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# Impact of predictive value of Fibrosis-4 index in patients hospitalized for acute heart failure

Naoki Shibata [a,1], Toru Kondo [a,*,1], Shingo Kazama [a,1], Yuki Kimura [a,1], Hideo Oishi [a,1], Yoshihito Arao [a,1], Hiroo Kato [a,1], Shogo Yamaguchi [a,1], Tasuku Kuwayama [a,1], Hiroaki Hiraiwa [a,1], Ryota Morimoto [a,1], Takahiro Okumura [a,1], Takuya Sumi [b,1], Akinori Sawamura [b,1], Kiyokazu Shimizu [b,1], Toyoaki Murohara [a,1]

[a] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[b] Department of Cardiology, Ichinomiya Municipal Hospital, Ichinomiya, Japan

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ABSTRACT

*Background:* Abnormalities in liver function tests commonly occur in patients with acute heart failure (AHF). The Fibrosis-4 (FIB4) index, a non-invasive and easily calculated marker, has been used for hepatic diseases and reflects adverse prognosis. It is not clearly established whether the FIB4 index at admission can predict adverse outcomes in patients with AHF.

*Methods and results:* From a multicenter AHF registry, we retrospectively evaluated 1162 consecutive patients admitted due to AHF (median age 78 [69–85] years and 702 patients [60.4%] were male). The FIB4 index at admission was calculated as: age (yrs) × aspartate aminotransferase [U/L]/(platelets count [$10^3$/μL] × √alanine aminotransferase [U/L]. The median value of the FIB4 index at admission was 2.79. All-cause mortality and rehospitalization due to HF at 12 months were investigated as a composite endpoint and occurred in 142 (12.2%) patients and 232 (20%) patients, respectively. Kaplan-Meyer analysis shows a significant increase in the composite endpoint from the first to fourth quartile group of the FIB4 index values (log-rank, $p < 0.001$). Multivariate Cox regression model revealed the FIB4 index was an independent risk predictor for composite endpoint in patients with AHF (3 months: HR ratio 1.013 [95% Confidence interval (CI):1.001–1.025]; $p = 0.03$, 12 months: HR 1.015 [95% CI:1.005–1.025]; $p = 0.003$, respectively). However, neither aspartate aminotransferase, alanine aminotransferase, nor platelet count was found to be a significant predictor.

*Conclusions:* Hepatic dysfunction evaluated with the FIB4 index at admission is a predictor of the composite endpoint of all-cause mortality and rehospitalization in AHF patients.



## 1. Introduction

Abnormalities in liver function tests (LFTs) occur in over 50–70% of acute heart failure (AHF) patients and are related to adverse outcomes [1,2]. In AHF, abnormalities in LFTs are induced by two hemodynamic features: one is the hypoperfusion due to decreasing cardiac output, leading to impaired organ perfusion related to acute centrilobular hepatocellular damage, ischemic hepatic injury, and hepatic necrosis [3]. The other is the systemic congestion due to the elevation in right atrial pressure, which often results from hypoperfusion, leading to congestive hepatic injury [4]. Whereas there is some evidence that individual LFT correlates with various hemodynamic states [5], it has been reported that multiple hepatic indexes, such as Model of End-Stage Liver Dysfunction (MELD) series score, are better at predicting prognosis in patients with AHF than single parameters [6–9]. The Fibrosis-4 (FIB4) index was developed as a noninvasive index to stage hepatic disease in subject with virus infection [10], and is a simple and inexpensive measure of hepatic disorder. This score has been used across many hepatic diseases [11], and several studies have described the association between a high level of the FIB4 index and poorer outcomes [12,13], not only for hepatic disease but also for non-hepatic disease. A previous report determined that the FIB4 index values at discharge was associated with the long-term mortality in patients who were able to recover from worsening decompensated heart failure (HF) [14]. On the other hand, using the FIB4 index at admission in patients with AHF can be strongly influenced by unstable general conditions due to hemodynamic changes; thus, the comprehensive and longitudinal profile of the FIB4 index at admission in this population is unknown. The aim of

*Abbreviations:* LFT, liver function test; AHF, acute heart failure; MELD, Model of End-Stage Liver Dysfunction; FIB4, Fibrosis-4; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

* Corresponding author at: Department of Cardiology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan.
*E-mail address:* toru.k0927@med.nagoya-u.ac.jp (T. Kondo).

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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the present study was to evaluate the predictive value of the FIB4 index at admission for adverse outcomes in patients with AHF.

## 2. Methods

### 2.1. Study population

We used the data of the AHF retrospective registry at the Nagoya University Hospital and Ichinomiya Municipal Hospital between January 2012 and December 2019. This study included consecutive AHF patients who were admitted to these two institutes, who met the modified Framingham criteria [15], and needed to use intravenous diuretics, vasodilators, or inotropes. Exclusion criteria were as follows: (1) <20 years of age, (2) subjects with other concomitant cause of hepatic disease such as viral hepatitis, acute hepatic failure, hepatic cirrhosis, Wilson disease, hepatic tumor, bile duct disease, (3) acute coronary syndrome requiring emergency revascularization, (4) hemodialysis or chronic peritoneal dialysis, (5) acute myocarditis, and (6) the life expectancy of <6 months due to non-cardiac disease such as end-stage cancer, as determined by the enrolling clinical investigator. However, the patients with cardiogenic shock were not excluded in this study.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of Nagoya University Hospital (approval number 2019–0521) and Ichinomiya Municipal Hospital (approval number 1250). As this was a retrospective study, informed consent from patients enrolled in the study was not required, and an opt-out method for participant recruitment was employed.

### 2.2. The FIB4 index

Patients' data were obtained from hospital medical records. The FIB4 index at admission and at discharge respectively were calculated by the formula: age (yrs) × aspartate aminotransferase (AST) [U/L]/(platelets count [$10^3$/μL] × √alanine aminotransferase (ALT) [U/L] [11]. The laboratory measurements at admission and at discharge were corrected. Data at discharge was sampled at the time of patient discharge as determined pathophysiologically. Because there is no obvious cut-off value of the FIB4 index regarding the hepatic fibrosis, patients were divided into interquartile ranges (IQR) according to the FIB4 index at admission: first quartile (FIB4 index <1.83, $n = 290$), second quartile (1.84 ≦ FIB4 index <2.79, $n = 291$), third quartile (2.8 ≦ FIB4 index <4.08, $n = 291$), and fourth quartile (4.09 ≦ FIB4 index, $n = 290$).

### 2.3. Study endpoint

The primary outcome of this study was the composite endpoint of all-cause death and rehospitalization due to HF. We evaluated the outcome at the time points of 3, 6, and 12 months after the first admission, respectively. Rehospitalization due to HF was defined by an experienced physician who assessed the need for additional intravenous medications including diuretics, vaso dilators, or inotropes to treat HF. Outcome data were accumulated with the medical records or a telephone call to the patients or their family.

### 2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) when normally distributed or median (IQR) when non-normally distributed. The characteristics of the four groups were compared using the Kruskal-Wallis test or chi-square test as appropriate. Categorical variables are presented as numbers (percentages) and were compared using Fisher's exact test or the chi-square test. Linear regression analyses were used to identify associations with LFTs and other parameters. A paired *t*-test was used to evaluate the difference between Fib 4 index at admission and discharge. Kaplan-Meier survival curves and log-rank statistics were performed to assess the prognostic value of the FIB4 index on primary outcome by quartile. COX proportional hazard models were used to estimate the predictive value of FIB4 index, AST, ALT, and platelet count for primary outcome at 3, 6, and 12 months after the first admission. In the Cox regression analyses, we adjusted the following clinical factors which are not included in the FIB4 index and judged to be of clinical significance for the risk of mortality in patients with HF: sex, systolic blood pressure, heart rate, serum creatinine, serum sodium, hemoglobin, and LVEF. Primary outcome at 12 months was also evaluated according to categorical value of FIB4 index in the Cox regression analyses. Statistical significance was defined as a *p*-value <0.05. All statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA).

## 3. Results

Among the 1222 consecutive patients admitted with AHF, 60 patients had inadequate data including AST, ALT, or platelets to calculate the FIB4 index at admission. After excluding these 60 patients, we evaluated 1162 patients in this study. Median age was 78 (69–85) years, 702 patients (60.4%) were male, New York Heart Association functional class III or IV was 84.3%, and medical history of hypertension, diabetes mellitus, ischemic heart disease, and HF hospitalization were 54.7%, 31.6%, 24.4%, and 37.4%, respectively. Median days of hospitalization were 15 (10−23) days. Patients' background data by the Fib4 index are presented in Table 1. The higher FIB4 index group was older, had a higher proportion of females, lower body mass index, lower prevalence of diabetes mellitus. Laboratory data showed the higher FIB4 index group had higher AST values, and lower hemoglobin values and platelet counts. Medications at admission were not significantly different between the four groups.

The FIB4 index at admission showed non-normally distributed values (Supplementary Fig. 1). The median FIB4 index was 2.79 (1.83–4.08), and of the individual components of the FIB4 index score, the median (IQR) values except for age were as follow: AST [29 (22–44) U/L], ALT [21 (13–35) U/L], and platelet count [19.2 (15.1–24) × $10^4$/μL], while 38.5% AST and 25.8% ALT in these patients showed abnormal values, respectively. In the regression analysis, all parameters had a very weak relationship with the FIB4 index ($r < 0.1$) except for four variable as age, AST, ALT, and platelet count, which are the components of FIB4 index.

Forty-five patients (3.8%) died during hospitalization. Whereas there was no patient who underwent heart transplantation, 8 patients needed ventricular assist device implantation during this hospitalization. During the 12-month follow-up after admission, 142 (12.2%) patients died and 232 (20.0%) patients required re-hospitalization due to HF. In the Kaplan-Meier survival analysis evaluated over 12 months, the event-free rate for the composite endpoints (log-rank, $p < 0.001$), all-cause mortality (log-rank, $p < 0.001$), and rehospitalization due to HF (log-rank, $p = 0.007$) decreased progressively with higher values of the FIB4 index quartile at admission (Fig. 1).

The univariate and multivariate COX regression models for the outcomes of composite endpoint are summarized in Table 2. Whereas AST, ALT, and platelet count, which are the hepatic components of the FIB4 index respectively, did not show any significant prognostic predictability, the FIB4 index was identified as an independent predictor for 3, 6, and 12 months composite endpoint in patients with AHF (3 months: hazard ratio [HR] 1.013 [95% confidence interval (CI); 1.001–1.025]; $p = 0.04$, 6 months: HR 1.013 [95% CI 1.002–1.025]; $p = 0.02$, 12 months: HR 1.015 [95% CI 1.005–1.025]; $p = 0.004$, respectively). We also indicated the multivariate COX regression models as a categorical variable at admission (Supplementary Table 1), clarifying that the highest quartile of the FIB4 index at admission had increased risk for primary outcome. (forth vs first quartile as reference: HR 1.916 [95% CI 1.329–2.764]; $p = 0.001$).

**Table 1**
Baseline patient characteristics at admission and in-hospital treatment.

| | First quartile ($n$ = 290) | Second quartile ($n$ = 291) | Third quartile ($n$ = 291) | Forth quartile ($n$ = 290) | $p$ value |
|---|---|---|---|---|---|
| Age, years | 65 (50–76) | 79 (71–84) | 81 (75–86) | 83 (77–87) | <0.001 |
| Male, *n* (%) | 201 (69.3) | 182 (62.5) | 162 (55.7) | 157 (54.1) | 0.001 |
| Body mass index, (%) | 24.3 (20.8–27.7) | 22.7 (20.3–25.2) | 22.1 (19.4–24.6) | 21.5 (18.8–23.9) | <0.001 |
| NYHA class III and IV, *n* (%) | 246 (85.4) | 241 (83.4) | 250 (86.5) | 243 (84.4) | 0.75 |
| Systolic blood pressure, mmHg | 138 (119–162) | 142 (121–165) | 138 (118–159) | 135 (114–162) | 0.18 |
| Heart rate, bpm | 98 (82–112) | 90 (76–110) | 92 (76–113) | 88 (74–106) | 0.001 |
| Ischemic etiology, *n* (%) | 72 (24.8) | 62 (21.3) | 83 (28.6) | 74 (25.5) | 0.24 |
| Medical history | | | | | |
| History of HF hospitalization, *n* (%) | 99 (34.1) | 102 (35.1) | 116 (39.9) | 118 (40.7) | 0.25 |
| Atrial fibrillation, *n* (%) | 76 (26.2) | 109 (37.5) | 95 (32.6) | 123 (42.4) | <0.001 |
| Hypertension, *n* (%) | 149 (51.4) | 173 (59.5) | 162 (55.7) | 152 (52.4) | 0.2 |
| Diabetes mellitus, *n* (%) | 108 (37.2) | 102 (35.1) | 82 (28.2) | 75 (25.9) | 0.008 |
| COPD, *n* (%) | 16 (5.5) | 15 (5.2) | 16 (5.5) | 23 (7.9) | 0.47 |
| ICD, *n* (%) | 7 (2.8%) | 9 (3.6%) | 9 (3.6%) | 5 (2%) | 0.67 |
| CRT, *n* (%) | 14 (5.6%) | 8 (3.2%) | 14 (5.5%) | 14 (5.5%) | 0.54 |
| Medication | | | | | |
| ACE-I/ARB, *n* (%) | 125 (43.1) | 125 (43.1) | 127 (43.6) | 112 (38.6) | 0.58 |
| β-blocker, *n* (%) | 119(41.0) | 110 (387.9) | 116 (39.9) | 120 (41.4) | 0.83 |
| MRA, *n* (%) | 80 (27.6) | 61 (21.0) | 74 (25.4) | 82 (28.3) | 0.18 |
| Diuretic, *n* (%) | 132 (45.5) | 129 (44.3) | 142 (48.8) | 148 (51) | 0.35 |
| Laboratory data | | | | | |
| Albumin, g/dL | 3.6 (3.2–4) | 3.7 (3.3–4) | 3.6 (3.3–4) | 3.5 (3.3–3.9) | 0.16 |
| Creatinine, mg/dL | 1.01 (0.81–1.29) | 1.02 (0.8–1.4) | 1.00 (0.82–1.33) | 1.18 (0.89–1.67) | <0.001 |
| Sodium, mEq/L | 140 (137–142) | 140 (137–142) | 140 (137–142) | 139 (137–142) | 0.53 |
| Hemoglobin, g/dL | 12.8 (10.9–14.8) | 12.0 (10.2–13.6) | 11.7 (10.2–13.1) | 11.3 (10.0−13.0) | <0.001 |
| Platelet count, $10^4/\mu L$ | 25.2 (21.1–30.7) | 20.2 (17.6–24.2) | 17.8 (15.3–21.7) | 13.2 (10.5–16.7) | <0.001 |
| AST, IU/L | 24 (18–31) | 26 (21–36) | 33 (25–46) | 42 (29–80) | <0.001 |
| ALT, IU/L | 21 (14–34) | 18 (13−31) | 21 (13−33) | 26 (14–48) | 0.001 |
| LVEF, % | 34 (22–48) | 42 (29–57) | 42 (29–57) | 37 (28–56) | <0.001 |
| Treatment | | | | | |
| NIV, *n* (%) | 54 (18.6) | 51 (17.5) | 64 (22.0) | 58 (20.0) | 0.56 |
| Endotracheal intubation, *n* (%) | 7 (2.4) | 7 (2.4) | 8 (2.7) | 8 (2.8) | 0.99 |
| Diuretics, *n* (%) | 234 (80.7) | 252 (86.6) | 238 (85.2) | 246 (85.1) | 0.23 |
| Vasodilator, *n* (%) | 116 (40.0) | 122 (41.9) | 117 (40.2) | 113 (39.0) | 0.91 |
| Inotropic agents, *n* (%) | 55 (19%) | 34 (11.7%) | 44 (15.1%) | 52 (17.9%) | 0.07 |

Values are presented as number (%) or median (lower quartiles-upper quartiles).
ACE-I = angiotensin-converting enzyme inhibition, ALT = alanine aminotransferase, ARB = angiotensin II receptor blocker, AST = aspartate aminotransferase, COPD = chronic obstructive pulmonary disease, CRT = cardiac resynchronization therapy, HF = heart failure, ICD = implantable cardioverter-defibrillator, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist, NIV = noninvasive ventilation, NYHA = New York Heart Association.

Of the 1117 patients who were able to discharge from hospital, data relative to the FIB4 index at discharge were not available in 88 patients. Therefore, in 1029 patients whose FIB4 index at discharge could be calculated, the individual components of the FIB4 index score except for age were as follows: AST [22 (17–29) U/L], ALT [17 (11–29) U/L], and platelet count [20.7 (16.4–26.2) × $10^4/\mu L$]. The

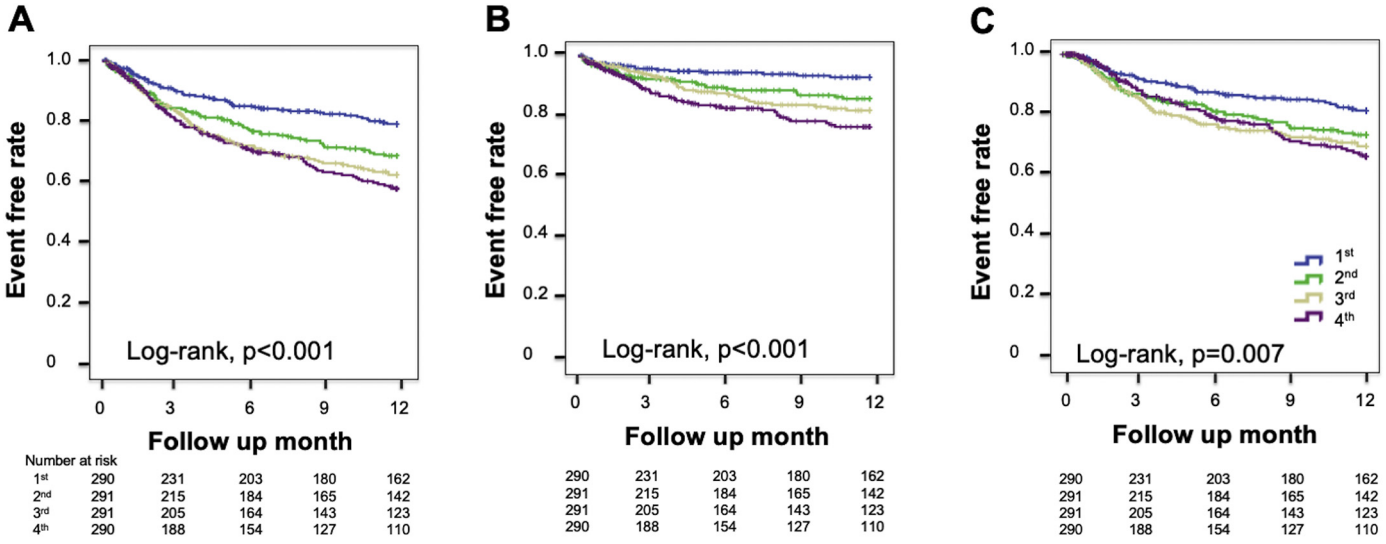


**Fig. 1.** Kaplan-Meier analysis for (A) the composite endpoint, (B) all-cause death, and (C) rehospitalization due to HF among the four groups (first to fourth quartile of the FIB4 index at admission). HF = heart failure, FIB4 = Fibrosis - 4.

**Table 2**
Univariate and Multivariate regression analysis for the association between composite endpoint and clinical findings during follow-up period.a, b

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p* value | HR | 95% CI | *p* value |
| *-3 months* | | | | | | |
| FIB4-index[a] | 1.010 | 1.003–1.025 | 0.011 | 1.013 | 1.001–1.025 | 0.04 |
| AST[b] | 0.999 | 0.998–1.001 | 0.56 | 0.999 | 0.997–1.001 | 0.40 |
| ALT[b] | 0.999 | 0.996–1.001 | 0.011 | 0.999 | 0.996–1.001 | 0.40 |
| Platelet count[b] | 0.986 | 0.966–1.006 | 0.16 | 0.999 | 0.983–1.016 | 0.95 |
| *-6 months* | | | | | | |
| FIB4-index[a] | 1.015 | 1.005–1.025 | 0.003 | 1.013 | 1.002–1.025 | 0.02 |
| AST[b] | 0.999 | 0.997–1.001 | 0.31 | 0.999 | 0.997–1.001 | 0.21 |
| ALT[b] | 0.997 | 0.994–1.000 | 0.09 | 0.998 | 0.996–1.001 | 0.15 |
| Platelet count[b] | 0.986 | 0.97–1.003 | 0.10 | 0.999 | 0.985–1.013 | 0.88 |
| *-12 months* | | | | | | |
| FIB4-index[a] | 1.016 | 1.007–1.025 | <0.001 | 1.015 | 1.005–1.025 | 0.004 |
| AST[b] | 0.999 | 0.997–1.001 | 0.17 | 0.999 | 0.997–1.000 | 0.13 |
| ALT[b] | 0.996 | 0.993–0.999 | 0.02 | 0.998 | 0.995–1.000 | 0.06 |
| Platelet count[b] | 0.982 | 0.968–0.997 | 0.02 | 0.995 | 0.982–1.008 | 0.45 |

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, FIB4 = Fibrosis - 4, HR = hazard ratio.
[a] Adjusted for sex, systolic blood pressure at admission, heart rate at admission, serum creatinine level, serum sodium level, hemoglobin, and left ventricular ejection fraction.
[b] Adjusted for above components plus age.

FIB4 index at discharge was 2.00 (1.36–2.77) and was lower than that at admission ($p < 0.001$) (Supplementary Table 2). There was a moderate relationship between the FIB4 index at admission and the FIB4 index at discharge ($r = 0.457$, $p < 0.001$). When these patients were divided into IQR according to the FIB4 index at discharge, Kaplan-Meier curve revealed that the outcome of composite endpoint, all-cause mortality, and rehospitalization due to HF after discharge worsened as the FIB4 index increased (log-rank, $p < 0.001$, $p < 0.001$, $p < 0.001$, respectively) (Fig. 2). In terms of multivariate COX regression models for the outcomes of composite endpoint, while there was no significant relationship between the FIB4 index at discharge and adverse outcome in the early phase (3 months: HR 1.042 [95% CI 0.976–1.112]; $p = 0.217$, 6 months: HR 0.985 [95% CI 0.897–1.080]; $p = 0.743$, respectively), this score was identified as an independent predictor for 12 months composite endpoint. (HR 1.077 [95% CI 1.023–1.133]; $p = 0.005$)

## 4. Discussion

There are three important findings from present study. (1) First, the data elucidated that the FIB4 index at admission, which is a marker of hepatic disorder, had good predictability for all-cause mortality and rehospitalization due to HF in patients with AHF. (2) Second, other individual LFTs, which are component of the FIB4 index, at admission could not significantly predict adverse outcomes in both the short and long term. (3) Finally, the FIB4 index at discharge tends to decrease compared with at admission. And, the FIB4 index at discharge had a moderate relationship with the FIB4 index at admission and was also a good predictor of adverse outcomes in these patients.

HF is a complex clinical syndrome with multiple interactions with many organs such as the heart, and kidney, as well as hemoglobin levels (anemia), which are associated with adverse outcomes [4,16–22]. Interaction between HF and hepatic dysfunction is also well known [4,23]. Abnormal LFTs are usually classified in function of hepatic cell injury (transaminase elevations) or cholestasis (bilirubin or alkaline phosphatase). Both these abnormalities can occur because of abnormal hemodynamic changes occurring during hospitalization in patients with AHF [2,24]. To date, several studies have evaluated the association between abnormal LFTs and adverse outcomes in patients with AHF [8,25,26]. In the present study, we adopted the FIB4 index as a marker of LFTs and evaluated its clinical significance in patients with AHF.

The reason for the elevation of the FIB 4 index at admission due to AHF can be explained by the following mechanisms. First, AST and ALT can change dramatically in the acute setting for AHF patients, which are described as having acute cardiogenic hepatic injury or ischemic hepatitis. When cardiac output becomes relatively insufficient for the metabolic demands of hepatic cells, hepatic lobules necrosis in the centrilobular zone due to hypoperfusion and/or hypooxgenation can occur [27,28]. In addition, higher hydrostatic pressure in the hepatic sinusoids also results in hepatic cell enlargement [29], which leads to passive congestion or congestive hepatopathy [2]. Because hepatic cells of the centrilobular region contain higher levels of AST than ALT, these mechanisms support the findings of AST-dominant elevation of transaminase level in patients with AHF [30]. Besides, AST-dominant elevation may be derived from differences in distribution between AST and ALT: ALT is expressed mainly in the liver, but AST expression derives from various organs including the liver, heart muscle, skeletal muscle, and red blood cells. In fact, our data at admission showed higher levels of AST than of ALT, which contributed

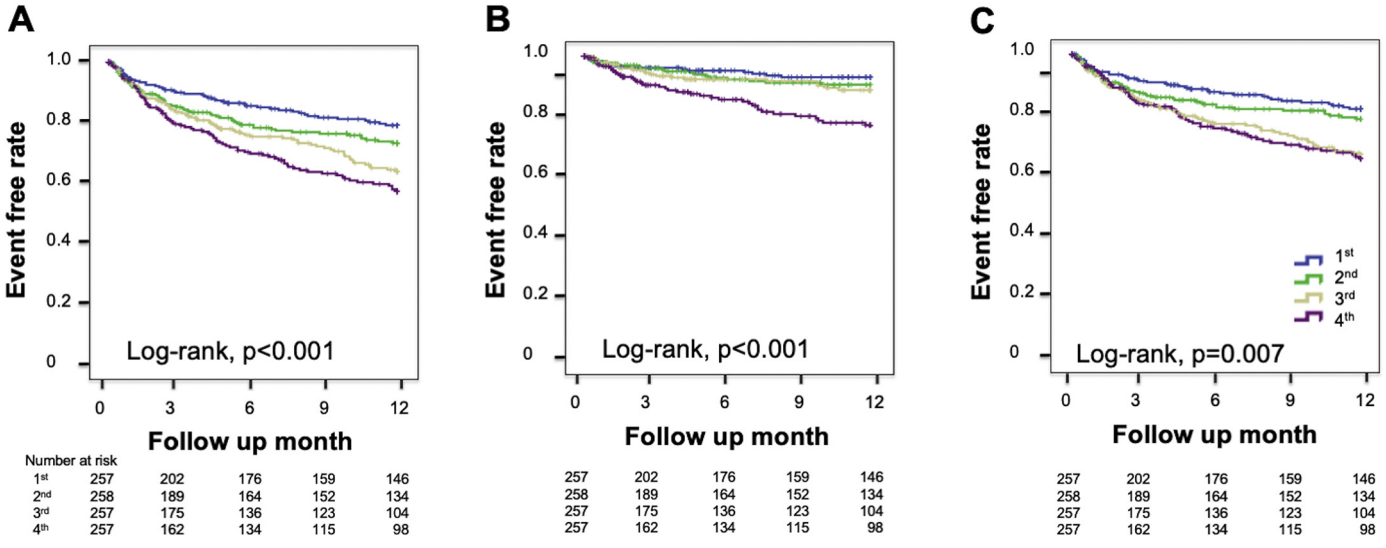


**Fig. 2.** Kaplan-Meier analysis for (A) composite endpoint, (B) all-cause death, and (C) rehospitalization due to HF among the four groups (first to fourth quartile of the FIB4 index at discharge). HF = heart failure, FIB4 = Fibrosis - 4.

to elevate FIB4 index. Next, platelet count can decrease not only due to hepatic congestion but also due to bone marrow dysfunction caused by congestion, and activation of the sympathetic nerve system in patients with AHF [31]. However, the inflammatory response can increase platelet count. Our study did not show any large differences in platelet count at admission and at discharge. Therefore, the FIB4 index would increase mainly due to changes in AST and/or ALT levels associated with abnormal hemodynamics of AHF. Considering the mechanism by which the FIB4 index increases, we think that the FIB4 index at admission is proportional to the hemodynamic severity of AHF.

However, acute hemodynamic changes alone are not the incident responsible for the development of liver injury [32,33]. In other words, abnormal LFTs at admission result from the combined effect of both baseline hepatic injury and acute dynamic change of hemodynamics [24]. The present study showed the moderate relationship between the FIB4 index at admission and at discharge may reflect this combination effect. In addition, after correction of hemodynamics owing to HF treatment, the peak in LFTs abnormality occurs a few days after the onset of symptoms and returns to baseline within 5–10 days after treatment [20,27,34]. This implies that in hospitalized patients who achieve good HF treatment, the LFTs at discharge would reflect their baseline hepatic function. Recently, Sato et al. showed that the FIB4 index at discharge had good predictability of 3-year all-cause death in patients with decompensated HF [14], showing a relationship between the baseline hepatic function and the adverse outcome. Our study also showed that a higher FIB4 index at discharge was associated with adverse outcomes in the clinical setting. In short, both chronic liver dysfunction and acute cardiogenic liver injury could lead to a higher FIB4 index, and the FIB4 index at both admission and at discharge might have good predictability for adverse outcome in patients with AHF. However, the FIB4 index at discharge may be related to the persistence of residual congestion at discharge, which reflected the association between FIB4 index at discharge and adverse outcomes [35].

Previous reports have indicated that the incidence of abnormal LFTs such as AST or ALT in patients with AHF was ranged 24% to 33% [2,26,36], which are consistent with our study. It has been shown that impaired cardiac output is associated with abnormalities in AST, ALT, and bilirubin, and increased central venous pressure is associated with all LFT including gamma-glutamyl transpeptidase and alkaline phosphatases [2,37,38]. Though these papers concluded that LFTs index such as AST and bilirubin had strong prognostic predictability; other reports showed the contrasting results, as a result, the definitive connection between hemodynamic abnormalities and specific LFTs were unknown [36]. Conversely, multiple hepatic dysfunction parameters such as the MELD-XI score, which is based on a patient's creatinine and total bilirubin levels, may be stronger predictors than a single hepatic index. While it has recently been shown to have good predictability of the adverse outcome in patients with AHF [8], the MELD-XI score has a weakness from the perspective of including creatinine levels as a component. Furthermore, whereas total bilirubin and ALBI grade could both predict the hepatic spare ability, [39,40] these data at admission were not significant prognostic predictability for the adverse outcome in patients with AHF (total bilirubin: HR 1.011 [95% CI 0.996–1.026]; $p = 0.14$, ALBI grade: HR 1.203 [95% CI 0.938–1.541]; $p = 0.15$, respectively).The FIB4 index is easily and immediately measured, inexpensive to apply, and has good predictability of early-stage hepatic fibrosis and impairment of hepatic reserve. This score has been developed as a non-invasive marker to stage hepatic disease in patients with viral hepatitis [41] and non-alchoholic fatty hepatic disease [11], and has shown to be superior for diagnosing all-cause mortality in several chronic diseases [12,13,42]. The present study elucidated that the FIB4 index had better prognostic value for adverse outcome in patients with HF than any single LFT like AST or ALT. Although the FIB4 index includes age as a component, AST/(platelets count [$10^3/\mu L$] $\times \sqrt{}$ALT) (excluding age from the FIB4 index) was also associated with the 12-month composite endpoint (HR 2.804 [95% CI: 1.216–6.467]; $p = 0.016$) in multivariate COX regression model. This means that, whereas age is well known as a strong predictor of poor outcome in patients with AHF [43], the FIB4 index excluding age independently could significant predict adverse outcomes. From a clinical point of view, the FIB4 index is a parameter that can be more easily used and effective for predicting prognosis in patients with AHF than other hepatic parameters.

We should describe several limitations in the present study. These limitations mainly derive from the retrospective nature of the study. There was insufficient data available on physical findings such as edema, jugular vein distention, and cold extremities. In addition, right heart catheterization parameters at admission were not analyzed because these examinations were not routinely performed. Thus, it is unclear which hemodynamic abnormality (hypoperfusion or congestion) mainly contributes to higher FIB4 index at admission. This should be identified in a prospective study. Second, we also could not evaluate the relationship between the FIB4 index and the severity of liver fibrosis because of the lack of some biomarkers which could indicate liver fibrosis. Finally, hemodynamic abnormalities due to AHF do not necessary reflect the changes in the FIB4 index linearly. The susceptibility of hepatic injury by abnormal hemodynamics is thought to differ in each case. It remains unclear whether the extent of hemodynamic abnormality due to AHF or the susceptibility of hepatic injury by abnormal hemodynamics more strongly defines the FIB4 index at admission. However, this susceptibility itself may be associated with adverse outcomes in patients with AHF.

## 5. Conclusion

The FIB4 index, which is a simple, inexpensive, and non-invasive marker reflecting hepatic disorder, is associated with the risk of all-cause mortality or rehospitalization due to HF in patients with AHF. Our findings revealed that the FIB4 index at admission has good predictability of adverse outcomes.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.09.056.

## Disclosures

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## Declaration of Competing Interest

None.

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