unclear what the differences of pathophysiological mechanisms are among these three types of HF.

Heart failure often causes liver dysfunction due to reduced arterial perfusion and passive congestion.[2–4] Liver congestion might be mutually associated with liver stiffness, resulting in fibrosis and adverse prognosis.[5] It has recently been reported that liver stiffness measured by transient elastography increases along with the development of decompensated HF and decreases with clinical improvement.[6,7] Hence, the assessment of liver stiffness and/or impairment of liver reserve could be useful in patients with HF, the fibrosis-4 (FIB4) index has been reported to be useful for evaluating liver fibrosis or stiffness in patients with non-alcoholic fatty liver disease (NAFLD)[8] and the FIB4 index, which can be calculated simply and repeatedly, indicates liver stiffness and impairment of liver reserve. A previous study reported that all types of HF patients with a high FIB4 index showed higher mortality than HF patients with a low FIB4 index.[9] However, few studies have compared the prognostic significance of FIB4 only in HFpEF patients. To elucidate the prognostic value of the FIB4 index in HFpEF, this study investigated the association of the FIB4 index on future cardiovascular events in patients with HF.

Methods

Study subjects and protocol

Consecutive HF patients who were referred for hospitalization at Kumamoto University Hospital, Japan, between 2006 and 2015 were registered. The diagnosis of decompensated HF was defined based on the Framingham criteria.[10] Patients were excluded for the following reasons: liver diseases (fat liver, cirrhosis, hepatitis B or C), human immunodeficiency virus patients, severe valvular diseases, active infective diseases, history of malignancy, and end stage of renal disease (estimated glomerular filtration rate <15 mL/min/1.73 m^2). Finally, 704 HF patients were enrolled in the study and were followed up prospectively until 2017 or the occurrence of total cardiovascular events. Primary outcome was the composite of total cardiovascular events. We divided whole population into three types according to LVEF (HFrEF, HFmrEF, and HFpEF).

Ethics statement

All procedures were conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the institutional review board of Kumamoto University (approval number: Senshin 2225). This study is registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000040227). Opt-out materials are available online (http://www.kumadai-junnai.com/home/wp-content/uploads/houkatsu.pdf).

Definition and severity of HFrEF, HFmrEF, and HFpEF

This study defined three types of HF according to the 2016 European Society of Cardiology guidelines as follows: HFrEF was defined as HF with an LVEF $<$ 40%; HFmrEF was defined as HF with a 40% $<$ LVEF $<$ 50%.[1]

HFpEF was clinically defined according to the European Society of Cardiology task force[11] as follows: symptoms or signs of HF; normal or mildly reduced LVEF (LVEF $>$ 50% and LV end-diastolic volume index $<$ 97 mL/m^2); and evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness. We excluded patients with HFpEF who had shown even a transient reduction in LVEF. Therefore, patients with HFpEF whose LVEF was $<$50% and was improved by optimal therapy were not included in the present study. In our study, we stratified the ratio of early transmitral flow velocity to early diastolic mitral annular velocity (E/e') as $\geq$15 or $>$8 and $<$15, and plasma B-type natriuretic peptide (BNP) levels with a cut-off at 100 pg/mL.

All patients were under optimal medical therapy for HF according to the European Society of Cardiology guideline,[12] including stable doses of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers,[13] beta-blockers, diuretics, and aldosterone blockers, if not contraindicated. Patients with HF were identified according to the New York Heart Association (NYHA) functional class for evaluating the severity of HF under stable conditions after optimal therapy.

FIB4 index measurements

We calculated the FIB4 index with the following formula using the data at the admission: age (years) × aspartate aminotransferase (IU/L)/platelet count (10^9/L) × square root of alanine aminotransferase (IU/L). FIB4 index is a non-invasive indicator of liver fibrosis; if FIB4 index is less than 1.30, the possibility of liver fibrosis is low, if it is 1.30 or higher, there is a possibility of liver fibrosis, and if it is 2.67 or higher, there is a high possibility of liver fibrosis. HF patients were divided into three groups according to the cut-off value of 1.30 and 2.67 according to a previous study; Group 1 (FIB4 index $<$1.3), Group 2 (FIB4 index: 1.3–2.67), and Group 3 (FIB4 index $>$2.67).[8] These cut-off values for advanced liver fibrosis were reported as a positive predictive value of 80% with a cut-off value of higher than 2.67 and a negative predictive value of 90% with a cut-off value of lower than 1.3.[8]

Definition of ischaemic heart disease

Ischaemic heart disease was defined as history of angina or myocardial ischaemia by stress tests coupled with coronary stenosis of $>$50% of the vessel diameter detected by

coronary angiography or computed tomography coronary angiography scan, or history of myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass grafting.

Follow-up and cardiovascular events

Patients were followed up prospectively at our outpatient clinics until July 2017 or until the occurrence of cardiovascular events, including cardiovascular-related death, hospitalization for HF decompensation, non-fatal MI, unstable angina pectoris (UAP), coronary revascularization for a new diagnosis of angina or in-stent restenosis after PCI, and non-fatal ischaemic stroke. Cardiovascular death was defined as death due to MI (within 28 days of onset), HF, or documented sudden death in the absence of non-cardiovascular causes. MI was diagnosed based on the rise or fall of cardiac biomarkers (plasma creatine kinase-MB and cardiac troponin-T) above the 99th percentile of the upper limit of the normal range and on evidence of myocardial ischaemia, as indicated at least by electrocardiogram changes (i.e. new ST–T changes, left bundle branch block, and pathological Q wave) or imaging evidence of either a new loss of viable myocardium or new abnormalities in regional wall motion (reference). UAP was diagnosed based on new or accelerating symptoms of myocardial ischaemia accompanied by new ischaemic ST–T changes. Ischaemic stroke was diagnosed based on focal neurological deficits with radiological evidence of brain infarction, excluding intracranial haemorrhage. Hospitalization for HF decompensation was defined as patients admitted with symptoms typical of HF and objective signs of worsening HF requiring intravenous drug administration. Coronary revascularization was diagnosed if the patient underwent PCI or coronary artery bypass grafting with evidence of myocardial ischaemia, except when expected at first coronary angiography. In addition to the above-mentioned cardiovascular events, non-fatal MI, UAP, and coronary revascularization were also defined as coronary-related events. Cardiovascular events were ascertained from a review of the medical records and confirmed by direct contact with the patients, their families, and physicians, or by annual telephone interview with each patient. An events committee comprising at least three independent physicians reviewed all events to avoid intra-observer biases.

Echocardiography and blood sampling

Echocardiography was performed by experienced cardiac sonographers without knowledge of the study data. LVEF, the ratio of early transmitral flow velocity to early diastolic mitral annular velocity determined by tissue Doppler (E/e'), and the LV mass index were measured by echocardiography (Vivid 7; GE-Vingmed Ultrasound, Horten, Norway, and Aplio XG; Toshiba, Tokyo, Japan) as reported previously.[14] The LV stroke volume (SV) was calculated as the product of the LV outflow tract and the integral of the velocity time. Thus, the SV index (SVI) was defined as SV/BSA. The Doppler-derived pulmonary artery systolic pressure (PAP) was estimated from the tricuspid regurgitation pressure gradient.[15] Echocardiography in patients in stable condition and treated with optimal therapy for HF was performed by seven experienced cardiac sonographers with no knowledge of the study data. The reproducibility and repeatability of the echo parameters were confirmed by two experienced sonographers. Blood tests were conducted early in the morning in fasted patients. The measured serum and plasma biochemical parameters included creatinine, sodium, haemoglobin, and BNP levels.

Statistical analysis

Continuous data are reported as the mean ± SD if normally distributed and as the median and interquartile range if not normally distributed. Categorical data are shown as numbers and percentages. Within-group comparisons for normal distributed continuous variables were made by one-way analysis of variance, for not normally distributed continuous variables by Kruskal–Wallis test, and for categorical variables by Fisher's exact test. Between-group comparisons for continuous variables were made by unpaired *t* test and Mann–Whitney *U* test, and for categorical variables by Fisher's exact test. Multiplicity of comparisons among groups was accounted by using Bonferroni correction.

A Kaplan–Meier curve was used to determine the cumulative incidence of composite cardiovascular events, and the log-rank test was used to compare the incidence of composite cardiovascular event between groups.

The Cox proportional hazards model was used to estimate composite cardiovascular event hazard ratios (HRs) by univariable and multivariable analyses with forced inclusion modelling. HRs and 95% confidence intervals (CIs) are presented. A P value <0.05 was considered statistically significant. The area under the curve (AUC), sensitivity, and specificity were calculated to predict the ability of the FIB4 index to detect patients with total cardiovascular events, with an AUC value of 0.50 indicating no accuracy and a value of 1.00 indicating maximal accuracy. Furthermore, the estimates of Harrell's C-statistics in the Cox proportional hazards regression models were compared after the addition of FIB4 index to BNP and PAP. The software Statistical Package for Social Sciences (SPSS) ver. 26.0 (IBM Japan, Tokyo, Japan) was used for other statistical analyses.

Results

Baseline clinical characteristics of HFpEF patients according to three FIB4 index groups

Heart failure with preserved LVEF patients were classified into three groups according to their FIB4 index values based on a previous study: Group 1 (FIB4 index <1.3), Group 2 (FIB4 index: 1.3–2.67), and Group 3 (FIB4 index >2.67).[8] *Table 1* shows the baseline characteristics of the three groups according to their FIB4 index in HFpEF. Overall, HFpEF patients had a mean FIB4 index of 2.5 ± 1.9 and BNP of 74.4 (28.9–205.5) pg/mL; and 16.7% of patients were NYHA Class 3/4. The Group 1 was associated with a higher prevalence of hypertension and dyslipidaemia and usage of beta-blockers (P = 0.01, P = 0.02, and P = 0.04, respectively, *Table 1*). The Group 3 had the lowest platelet count and the highest levels of AST ($P < 0.001$ and $P < 0.001$, respectively, *Table 1*) among the three groups. The Group 3 showed the highest levels of tricuspid regurgitation pressure gradient (TR-PG) and echocardiography-estimated PAP (P = 0.002 and $P < 0.001$, respectively, *Table 1*) among the three groups. By contrast, LVEF, cardiac output (CO), SVI and E/e' levels, and plasma BNP value did not differ among the three groups.

Baseline clinical characteristics of HFmrEF patients according to three FIB4 index groups

Table 2 shows the baseline characteristics of the three groups according to the FIB4 index in HFmrEF patients. Overall, HFmrEF patients had a mean FIB4 index of 2.2 ± 1.4 and BNP of 108.5 (59.5–253.8) pg/mL; and 15.4% of patients were NYHA Class 3/4. The Group 1 was the youngest ($P < 0.001$, *Table 2*) and had the highest levels of CO (P = 0.003, *Table 2*)

Table 1 Baseline characteristics of HFpEF patients with FIB4 counts measurement

	All HFpEF patients, n = 504	Group 1, n = 86	Group 2, n = 265	Group 3, n = 153	P value
Age (years)	71.6 ± 9.4	71.4 ± 9.8	71.2 ± 9.8	72.3 ± 8.4	0.5
Sex [male (%)]	54.6	62.8*	49.4	58.8	0.04
SBP (mmHg)	130.1 ± 21.2	128.6 ± 19.2	130.1 ± 21.8	130.9 ± 21.2	0.7
DBP (mmHg)	70.9 ± 13.0	70.7 ± 11.3	71.8 ± 13.5	69.6 ± 12.8	0.2
BMI (kg/m^2)	24.1 ± 3.6	24.0 ± 3.5	24.3 ± 3.7	23.7 ± 3.6	0.2
Hypertension (%)	78.2	88.4* **	77	74.5	0.01
Diabetes (%)	31	33.7	32.8	26.1	0.2
Dyslipidaemia (%)	77.8	86*	73.6	80.4	0.02
Atrial fibrillation (%)	28.6	25.6	26	34.6	0.1
ACE-I or ARB (%)	71	72.1	70.2	71.9	0.9
CCB (%)	62.5	68.6	60.8	62.1	0.4
Beta-blocker (%)	64.7	75.6* **	62.6	62.1	0.04
Diuretics (%)	22.4	16.3	20.8	28.8	0.06
IHD (%)	53	60	54	46	0.09
NYHA III or IV (%)	16.7	11.6	18.5	16.3	0.2
AST (U/L)	25 ± 12	21 ± 9**	23 ± 8**	30 ± 17	<0.001
ALT (U/L)	20 ± 13	23 ± 16	20 ± 13	19 ± 13	0.1
platelet count (×10^3/μL)	198 ± 65.1	274 ± 67.2* **	205 ± 43.8**	141 ± 39	<0.001
eGFR (mL/min per 1.73m^2)	62.3 ± 19.4	63.4 ± 16.1	62.5 ± 21.5	61.3 ± 17.4	0.6
Haemoglobin (g/dL)	12.7 ± 1.8	13.1 ± 1.8	12.6 ± 1.8	12.7 ± 1.8	0.08
BNP (pg/mL)	74.4 (28.9–205.5)	43.4 (23.1–164.6)	77.3 (31.7–1987.7)	108.2 (30.3–255.6)	0.1
LVEF (%)	62.6 ± 5.8	62.8 ± 4.9	62.8 ± 5.9	62.3 ± 6.1	0.6
LAD (mm)	39.5 ± 7.0	38.6 ± 6.7	39.8 ± 7.3	39.4 ± 6.6	0.4
E/e'	17.6 ± 5.0	18.6 ± 5.3	17.5 ± 4.1	17.0 ± 6.1	0.07
SVI	40.2 ± 9.9	41.2 ± 9.5	40.6 ± 9.6	39.1 ± 10.6	0.2
TR-PG (mmHg)	25.3 ± 8.0	23.5 ± 6.5**	24.6 ± 7.8**	27.2 ± 8.6	0.002
PAP (mmHg)	31.6 ± 9.1	29.6 ± 7.6**	30.5 ± 8.9**	34.4 ± 9.5	<0.001
CO	4.3 ± 1.2	4.5 ± 1.5	4.3 ± 1.1	4.1 ± 1.2	0.2
FIB4	2.5 ± 1.9	1.02 ± 0.2* **	1.92 ± 0.37**	4.26 ± 2.47	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; BMI, body mass index; cardiac resynchronization therapy defibrillator; BNP, brain natriuretic peptide; CO, cardiac output; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4; HFpEF, heart failure with preserved left ventricular ejection fraction; IHD, ischaemic heart disease; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery systolic pressure; SBP, systolic blood pressure; SVI, stroke volume index; TR-PG, tricuspid regurgitation pressure gradient.
Data are presented as the mean ± SD, median (interquartile range), or number (percentage).
*$P < 0.05$ vs. Group 2.
**$P < 0.05$ vs. Group 3.

Table 2 Baseline characteristics of HFmrEF patients with FIB4 counts measurement

	All HFmrEF patients, $n = 117$	Group 1, $n = 29$	Group 2, $n = 56$	Group 3, $n = 32$	P value
Age (years)	69.4 ± 11.8	57.1 ± 13.2* **	72.2 ± 8.3	75.6 ± 6.7	<0.001
Sex [male (%)]	76.1	79.3	80.4	65.6	0.3
SBP (mmHg)	122 ± 20.1	119 ± 19.3	124 ± 20.4	119 ± 20.1	0.3
DBP (mmHg)	69 ± 14	74 ± 19	69 ± 11	65 ± 11	0.055
BMI (kg/m^2)	23.6 ± 3.8	24.8 ± 4.4	23.3 ± 3.7	23.1 ± 3.3	0.1
Hypertension (%)	72.6	58.6	80.4	71.9	0.1
Diabetes (%)	43.6	37.9	48.2	40.6	0.6
Dyslipidaemia (%)	64.1	75.9	57.1	65.6	0.2
Atrial fibrillation (%)	28.2	20.7	28.6	34.4	0.5
ACE-I or ARB (%)	85.5	89.7	85.7	81.3	0.6
CCB (%)	36.8	20.7	39.3	46.9	0.06
Beta-blocker (%)	85.5	89.7	89.3	75	0.2
Diuretics (%)	59	58.6	58.9	59.4	0.9
IHD (%)	53	48	55	56	0.7
NYHA III or IV (%)	15.4	17.2	12.5	18.8	0.7
AST (U/L)	24 ± 11	20 ± 9**	22 ± 8**	32 ± 14	0.001
ALT (U/L)	21 ± 14	24 ± 17	19 ± 12	23 ± 16	0.1
platelet count ($\times 10^3/\mu L$)	200 ± 65	257 ± 66* **	207 ± 45**	138 ± 32	<0.001
eGFR (mL/min per $1.73m^2$)	59.1 ± 18.6	68.8 ± 15.5* **	58.6 ± 18.6	51.4 ± 17.7	0.001
Haemoglobin (g/dL)	13.6 ± 5.0	13.4 ± 1.8	14.2 ± 7.0	12.7 ± 2.0	0.4
BNP (pg/mL)	108.5 (59.5–253.8)	66.9 (19.3–137)	114 (68.8–284)	108.2 (30.3–255.6)	0.09
LVEF (%)	45.2 ± 2.7	44.9 ± 2.8	45.3 ± 2.7	45.2 ± 2.4	0.8
LAD (mm)	39.4 ± 7.1	39.2 ± 6.4	38.6 ± 6.5	41 ± 8.6	0.3
E/e′	14.6 ± 5.9	12.9 ± 5.6	14.7 ± 5.5	15.9 ± 6.6	0.1
SVI	40.2 ± 9.9	33.2 ± 8.0	36.1 ± 8.8	32.6 ± 9.0	0.1
TR-PG (mmHg)	24.5 ± 9.0	21.9 ± 6.3	25.7 ± 9.8	24.6 ± 9.3	0.2
PAP (mmHg)	30.3 ± 10.1	27.8 ± 7.0	31.1 ± 11.3	31.2 ± 10.2	0.3
CO	3.6 ± 1.0	4.2 ± 1.2* **	3.6 ± 0.7	3.3 ± 1.1	0.003
FIB4	2.2 ± 1.4	0.97 ± 0.26* **	1.86 ± 0.38**	4.0 ± 1.35	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; BMI, body mass index; cardiac resynchronization therapy defibrillator; BNP, brain natriuretic peptide; CCB, calcium channel blocker; CO, cardiac output; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4; HFmrEF, heart failure with mid-range left ventricular ejection fraction; IHD, ischaemic heart disease; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery systolic pressure; SBP, systolic blood pressure; SVI, stroke volume index; TR-PG, tricuspid regurgitation pressure gradient.
Data are presented as the mean ± SD, median (interquartile range), or number (percentage).
*$P < 0.05$ vs. Group 2.
**$P < 0.05$ vs. Group 3.

among the three groups. By contrast, LVEF, TR-PG, echocardiography-estimated PAP, SVI and E/e′ levels, and plasma BNP value did not differ among the three FIB4 index groups.

Baseline clinical characteristics of HFrEF patients according to three FIB4 index groups

Table 3 shows the baseline characteristics of the three groups according to the FIB4 index in HFrEF patients. Overall, HFrEF patients had a mean FIB4 index of 1.2 ± 3.3 and BNP of 189 (68.8–575.0) pg/mL; and 39.8% of patients were NYHA Class 3/4. The Group 1 was the youngest ($P < 0.001$, *Table 3*) and had the highest systolic blood pressure (BP) and diastolic BP ($P = 0.01$, and $P = 0.02$, respectively, *Table 3*) among the three groups. By contrast, LVEF, CO, TR-PG, echocardiography-estimated PAP, SVI and E/e′ levels, and plasma BNP value did not differ among the three FIB4 index groups.

Comparison of clinical characteristics among HFpEF, HFmrEF, and HFrEF patients

Plasma BNP value and prevalence of NYHA Class 3/4 in HFrEF patients were higher than in those HFpEF and HFmrEF patients ($P < 0.001$, *Table 4*). By contrast, the FIB4-index in HFpEF and HFmrEF patients were higher than in HFrEF patients ($P < 0.001$, *Table 4*).

Follow-up of HFpEF and HFmrEF and HFrEF patients

Follow-up data on total cardiovascular events were available in 504 patients with HFpEF. During the follow-up period (1–1500 days; median 1159 days), 237 (47%) total cardiovascular events were recorded (*Table 5*).

Follow-up data on total cardiovascular events were available in 117 patients with HFmrEF. During the follow-up

Table 3 Baseline characteristics of HFrEF patients with FIB4 counts measurement

	All HFrEF patients, n = 83	Group 1, n = 26	Group 2, n = 41	Group 3, n = 16	P value
Age (years)	64.5 ± 12.6	57 ± 12.9* **	66 ± 11.4	72.6 ± 8.4	<0.001
Sex [male (%)]	74.7	73.1	75.6	75	0.9
SBP (mmHg)	121 ± 25.3	135 ± 32.5* **	115 ± 18.9	112 ± 15.9	0.01
DBP (mmHg)	74 ± 17	81 ± 20**	72 ± 14	67 ± 16	0.02
BMI (kg/m^2)	23 ± 4.1	23.5 ± 4.2	23.3 ± 4.3	21.6 ± 3.6	0.3
Hypertension (%)	59	53.8	61	62.5	0.8
Diabetes (%)	42.2	42.3	43.9	37.5	0.9
Dyslipidaemia (%)	59	61.5	63.4	43.8	0.3
Atrial fibrillation (%)	27.7	15.4	29.3	43.8	0.4
ACE-I or ARB (%)	88	84.6	92.7	81.3	0.1
CCB (%)	25.3	34.6	24.4	12.5	0.4
Beta-blocker (%)	95.2	92.3	100	87.5	0.2
Diuretics (%)	75.9	69.2	75.6	87.5	0.3
IHD (%)	42	34	43	50	0.5
NYHA III or IV (%)	39.8	46.2	36.6	37.5	0.7
AST (U/L)	25 ± 10	22 ± 6**	26 ± 10	31 ± 12	0.01
ALT (U/L)	24 ± 15	27 ± 16	23 ± 14	20 ± 13	0.2
platelet count (×10^3/μL)	205 ± 67	249 ± 65* **	208 ± 49**	126 ± 30	<0.001
eGFR (mL/min per 1.73m^2)	57 ± 19.3	61.9 ± 22	56.4 ± 17.6	49.8 ± 17.5	0.1
Haemoglobin (g/dL)	13.3 ± 2.3	13.4 ± 2.0	13.3 ± 2.5	13.1 ± 2.2	0.8
BNP (pg/mL)	189 (68.8–575.0)	93 (39–600.5)	189 (103–285)	483.5 (80.9–352)	0.3
LVEF (%)	31.8 ± 6.1	32.1 ± 6.6	31 ± 6.4	33.1 ± 4.4	0.4
LAD (mm)	41.8 ± 7.4	40.4 ± 6.5	42.7 ± 7.8	41.5 ± 7.9	0.4
E/e′	17 ± 9.4	16.4 ± 8.9	15.1 ± 5.8	22.7 ± 14.3	0.1
SVI	29.8 ± 10.5	28.8 ± 10.7	30.9 ± 10.5	28.8 ± 10.4	0.6
TR-PG (mmHg)	27.1 ± 13.4	24.1 ± 10.2	29.2 ± 15.7	26.7 ± 11.3	0.3
PAP (mmHg)	33.8 ± 14.8	31.6 ± 13.3	35.8 ± 16.7	32.3 ± 11.9	0.4
CO	3.4 ± 1.0	3.6 ± 1.1	3.5 ± 0.9	3.1 ± 1.0	0.3
FIB4	1.2 ± 3.3	1.01 ± 0.19* **	1.79 ± 0.35**	4.35 ± 1.46	<0.001

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; BMI, body mass index; cardiac resynchronization therapy defibrillator; BNP, brain natriuretic peptide; CCB, calcium channel blocker; CO, cardiac output; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4; HFrEF, heart failure with reduced left ventricular ejection fraction; IHD, ischaemic heart disease; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery systolic pressure; SBP, systolic blood pressure; SVI, stroke volume index; TR-PG, tricuspid regurgitation pressure gradient.
Data are presented as the mean ± SD, median (interquartile range), or number (percentage).
*$P < 0.05$ vs. Group 2.
**$P < 0.05$ vs. Group 3.

Table 4 Characteristics of HFpEF, HFmrEF, and HFrEF patients

	All HF patients, n = 704	HFpEF patients, n = 504	HFmrEF patients, n = 117	HFrEF patients, n = 83	P value
NYHA III or IV (%)	19.2	16.7*	15.4**	39.8	<0.001
BNP (pg/mL)	93.4 (34.0–236)	74.4 (28.9–205.5)*, ***	108.5 (59.5–253.8)**	189.0 (68.8–575.0)	<0.001
FIB4 index	2.3 ± 2.1	2.5 ± 1.9*	2.2 ± 1.4**	1.2 ± 3.3	<0.001

BNP, brain natriuretic peptide; FIB4, fibrosis-4; HF, heart failure; HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; NYHA, New York Heart Association.
*$P < 0.001$ vs. HFrEF patients.
**$P < 0.05$ vs. HFrEF patients.
***$P = 0.032$ vs. HFmrEF patients.

period (11–1500 days; median 632 days), 26 (23.9%) total cardiovascular events were recorded (*Table 6*). Follow-up data on total cardiovascular events were available in 83 patients with HFrEF. During the follow-up period (37–1500 days; median 695 days), 19 (21.6%) total cardiovascular events were recorded (*Table 7*).

The Kaplan–Meier curve showed that Group 3 in HFpEF patients was at higher risk of total cardiovascular events than the other groups (log-rank test, P = 0.027 vs. Group 1, and P = 0.003 vs. Group 2, *Figure 1A*). By contrast, HFmrEF and HFrEF patients had no significant difference in total cardiovascular events among the three groups (log-rank test, P = 0.30, and P = 0.10, respectively, *Figure 1B* and *1C*).

Cox proportional hazard analysis of and total cardiovascular events in HFpEF patients

Table 8 shows the results of univariable and multivariable Cox proportional hazards analysis for cardiovascular events.

Table 5 Total cardiovascular events in heart failure with preserved left ventricular ejection fraction patients according to groups defined by three FIB4 index groups

FIB4 index	All $n = 504$	Group 1, $n = 86$	Group 2, $n = 265$	Group 3, $n = 153$	P value
Total cardiovascular events, n (%)	237 (47.0)	35 (40.7)	115 (43.4)	87 (56.9)**	0.025
Cardiovascular death, n (%)	31 (6.2)	1 (1.2)	10 (3.8)	20 (13.1)* **	<0.001
Hospitalization for HF decompensation, n (%)	109 (21.6)	18 (20.9)	50 (18.9)	41 (26.8)	0.165
Non-fatal myocardial infarction, n (%)	6 (1.1)	1 (1.2)	3 (1.1)	2 (1.3)	0.999
Unstable angina pectoris, n (%)	15 (3)	2 (2.3)	10 (3.8)	3 (2.0)	0.64
Coronary revascularization, n (%)	61 (12.1)	12 (14.0)	35 (13.2)	14 (9.2)	0.4
Non-fatal ischaemic stroke, n (%)	15 (2.7)	1 (1.2)	7 (2.6)	7 (4.6)	0.37

FIB4, fibrosis-4; HF, heart failure.
Group 1: FIB4 index $<$ 1.3.
Group 2: 1.3 $\leq$ FIB4 index $<$ 2.67.
Group 3: 2.67 $\leq$ FIB4 index.
*$P<0.05$ vs. Group 1.
**$P<0.05$ vs. Group 2.

Table 6 Total cardiovascular events in heart failure with mid-range left ventricular ejection fraction patients according to groups defined by three FIB4 index groups

FIB4 index	All $n = 117$	Group 1, $n = 29$	Group 2, $n = 56$	Group 3, $n = 32$	P value
Total cardiovascular events, n (%)	26 (23.9)	5 (17.2)	12 (23.2)	9 (31.3)	0.44
Cardiovascular death, n (%)	1 (0.9)	0 (0)	1 (1.8)	0 (0)	0.99
Hospitalization for HF decompensation, n (%)	14 (11.9)	3 (10.3)	5 (8.9)	6 (18.8)	0.37
Non-fatal myocardial infarction, n (%)	1 (0.9)	0 (0)	1 (1.8)	0 (0)	0.99
Unstable angina pectoris, n (%)	1 (0.9)	0 (0)	1 (1.8)	0 (0)	0.99
Coronary revascularization, n (%)	8 (6.8)	1 (3.4)	4 (7.1)	3 (9.4)	0.72
Non-fatal ischaemic stroke, n (%)	1 (0.9)	1 (3.4)	0 (0)	0 (0)	0.24

FIB4, fibrosis-4; HF, heart failure.
Group 1: FIB4 index $<$ 1.3.
Group 2: 1.3 $\leq$ FIB4 index $<$ 2.67.
Group 3: 2.67 $\leq$ FIB4 index.

Table 7 Total cardiovascular events in heart failure with reduced left ventricular ejection fraction patients according to groups defined by three FIB4 index groups

FIB4 index	All $n = 83$	Group 1, $n = 26$	Group 2, $n = 41$	Group 3, $n = 16$	P value
Total cardiovascular events, n (%)	19 (21.6)	5 (19.2)	9 (22.0)	5 (31.3)	0.69
Cardiovascular death, n (%)	1 (1.2)	0 (0)	0 (0)	1 (6.3)	0.19
Hospitalization for HF decompensation, n (%)	15 (18.1)	4 (15.4)	9 (22.0)	2 (12.5)	0.8
Non-fatal myocardial infarction, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	—
Unstable angina pectoris, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	—
Coronary revascularization, n (%)	3 (3.6)	1 (3.8)	0 (0)	2 (12.5)	0.07
Non-fatal ischaemic stroke, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	—

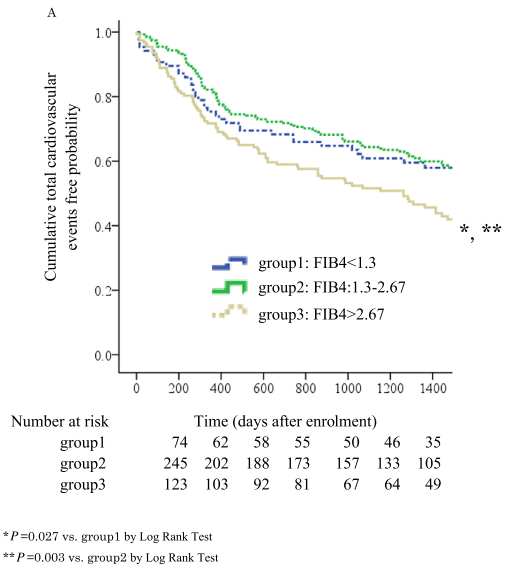
FIB4, fibrosis-4; HF, heart failure.
Group 1: FIB4 index $<$ 1.3.
Group 2: 1.3 $\leq$ FIB4 index $<$ 2.67.
Group 3: 2.67 $\leq$ FIB4 index.

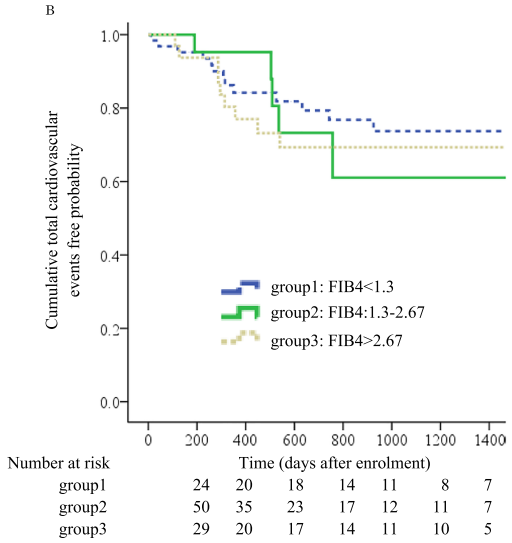
Univariate Cox proportional analysis identified age (HR: 1.01, 95% CI: 1.00–1.03, P = 0.031), use of diuretics (HR: 1.48, 95% CI: 1.12–1.95, P = 0.005), NYHA class (HR: 1.80, 95% CI: 1.33–2.43, $P < 0.001$), AST (HR: 1.01, 95% CI: 1.00–1.02, P = 0.006), haemoglobin (HR: 0.87, 95% CI: 0.81–0.93, $P < 0.001$), Ln-BNP (HR: 1.16, 95% CI: 1.05–1.28, P = 0.003), left atrium diameter (HR: 1.01, 95% CI: 1.00–1.03, P = 0.047), PAP (HR: 1.01, 95% CI: 1.00–1.03, P = 0.018), and FIB4 index (HR: 1.08, 95% CI: 1.03–1.14, P = 0.002) as significant factors associated with total cardiovascular events. Multivariable Cox proportional hazard analysis identified the FIB4 index as an independent and significant predictor of total cardiovascular events in HFpEF patients (HR:1.09, 95%CI: 1.03–1.15, P = 0.001, *Table 8*).

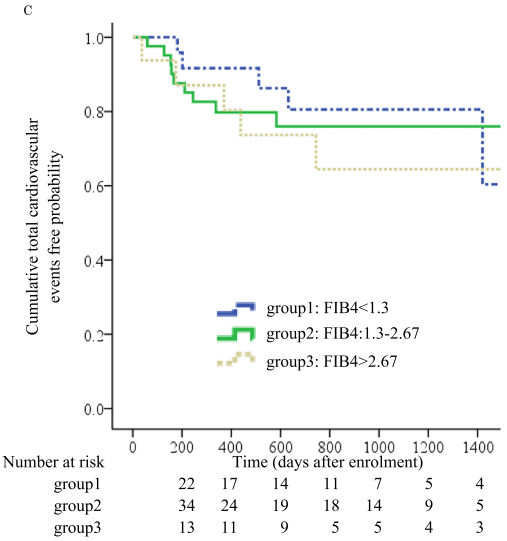
Receiver operating characteristic curves for FIB4 index identifying total cardiovascular events in HFpEF patients

As mentioned above, only in HFpEF patients showed a significant difference in Kaplan–Meier curve; receiver operating characteristic (ROC) curves were constructed to assess the ability of the FIB4 index to predict the occurrence of total

Figure 1 (A) Kaplan–Meier analysis of total cardiovascular events in heart failure with preserved left ventricular ejection fraction patients according to fibrosis-4 (FIB4) values. (B) Kaplan–Meier analysis of total cardiovascular events in heart failure with mid-range left ventricular ejection fraction patients according to FIB4 values. (C) Kaplan–Meier analysis of total cardiovascular events in heart failure with reduced left ventricular ejection fraction patients according to FIB4 values.







cardiovascular events in HFpEF patients. The AUC for detection of total cardiovascular events was 0.61 (95% CI: 0.56–0.67; $P < 0.001$) of the FIB4 index in HFpEF patients (*Figure 2A*). In HFpEF patients, the sensitivity and specificity for the detection of total cardiovascular events by a cut-off level of 2.63 of the FIB4 index were 45% and 74%, respectively.

Furthermore, ROC curves were constructed to assess the additive predictive value of the Ln-BNP and PAP assessed by echocardiography for the occurrence of total cardiovascular events in HFpEF patients. As a result, the AUC of the Ln-BNP for the prediction of total cardiovascular events in HFpEF patients was 0.57 (95% CI: 0.52–0.62; $P = 0.005$, *Figure 2B*), and the AUC of the PAP value for prediction of total cardiovascular events was 0.56 (95% CI: 0.50–0.61; $P = 0.03$, *Figure 2C*). Furthermore, the AUC of the Ln-BNP plus PAP was also slightly increased to 0.59 (95% CI: 0.53–0.64; $P = 0.001$, *Figure 2D*) in HFpEF patients. C-statistics constructed to assess the ability of Ln-BNP plus PAP for the detection of total cardiovascular events was 0.557 (*Table 9*).

Moreover, the AUC of the Ln-BNP and PAP plus FIB4 index was also slightly increased to 0.62 (95% CI: 0.56–0.67;

Table 8 Cox hazard analysis of total cardiovascular events in HFpEF patients

	Simple regression			Multiple regression		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years)	1.01	1.00–1.03	0.031	—	—	—
Male sex (yes)	0.90	0.73–1.17	0.453	—	—	—
SBP (mmHg)	1.00	0.99–1.00	0.877	—	—	—
DBP (mmHg)	0.99	0.98–1.00	0.126	—	—	—
BMI (kg/m^2)	0.96	0.93–1.00	0.091	—	—	—
Hypertension (yes)	0.77	0.57–1.03	0.083	—	—	—
Diabetes (yes)	1.14	0.87–1.49	0.327	—	—	—
Dyslipidaemia (yes)	0.99	0.72–1.36	0.977	—	—	—
Atrial fibrillation (yes)	1.18	0.89–1.34	0.237	—	—	—
ACE-I or ARB (yes)	1.07	0.82–1.40	0.578	—	—	—
CCB (yes)	0.90	0.69–1.16	0.437	—	—	—
Beta-blocker (yes)	0.96	0.74–1.24	0.792	—	—	—
Diuretics (yes)	1.48	1.12–1.95	0.005	0.85	0.59–1.23	0.410
IHD (yes)	1.04	0.8–1.34	0.740	—	—	—
NYHA III or IV (yes)	1.80	1.33–2.43	<0.001	0.95	0.63–1.44	0.835
AST (IU/L)	1.01	1.003–1.02	0.006	—	—	—
ALT (IU/L)	1.003	0.99–1.01	0.548	—	—	—
platelet count (/μL)	0.99	0.99–1.00	0.100	—	—	—
eGFR (mL/min/1.73m^2)	1.00	0.97–1.01	0.351	—	—	—
Haemoglobin (g/dL)	0.87	0.81–0.93	<0.001	0.99	0.92–1.07	0.933
Ln-BNP	1.16	1.05–1.28	0.003	1.12	0.99–1.26	0.07
LVEF (%)	0.99	0.97–1.01	0.552	—	—	—
LAD (mm)	1.01	1.00–1.03	0.047	1.001	0.98–1.02	0.894
E/e′	1.02	0.99–1.04	0.082	—	—	—
SVI (L/min)	0.99	0.98–1.00	0.555	—	—	—
TR-PG (mmHg)	1.01	0.99–1.04	0.124	—	—	—
PAP (mmHg)	1.01	1.00–1.03	0.018	1.01	0.99–1.02	0.071
CO (L/min)	0.93	0.81–1.07	0.319	—	—	—
FIB4 index	1.08	1.03–1.14	0.002	1.09	1.03–1.15	0.001

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; BMI, body mass index; cardiac resynchronization therapy defibrillator; BNP, brain natriuretic peptide; CCB, calcium channel blocker; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4; HFpEF, heart failure with preserved left ventricular ejection fraction; HR, hazard ratio; IHD, ischaemic heart disease; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery systolic pressure; SBP, systolic blood pressure; SVI, stroke volume index; TR-PG, tricuspid regurgitation pressure gradient.

$P < 0.001$, *Figure 2E*) in HFpEF patients. C-statics of Ln-BNP and PAP plus FIB4 index for the detection of total cardiovascular events was 0.573 (*Table 9*).

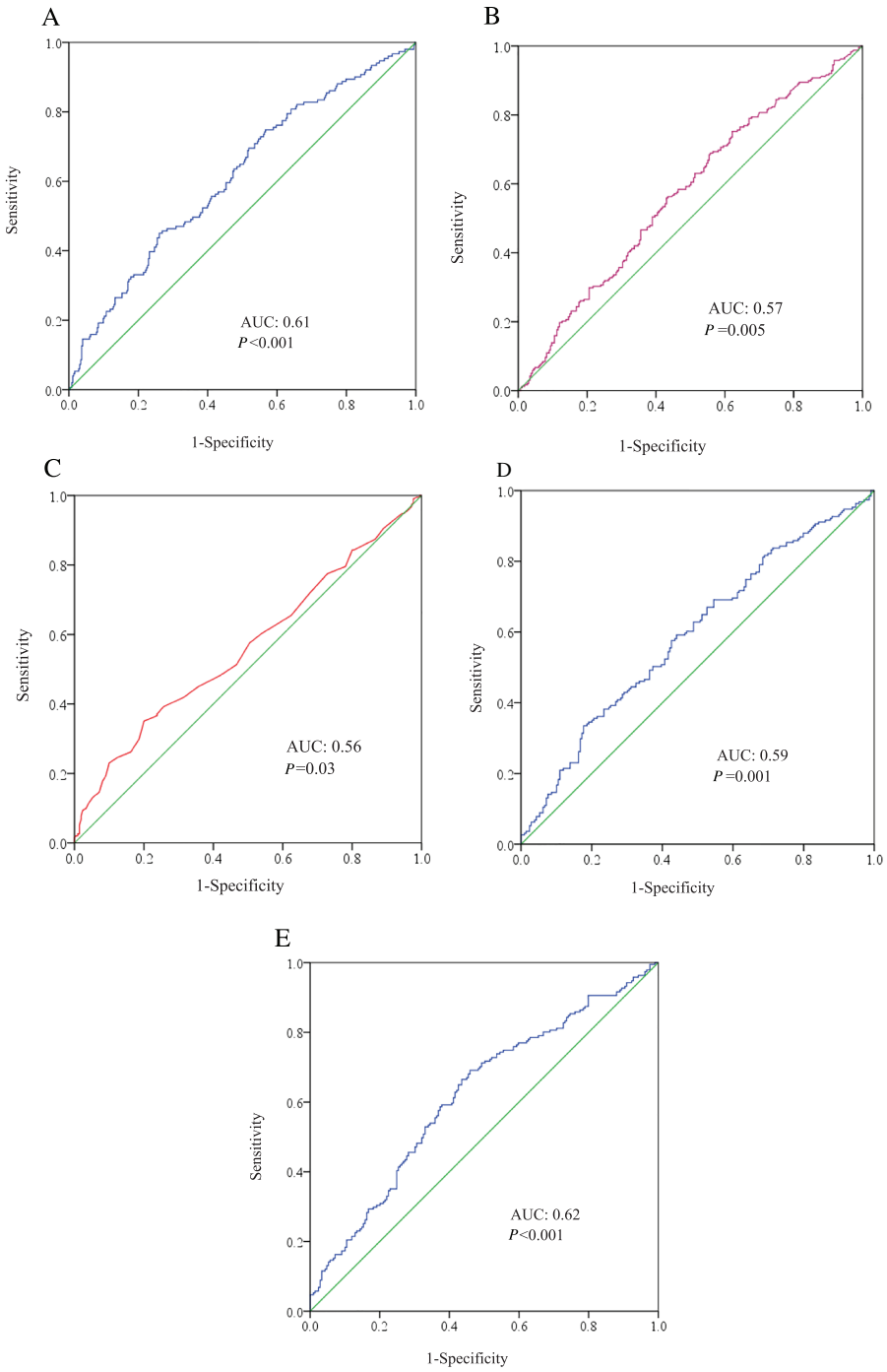
Discussion

This study demonstrated the following associations in HF patients: (i) the risk of total cardiovascular events was significantly higher in patients with a high FIB4 index (FIB4 index >2.67) in HFpEF and (ii) a high FIB4 index was a significant and independent predictor of total cardiovascular events in HFpEF patients.

The presence of chronic HF is associated with an increased risk of death, and patients with HF have a poor prognosis. Systemic venous congestion elevates neurohormonal activation, which leads to HF progression and may contribute to more severe multiple organ failure[5,16,17] and result in a poor prognosis.[18] HF, especially decompensated HF, sometimes consists of both congestion and reduced arterial flow, that is, hypoxic hepatopathy. Hypoxia causes centrilobular necrosis in the liver and leads to the elevation of transaminase.[19] In addition, increased central venous pressure causes hepatocyte atrophy and perisinusoidal oedema of the liver.[2,4] Hence, HF-related congestive hepatopathy is a well-recognized problem in the management of HF, and the association between HF and liver dysfunction remains a topic of interest and research. There is evidence that liver congestion is mutually associated with liver stiffness, resulting in fibrosis and adverse prognosis.[5] The FIB4 index, calculated using only four parameters that are measured in daily medical care was reported to reflect the liver stiffness and liver congestion associated with HF.[9] However, the relationship between FIB4 index and the prognosis especially in HFpEF patients remains unclear. In the present study, the occurrence of total cardiovascular events was only significantly higher in HFpEF patients with a high FIB4 index than those with a low FIB4 index, suggesting that liver stiffness may contribute to the state of HF and total cardiovascular events at least in HFpEF patients. In HFmrEF and HFrEF patients, by contrast, there were no significant differences in total cardiovascular events regardless of the FIB4 index values.

However, the statistical power calculated by post-hoc power analysis was sufficient in HFpEF but insufficient in

Figure 2 (A) Receiver operating characteristic (ROC) curves for fibrosis-4 (FIB4) count identifying total cardiovascular event in heart failure with preserved left ventricular ejection fraction (HFpEF) patients. (B) ROC curves for Ln-brain natriuretic peptide (BNP) identifying total cardiovascular event in HFpEF patients. (C) ROC curves for pulmonary artery systolic pressure (PAP) identifying total cardiovascular event in HFpEF patients. (D) ROC curves for Ln-BNP plus PAP identifying total cardiovascular event in HFpEF patients. (E) ROC curves for FIB4 count plus Ln-BNP and PAP identifying total cardiovascular event in HFpEF patients. AUC, area under the curve.



HFmrEF and HFrEF in this study (data not shown). Differences in the number of events and patients among these three groups are important limitations in this study. Therefore, in this regard, it is necessary to elucidate the significance of FIB4 index in both HFmrEF and HFrEF by increasing their sample size.

The latest report by Maeda *et al.*[20] showed that FIB-4 index could non-invasively reflect right-sided filling pressure and

Table 9 Harrell's C-statistics for the Cox hazard model to predict total cardiovascular events in patients with heart failure with preserved left ventricular ejection fraction by the addition of FIB4 index to Ln-BNP and PAP

		Cox hazard analysis		
	C-statistics	HR	95% CI	*P* value
Ln-BNP	0.557	1.116	1.001–1.245	0.049
PAP		1.016	1.002–1.031	0.024
Ln-BNP	0.573	1.097	0.983–1.225	0.099
PAP		1.014	1.000–1.029	0.048
FIB4 index		1.097	1.038–1.159	0.001

BNP, brain natriuretic peptide; CI, confidence interval; FIB4, fibrosis-4; HR, hazard ratio; PAP, pulmonary artery systolic pressure.

that event-free rates were lower among patients with a high than a low FIB-4 index in Kaplan–Meier analysis. However, HF patients in this report were not classified into new categories of HF such as HFrEF, HFmrEF and HFpEF. Interestingly, by contrast, the FIB4 index of the HFpEF patients tended to be higher than those of HFrEF and HFmrEF patients, despite a significantly lower plasma BNP value and prevalence of NYHA Class 3/4 in HFpEF patients. This observation might indicate that HFpEF patients are more likely to have severe liver congestion than HFrEF and HFmrEF patients, even if the severity of HF is relatively low.

Previous basic reports demonstrated that systemic fibrosis, fibrogenesis, and collagen turnover could represent plausible links between HFpEF and NAFLD.[21–27] Extracellular matrix alternations, which include the synthesis and degradation of collagen, occur not only in the myocardium but also in the arterial wall, kidneys, lungs, and liver in systemic disease.[24,26] In addition, HF and NAFLD have some common pathophysiologies and comorbidities. An elevated renin angiotensin system, oxidative stress, insulin resistance, and inflammation cause atherosclerosis and increase organ fibrosis in patients with both HF and NAFLD.[28,29] NAFLD has been reported to be associated with atherosclerosis,[30,31] reduced coronary flow reserve,[32] LV dysfunction, and high cardiovascular mortality.[29,33,34]

The present study first demonstrated that the FIB4 index is a significant and independent predictor of cardiovascular events in patients with HFpEF, indicating a relatively close association between HFpEF and systemic congestion, as represented by hepatic congestion, which leads to a vicious cycle of pathologies.

The optimal drug treatment for HFpEF has not been established. The results of this study suggest that systemic congestion, represented by the FIB4 index, is predictive of future cardiovascular events, especially in HFpEF, and that systemic congestion could provide a therapeutic target for HFpEF. Because our study was observational rather than interventional and we did not investigate if decreasing systemic congestion via drugs improves the prognosis of HFpEF patients, further large-scale interventional studies in these patients are necessary.

In addition, the pathophysiological and biochemical assessments were insufficient to demonstrate the precise mechanisms underlying the relationship between liver congestion and the prognosis of HFpEF. Hence, further pathophysiological and biochemical assessments including circulating fibrotic growth factors such as transforming growth factor-β or bone morphogenetic proteins, established inducers of liver fibrosis, during basic and clinical research are required to address these questions.

Study limitations

There were several limitations in this study. First, this was a single-centre study of a relatively small population. Second, all patients in our study were Japanese, which might limit the generalization of our findings to other cohorts, particularly those in Western countries. Third, the sample sizes of the three groups are very different: 504 HFpEF patients (237 events), 117 HFmrEF patients (28 events), and 83 HFrEF patients (19 events). Therefore, given the limited number of patients and events, the HFmrEF and HFrEF groups lack the statistical power to allow the comparison with HFpEF. Indeed, the lack of differences found in those groups may be related to the sample size and rate of events. Forth, the performance of the ROC curve is modest (AUC 0.61), and even adding the FIB4 index to known risk factors such as BNP and PAP did not improve AUC value in ROC curve and C-statics. Moreover, the cut-off value selected has a poor sensitivity (45%), which would be of limited usefulness in the clinical practice. However, even in this small population, the FIB4 index was found to be closely associated with the prognosis for HFpEF. Further larger multicentre studies involving more patients are required to determine the importance of the FIB4 index in HF. Despite these limitations, the prognostic significance of the FIB4 index in HFpEF patients was clearly demonstrated. The FIB4 index could be a useful predictor of total cardiovascular events in HFpEF patients.

Conclusion

This study demonstrated the prognostic significance of the FIB4 index in HFpEF patients.

Conflict of interest

None.

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