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# Prognostic value of the liver fibrosis marker fibrosis-5 index in patients with acute heart failure

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## Abstract

**Aims**    Recently, liver fibrosis markers, such as the fibrosis-4 index (FIB-4), have been shown to be associated with prognosis in patients with heart failure. The fibrosis-5 (FIB-5) index, which assesses albumin, alkaline phosphatase, aspartate transaminase, alanine aminotransferase and platelet count, is a simple liver fibrosis marker that was reported to be superior to FIB-4 for differentiation of liver fibrosis. This study aimed to compare the prognostic value of FIB-4 and FIB-5 in patients with heart failure.
**Methods and results**    The FIB-4 and FIB-5 scores were calculated at discharge in 906 patients hospitalized with heart failure. The patients were stratified into three groups based on their FIB-5 scores: low ($n$ = 303), middle ($n$ = 301), and high ($n$ = 302) FIB-5 groups. The primary endpoint was a composite of cardiac death or rehospitalization for heart failure. The low FIB-5 group was older and had larger inferior vena cava diameters and higher brain natriuretic peptide levels than the other two groups. The primary endpoint occurred in 156 (51.5%), 110 (36.5%), and 54 patients (17.9%) in the low, middle, and high FIB-5 groups, respectively ($P < 0.001$). On Cox proportional hazard analysis, the low FIB-5 was independently associated with the primary endpoint after adjustment for confounding factors. The association was consistent in both patients with preserved and reduced left ventricular ejection fraction (LVEF), and there was no significant interaction between LVEF phenotypes in terms of the prognostic impact of FIB-5 ($P$ for interaction = 0.311). FIB-5 was superior to FIB-4 as a prognostic indicator of the primary endpoint (continuous net reclassification improvement, 0.530; 95% confidence interval [CI], 0.399–0.662; $P < 0.001$; integrated discrimination improvement, 0.072; 95% CI, 0.057–0.088; $P < 0.001$).
**Conclusions**    The FIB-5 is a useful risk stratification marker with better prognostic value than FIB-4 in patients hospitalized with heart failure.

## Introduction

Globally, heart failure is one of the leading causes of health concerns, and its prevalence has been increasing with the ageing of society.[1] Because the heart is responsible for pumping blood to the entire body, deterioration of heart function has negative effects on all organs, including the liver. Systemic venous congestion and hypoperfusion due to heart failure lead to liver dysfunction and abnormal liver function tests, with a subsequent increase in liver fibrosis markers.[2] So far, numerous liver fibrosis markers have been reported to be associated with poor prognosis in patients with heart failure[3–5]; however, the optimal liver fibrosis marker for heart failure has not been elucidated.

The fibrosis-4 index (FIB-4), which considers age, aspartate transaminase (AST), alanine aminotransferase (ALT), and platelet (PLT) count,[6] is one of the most widely accepted liver fibrosis markers in patients with liver disease, such as those

with hepatitis B virus (HBV)[7] and hepatitis C virus (HCV) infections.[8] FIB-4 has also been shown to be a good prognostic marker of death or rehospitalization due to heart failure in patients with heart failure.[9–11] On the other hand, the fibrosis-5 (FIB-5) index, which is calculated using albumin, alkaline phosphatase (ALP), AST to ALT ratio, and PLT count, was recently proposed as a simple liver fibrosis marker.[12] The predictive value of FIB-5 for liver fibrosis was first validated in patients with HCV infection.[12] Recent studies have suggested that FIB-5 is superior to FIB-4 for assessment of liver fibrosis in patients with HBV[13] and HCV infections.[14] Based on these studies, we hypothesized that the FIB-5 index would also have a better prognostic value compared with FIB-4 in patients with heart failure. Therefore, we aimed to evaluate the value of FIB-5 as a risk stratification marker in patients with acute heart failure.

## Methods

This was a retrospective observational study. Between January 2015 and December 2020, 1505 consecutive patients hospitalized with acute heart failure were enrolled in the study. Heart failure was diagnosed using Framingham criteria.[15] All study patients were 20 years or older. We enrolled both patients with reduced and preserved ejection fraction, and both those with ischaemic and non-ischaemic aetiology in the study. Exclusion criteria were as follows: patients with (i) haemodialysis, (ii) acute coronary syndrome, (iii) chronic liver disease including HBV or HCV, (iv) in-hospital death, (v) missing data on FIB-5 scores and (vi) no post-discharge data.

All procedures performed followed the ethical standards for studies involving human participants of the institutional and national research committee and the Declaration of Helsinki in 1964 and its subsequent amendments or comparable ethical principles. The current study was approved by the Ethics Review Board of Osaka Medical and Pharmaceutical University with a waiver of informed consent (Number 2194).

The patients' demographic data, medical history and medication information were obtained at discharge. Blood samples were also collected at discharge, and FIB-4 and FIB-5 were calculated as follows:

$$FIB\text{-}4 = \text{age (years)} \times AST\,(U/L) / \left( PLT\,count\,\left[10^9/L\right] \times ALT\,\left[U/L\right]^{1/2} \right) \tag{6}$$

$$FIB\text{-}5 = \left( albumin\,[g/L] \times 0.3 + PLT\,count\,\left[10^9/L\right] \times 0.05 \right) - \left( ALP\,[U/L] \times 0.014 + AST\,to\,ALT\,ratio \times 6 + 14 \right) \tag{12}$$

Higher FIB-4 scores and lower FIB-5 scores indicate more severe liver fibrosis.

Right heart catheterization (RHC) was performed using a thermodilution pulmonary artery catheter (Edwards Lifesciences, Irvine, CA, USA) when patients were stable. Cardiac output was obtained by thermodilution, and cardiac index was calculated as: cardiac output (L/min) /body surface area ($m^2$).

Clinical outcomes were retrospectively obtained from the patients' medical charts. The primary endpoint of the study was a composite of cardiac death or heart failure rehospitalization.

Continuous variables with normal distribution are expressed as mean ± standard deviation, and those with non-normal distribution are described as median and (25th–75th percentiles). Continuous variables were compared using the Student's $t$ test or Mann–Whitney $U$ test, as appropriate. Categorical variables are reported as numbers and percentages and were compared using $\chi^2$ or Fisher's exact tests, as appropriate. Cumulative event rates were evaluated using Kaplan–Meier analysis and compared using log-rank tests. The associations between FIB-5 (as a categorical and continuous variable) and clinical outcomes were evaluated using univariate and multivariate Cox proportional hazard models. In the models, Get With The Guidelines®-Heart Failure (GWTG-HF) risk score[16] was used as the adjustment variable. The GWTG-HF risk score was previously shown to be a useful predictive model for long-term mortality and cardiac events (cardiac death and/or heart failure rehospitalization) in patients hospitalized with heart failure.[17] Adding New York Heart Association (NYHA) class, presence of anaemia, left ventricular ejection fraction (LVEF), and brain natriuretic peptide (BNP) levels to the GWTG-HF score was reported to improve performance of the model in Japanese populations.[17] Therefore, we adjusted for GWTG-HF risk score, NYHA class, anaemia, LVEF, log-transformed BNP, age, sex, and body mass index (Model 1). Model 2 included Model 1 plus history of heart failure, hypertension, diabetes, dyslipidaemia, coronary artery disease, serum creatinine levels, left atrial diameter, estimated pulmonary artery pressure, prescription of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists, because these are well-accepted prognostic factors in acute heart failure. The presence of anaemia was defined as haemoglobin levels <13 g/dL for men and <12 g/dL for women.[18]

The area under the receiver operating characteristic curve was described to compare the predictive value of FIB-4 and FIB-5 for the primary endpoint. Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were also analysed to assess the prognostic value of FIB-4 and FIB-5.[19]

All data were analysed using R software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900 051-07-0, URL http://www.r-project.org). A $P$ value of <0.05 was considered statistically significant.

# Results

Of the 1505 patients enrolled, 906 patients (mean age, 75.0 ± 12.0 years; 58% males; 32.6% ischaemic aetiology; 47.2% preserved LVEF) were included in the study (*Figure 1*). The median values of FIB-4 and FIB-5 were 2.20 (interquartile range [IQR], 1.49–3.20), and −5.72 (IQR, −9.87—2.07), respectively. Patients were divided into three groups according to tertile of FIB-5 scores: low (< − 8.20, *n* = 303), middle (−8.20 ≤ FIB-5 < −3.27, *n* = 301), and high (≥ − 3.27, *n* = 302) FIB-5 groups. Baseline characteristics of the groups are shown *Table 1*. Overall, patients in the low FIB-5 group were older, more likely to be female, had a history of heart failure, preserved LVEF, and use of diuretics, lower values of body mass index, systolic/diastolic blood pressure, haemoglobin, PLT count and albumin, and higher values of creatinine, blood urea nitrogen and BNP compared with the other two groups.

Out of 906 study patients, 239 RHC data were available. Linear regression analysis demonstrated that mean right atrial pressure was significantly associated with FIB-5 ($\beta$ = −0.16, *t* value = −2.49, *P* = 0.013). Whereas, pulmonary capillary wedge pressure ($\beta$ = −0.03, *t* value = −0.52, *P* = 0.606), systolic pulmonary artery pressure ($\beta$ = −0.09, *t* value = −1.31, *P* = 0.192), diastolic pulmonary artery pressure ($\beta$ = −0.01, *t* value = −0.16, *P* = 0.871) and cardiac index ($\beta$ = 0.10, *t* value = 1.53 *P* = 0.101) were not significantly associated with FIB-5.

During the median follow-up period of 152 days (IQR, 48–386 days) in patients who experienced the primary endpoint, and 503 days (IQR, 154–930 days) in censored patients, the primary endpoint occurred in 320 patients: 156 patients (51.5%) in the low, 110 (36.5%) in the middle and 54 patients (17.9%) in the high FIB-5 group (*P* < 0.001). Kaplan–Meier curves revealed that event-free rates were lower in patients in the low FIB-5 group than the other two groups (log-rank *P* < 0.001) (*Figure 2*). Regarding each cardiac death or heart failure rehospitalization, the incidence was significantly higher in patients in the low FIB-5 group than the other two groups (cardiac death: low 2.6%, middle 9.3%, high 16.2%, *P* < 0.001; heart failure rehospitalization: low 17.9%, middle 33.1%, high 47.4%, *P* < 0.001) (*Figure* S1). When patients were divided into reduced (<50%) and preserved (≥50%) LVEF subgroups, the results for the primary endpoint were consistent in both groups (log-rank *P* < 0.001, respectively) (*Figure 3*).

Cox proportional hazard analysis showed that low FIB-5 index was an independent prognostic indicator of cardiac death and rehospitalization due to heart failure even after adjustment for confounding factors (*Table 2*). This observation was consistent in patients with both reduced and preserved LVEF after adjustment for Model 2. FIB-5 as continuous variables was independently associated with a higher incidence of the primary endpoint in both patients with reduced [hazard ratio (HR), 0.91, 95% confidence interval (CI), 0.88–0.95; *P* < 0.001] and preserved LVEF (HR, 0.96, 95% CI, 0.92–0.95; *P* = 0.025). No significant interaction was observed between LVEF phenotypes with regard to the prognostic impact of FIB-5 after adjustment for Model 2 (*P* for interaction = 0.311).

In unadjusted model, the area under the curve for FIB-5 was superior to those for FIB-4 (FIB-4, 0.647; 95% CI,

Figure 1 Flow chart of the study. A total of 906 patients were analysed in the study. Patients were stratified into three groups according to their fibrosis-5 (FIB-5) scores. AHF, acute heart failure.
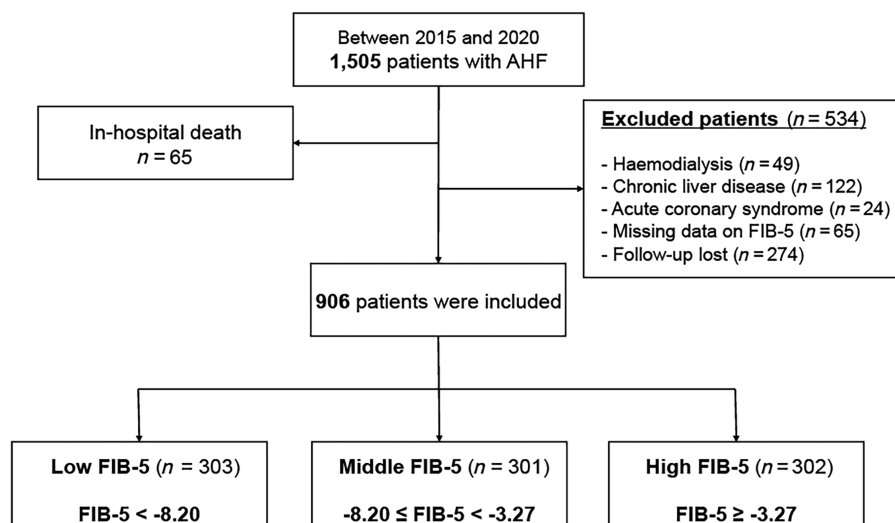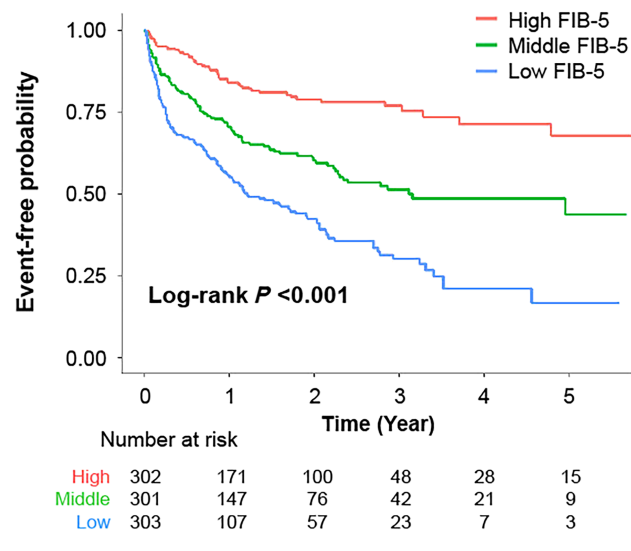
**Table 1** Patient baseline characteristics

| Variables | All population | Tertile | | | P value |
|---|---|---|---|---|---|
| | | Low FIB-5 | Middle FIB-5 | High FIB-5 | |
| | $n = 906$ | $n = 303$ | $n = 301$ | $n = 302$ | |
| FIB-5 at discharge | −5.72 [−9.87−−2.07] | −11.72 [−15.54−−9.86] | −5.71 [−7.02−−4.59] | −0.30 [−2.06−2.34] | <0.001 |
| FIB-4 at discharge | 2.18 [1.49–3.20] | 3.37 [2.70–4.34] | 2.27 [1.75–2.87] | 1.34 [1.03–1.70] | <0.001 |
| Age (years) | 77 [70–83] | 79 [74–85] | 77 [72–83] | 74 [66–80] | <0.001 |
| Male, n (%) | 525 (58.0) | 157 (51.8) | 180 (59.8) | 188 (62.3) | 0.024 |
| Body mass index (kg/m$^2$) | 22.7 [20.5–25.8] | 21.8 [20.0–24.7] | 22.7 [20.4–25.8] | 23.8 [21.2–26.5] | <0.001 |
| Systolic blood pressure (mmHg) | 107 [97–120] | 105 [95–117] | 108 [99–117] | 109 [99–123] | 0.005 |
| Diastolic blood pressure (mmHg) | 61 [54–70] | 60 [52–68] | 62 [54–70] | 62 [56–70] | 0.004 |
| Heart rate (bpm) | 72 [64–81] | 72 [65–80] | 72 [63–80] | 72 [64–82] | 0.725 |
| NYHA class III/IV at admission, n (%) | 684 (75.5) | 229 (76.8) | 223 (77.2) | 232 (82.3) | 0.206 |
| Coronary artery disease, n (%) | 267 (32.6) | 84 (29.4) | 102 (37.2) | 81 (31.2) | 0.118 |
| Diabetes, n (%) | 285 (31.5) | 94 (31.0) | 93 (30.9) | 98 (32.5) | 0.893 |
| Hypertension, n (%) | 671 (74.1) | 228 (75.2) | 237 (78.7) | 206 (68.2) | 0.013 |
| History of heart failure, n (%) | 328 (36.2) | 154 (50.8) | 114 (37.9) | 60 (19.9) | <0.001 |
| Echocardiographic data | | | | | |
| Left atrial dimension (cm) | 4.7 [4.1–5.3] | 4.9 [4.3–5.6] | 4.7 [4.0–5.2] | 4.5 [4.0–5.1] | <0.001 |
| LVDD (cm) | 5.2 [4.6–5.8] | 5.2 [4.5–5.7] | 5.3 [4.7–5.8] | 5.2 [4.6–5.8] | 0.274 |
| LVDS (cm) | 3.9 [3.1–4.7] | 3.8 [3.0–4.6] | 3.9 [3.1–4.8] | 3.9 [3.1–5.0] | 0.235 |
| LVEF (%) | 49 [36–61] | 51 [38–61] | 49 [36–60] | 45 [34–60] | 0.060 |
| LVEF ≥50%, n (%) | 428 (47.2) | 156 (53.2) | 145 (48.5) | 127 (42.6) | 0.035 |
| Estimated PAP (mmHg) | 38 [28–50] | 42 [31–54] | 38 [28–50] | 35 [26–46] | <0.001 |
| Right ventricular diameter (cm) | 3.3 [2.9–4.2] | 3.7 [3.1–4.2] | 3.2 [2.9–4.0] | 3.2 [2.7–3.8] | 0.112 |
| Inferior vena cava (cm) | 1.70 [1.30–2.10] | 1.82 [1.42–2.30] | 1.70 [1.21–2.10] | 1.60 [1.20–2.00] | <0.001 |
| TAPSE (mm) | 16 [13–19] | 14 [12–19] | 18 [15–20] | 16 [13–19] | 0.161 |
| Laboratory data | | | | | |
| Haemoglobin (g/dL) | 11.7 [10.2–13.3] | 10.8 [9.7–12.2] | 12.0 [10.5–13.6] | 12.4 [11.0–14.0] | <0.001 |
| Platelet counts (10$^9$/L) | 193 [155–252] | 162 [124–193] | 184 [151–226] | 257 [216–310] | <0.001 |
| Albumin (g/dL) | 3.4 [3.1–3.7] | 3.2 [3.0–3.6] | 3.4 [3.2–3.7] | 3.5 [3.2–3.8] | <0.001 |
| ALT (U/L) | 16 [11–26] | 12 [8–16] | 17 [12–25] | 22 [15–36] | <0.001 |
| AST (U/L) | 23 [18–31] | 23 [18–31] | 23 [18–31] | 23 [18–31] | 0.938 |
| ALP (U/L) | 225 [179–296] | 250 [193–352] | 221 [177–279] | 211 [155–265] | <0.001 |
| Creatinine (mg/dL) | 1.10 [0.86–1.52] | 1.22 [0.92–1.74] | 1.11 [0.87–1.52] | 1.00 [0.83–1.35] | <0.001 |
| Blood urea nitrogen (mg/dL) | 26 [19–37] | 30 [21–43] | 25 [19–35] | 22 [17–32] | <0.001 |
| Sodium (mEq/L) | 140 [137–142] | 139 [137–142] | 140 [138–142] | 140 [138–142] | 0.051 |
| Potassium (mEq/L) | 4.4 [4.0–4.7] | 4.3 [4.0–4.7] | 4.4 [4.0–4.8] | 4.4 [4.1–4.7] | 0.074 |
| BNP (pg/mL) | 191.3 [84.1–382.6] | 234.9 [115.9–476.3] | 194.9 [85.0–423.9] | 138.9 [70.2–276.5] | <0.001 |
| Prescription, n (%) | | | | | |
| Loop diuretics | 761 (84.0) | 269 (88.8) | 254 (84.4) | 238 (78.9) | 0.005 |
| ACE-I/ARB | 525 (58.0) | 151 (49.8) | 177 (58.8) | 197 (65.2) | <0.001 |
| Beta-blockers | 592 (65.3) | 181 (59.7) | 190 (63.1) | 221 (73.2) | 0.001 |
| MRA | 422 (46.6) | 144 (47.5) | 133 (44.2) | 145 (48.0) | 0.575 |

ACE-I, angiotensin-converting enzyme inhibitor; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; FIB-4, fibrosis-4 index; LVDD, left ventricular end-diastolic dimension; LVDS, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PAP, pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion. Variables are presented as median [25–75%].

**Figure 2** Kaplan–Meier curves for the composite endpoint of cardiac death or rehospitalization due to heart failure. Low fibrosis-5 (FIB-5) index was significantly associated with a higher incidence of the primary endpoint than medium and high values of the index.



model was changed from FIB-4 + Model 2 to FIB-5 + Model 2 (continuous NRI, 0.386; 95% CI, 0214–0.558; *P* < 0.001; IDI, 0.024, 95% CI 0.011–0.037; *P* < 0.001).

## Discussion

In the present study involving 906 patients hospitalized with acute heart failure, we found that (i) low FIB-5 at discharge was significantly associated with poor prognosis regardless of LVEF, and (ii) FIB-5 was better than FIB-4 as a prognostic indicator of cardiac death and heart failure rehospitalization. To the best of our knowledge, this is the first report of investigation of the prognostic value of FIB-5 in patients with heart failure.

Heart failure often causes liver dysfunction or abnormal liver enzymes. Increased central venous pressure due to heart failure leads to elevated hepatic venous pressure and perisinusoidal oedema.[20] These, in turn, lead to bile duct compression and centrilobular hepatic cell necrosis.[20] The former results in elevation of ALP or bilirubin, and the latter causes increased transaminases. AST is predominantly produced in the centrilobular region; therefore, AST elevation might occur more easily than ALT elevation with centrilobular hepatic cell necrosis.[2] Increased central venous pressure also causes post-hepatic portal hypertension, which contributes to splenomegaly and hypersplenism, resulting in a decrease in PLT counts.[21] All of these facts suggest that venous congestion can lead to a decrease in FIB-5 and increase in FIB-4. In the current study, patients in the low FIB-5 group were more likely to be given diuretics and had high values of BNP and a larger diameter of the inferior vena cava. Moreover, mean

0.611–0.683; FIB-5, 0.686; 95% CI, 0.651–0.722; *P* = 0.007) (*Figure 4*). Moreover, we found that changing from a FIB-4 to FIB-5 model provided significant continuous NRI (0.530; 95% CI, 0.399–0.662; *P* < 0.001) and IDI (0.072; 95% CI, 0.057–0088; *P* < 0.001). After adjustment for Model 2, the area under the curve for FIB-5 tended to be larger than those for FIB-4 (FIB-4, 0.801; 95% CI, 0.762–0.840; FIB-5, 0.813; 95% CI, 0.776–0.850; *P* = 0.085). Significant NRI change was achieved when the
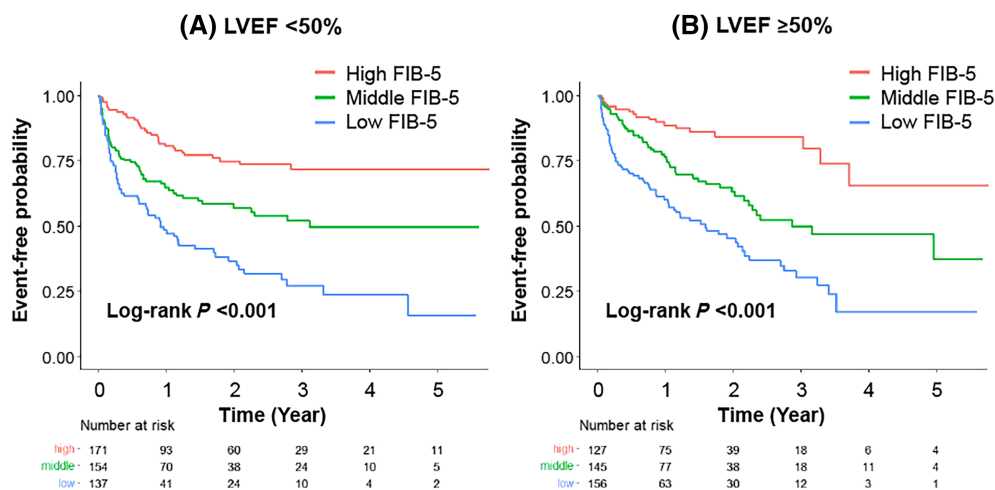
**Figure 3** Kaplan–Meier curves for the composite endpoint of cardiac death or rehospitalization due to heart failure according to LVEF. The event-free rates were significantly lower among patients with low FIB-5 scores compared to the other two groups in both cohorts of (A) reduced and (B) preserved LVEF. LVEF, left ventricular ejection fraction.

**Table 2** Cox proportional hazard analysis for cardiovascular death or readmission for heart failure according to FIB-5 scores

| | Unadjusted model | | | Model 1[a] | | | Model 2[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | HR | 95% CI | P value | HR | 95% CI | P value |
| FIB-5 as categorical variables | | | | | | | | | |
| High | 1 | (Reference) | | 1 | (Reference) | | 1 | (Reference) | |
| Middle | 2.29 | 1.65–3.17 | <0.001 | 1.72 | 1.17–2.51 | 0.005 | 1.38 | 0.89–2.13 | 0.149 |
| Low | 4.10 | 3.01–5.60 | <0.001 | 2.81 | 1.93–4.08 | <0.001 | 2.14 | 1.39–3.30 | <0.001 |
| FIB-5 as continuous variables | 0.92 | 0.90–0.93 | <0.001 | 0.93 | 0.91–0.95 | <0.001 | 0.94 | 0.91–0.96 | <0.001 |

CI, confidence interval; HR, hazard ratio.
[a]Model 1: adjusted for age, sex, body mass index, Get With The Guidelines®-Heart Failure score, log-transformed brain natriuretic peptide, New York Heart Association class, anaemia, and left ventricular ejection fraction.
[b]Model 2: adjusted for Model 1 + a history of heart failure, hypertension, diabetes, dyslipidaemia, coronary artery disease, serum creatinine, left atrial diameter, estimated pulmonary artery pressure, and the prescription of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, and mineralocorticoid receptor antagonist.



**Figure 4** Area under the receiver operating characteristic curve for prediction of the primary endpoint. The predictive value of fibrosis-5 (FIB-5) significantly outperformed that of fibrosis-4 (FIB-4).

FIB-4 (AUC=0.647)
FIB-5 (AUC=0.686)
$P = 0.007$
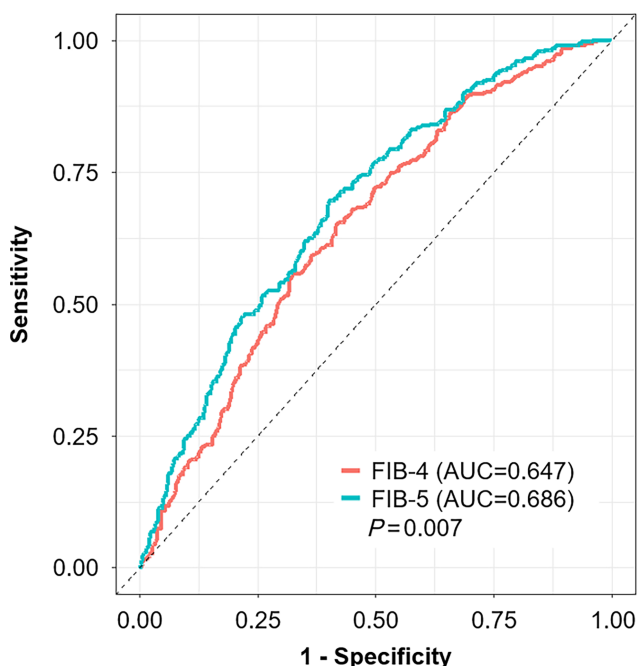
right artery pressure evaluated by RHC was significantly correlated with FIB-5. Low FIB-5 might reflect volume overload, resulting in poor clinical outcomes in patients with heart failure. We speculate that low FIB-5 index at discharge reflects increased central venous pressure; therefore, further volume reduction or careful observation is needed.

The FIB-4 is a well-validated prognostic marker in patients with heart failure. A previous report involving 1058 patients hospitalized with heart failure revealed that high FIB-4 index at discharge was significantly associated with all-cause mortality.[9] Another study including 1162 patients with acute heart failure demonstrated that high FIB-4 at admission was a significant predictor of the composite of all-cause death and rehospitalization due to heart failure.[22] However, a post-hoc analysis of the TOPCAT trial, which included only heart failure patients with preserved LVEF, reported that FIB-4 was not a significant risk factor for cardiac events.[23] Although several studies have evaluated the prognostic significance of FIB-4, there have been no reports evaluating the association between FIB-5 and prognosis in patients with heart failure. FIB-5 was first reported as an index to differentiate between a cirrhotic and a non-cirrhotic liver in patients with HCV in 2006.[12] In populations with HBV and HCV infections, it was reported that FIB-5 was more specific compared to FIB-4 for differentiation between the absence and presence of significant liver fibrosis assessed by liver biopsy.[13,14] In the current study, FIB-5 was superior to FIB-4 for prediction of cardiac events in patients with acute heart failure. Furthermore, when focusing on heart failure with preserved LVEF, our results showed that FIB-5 was a significant risk stratification marker even after adjustment for other covariates.

Possible explanations for the superiority of FIB-5 over FIB-4 might be the different parameters used in calculation of the two scores. Serum albumin and ALP, which are included in calculation of FIB-5 but not FIB-4, are well-known prognostic factors in patients with heart failure. Low albumin levels were shown to be a significant risk factor for heart failure with both reduced[24] and preserved LVEF.[25] High ALP was also reported to be associated with poor outcomes in patients with heart failure.[26–28] In a secondary analysis of the Pre-RELAX-AHF trial involving 234 acute heart failure patients, elevated ALP was independently associated with the composite of death or readmission for heart failure within 60 days.[26] These factors might contribute to the better prognostic value of FIB-5 than FIB-4 even though the FIB-4 index includes age, which is one of the most powerful risk factors in patients with heart failure.

Several limitations of the present study should be noted. First, this was a retrospective single-center study in which a fair number of cases were lost to follow-up. This loss to follow-up could have led to selection bias. Second, because there were numerous differences in baseline characteristics between the three groups (low, middle, and high FIB-5 groups), residual confounding factors cannot be completely excluded even after adjustment for well-accepted prognostic factors. Third, although liver-specific tests such as abdominal ultrasonography, computed tomography, magnetic resonance imaging, or liver biopsy can be helpful to discriminate between heart failure-induced and liver disease-induced liver dysfunction, these were not performed in the study subjects. Fourth, we did not have data on bone marrow examinations even though marrow function may be associated with the value of FIB-5. Finally, we had no accurate information on the prevalence of right sided heart failure because there is no the universal definition. When the diagnostic criteria of pulmonary artery pulsatility index (PAPi) $< 1.85$[29] was used, out of 232 patients who were able to evaluate PAPi in our study, 44 (19.0%) were defined as right ventricular failure.

In conclusion, FIB-5, which is an easily available and non-expensive marker, is a useful risk stratification tool in patients with acute heart failure. FIB-5 might be superior to FIB-4 as a prognostic indicator of cardiac events in patients with both preserved and reduced LVEF.

## Acknowledgements

## Conflict of interest

The authors declare that they have no conflicts of interest.

## Funding

## Supporting information

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

**Figure S1.** Kaplan–Meier curves for (a) cardiac death and (b) heart failure rehospitalization.
Patients with low FIB-5 scores had significantly higher event rates of (a) cardiac death and (b) heart failure rehospitalization.

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