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ORIGINAL ARTICLE

Associations of the fibrosis-4 index with left atrial low-voltage areas and arrhythmia recurrence after catheter ablation: cardio-hepatic interaction in patients with atrial fibrillation

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Abstract

Background: The relationship between liver fibrosis and left atrial (LA) remodeling in atrial fibrillation (AF) remains uncertain. We examined the associations between the fibrosis-4 (FIB4) index, an indicator of liver fibrosis, and both LA low-voltage areas (LVAs) on electroanatomic mapping and AF recurrence postablation.

Methods: We recruited 343 patients who underwent radiofrequency catheter ablation (RFCA) or cryoballoon ablation (CBA) for AF. First, the association between the FIB4 index and LA LVAs (<0.5 mV) was evaluated in RFCA using electroanatomic mapping ($n = 214$). Next, the utility of a FIB4 index ≥1.3, recommended cut-off value of liver fibrosis, was verified to assess the risk for AF recurrence in CBA without additional LVA ablation ($n = 129$).

Results: Patients with a FIB4 index ≥1.3 had a higher prevalence of LA LVAs (>5 cm^2) compared to those without. Additionally, the quantitative size of LVAs showed a positive correlation with the FIB4 index ($R = .642$, $p < .001$). In multivariate logistic models, a FIB4 index ≥1.3 was related to the presence of LVAs after adjusting for LA diameter, right atrial end-systolic area, and nonparoxysmal AF (odds ratio 2.508; $p = 0.039$). In CBA, AF recurrence rate was 13.1% during 3–12 months postablation. In multivariate Cox models, a FIB4 index ≥1.3 was an important predictor of AF recurrence (hazard ratio 3.796; $p = .037$), suggesting that LVAs might be associated with AF recurrence after CBA.

Conclusion: The FIB4 index was a novel predictor of the existence of LA LVAs on electroanatomic mapping and AF recurrence after CBA.

KEYWORDS
ablation, atrial fibrillation, cardio-hepatic interaction, fibrosis-4 index, low-voltage areas

1 | INTRODUCTION

Trigger elimination by pulmonary vein isolation (PVI) is a proven rhythm control treatment for atrial fibrillation (AF).[1,2] Nevertheless, in selective patients, additional approaches are required to maintain sinus rhythm after PVI. Left atrial (LA) remodeling involving atrial fibrosis has a significant impact on the pathogenesis of AF,[3] and low-voltage areas (LVAs), determined by electroanatomic mapping, are considered to indicate atrial remodeling process in patients with paroxysmal and persistent AF.[4,5] Accordingly, additional ablation of LVAs is one of the key approaches for preventing arrhythmia recurrence in any type of AF. Although PVI can be performed using balloon-based ablations,[6] radiofrequency catheter ablation (RFCA) is generally needed for additional ablation of LVAs. Therefore, preprocedural predictors for the presence of LVAs are required to enable the selection of appropriate ablation devices.

It has been reported that cardiovascular disease is related to multi-organ dysfunction, and liver diseases, such as nonalcoholic fatty liver disease and liver cirrhosis, are correlated with an increased risk of AF.[7,8] However, the association of liver fibrosis with LA remodeling in AF remains unclear. We hypothesized that liver fibrosis is related to the existence of LA LVAs on electroanatomic mapping and AF recurrence after PVI. The fibrosis-4 (FIB4) index, which is derived from the patient's age, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count, has been indicated as a reliable marker of liver fibrosis.[9] Thus, preprocedural assessment of the FIB4 index may provide crucial information on the existence of LA LVAs and the necessity of additional LVA ablation after PVI. The purpose of our study was to (1) evaluate the association of the FIB4 index with LA LVAs in patients who underwent RFCA using electroanatomic mapping, and (2) verify the utility of the FIB4 index for the prediction of AF recurrence after PVI in patients who underwent cryoballoon ablation (CBA) without using electroanatomic mapping.

2 | METHODS

2.1 | Study design

This study was designed in 2 parts. First, we investigated the association of the FIB4 index with LA LVAs in patients who underwent RFCA using electroanatomic mapping. Second, we verified the utility of the FIB4 index to evaluate the risk for AF recurrence after PVI in patients who underwent CBA without using electroanatomic mapping.

2.2 | Study population

This retrospective study enrolled 448 consecutive patients, who successfully underwent their first PVI using RFCA or CBA for paroxysmal and nonparoxysmal AF at Fukushima Medical University Hospital between May 2019 and March 2022 (Figure 1). Paroxysmal and nonparoxysmal (persistent or longstanding persistent) AF were defined based on the current guidelines.[10] The selection between RFCA and CBA was performed based on the operator's judgment according to each patient's background. In the present study, 65 patients with heart failure, defined based on the heart failure guidelines,[11] 29 patients with preexisting liver disease (hepatitis, cirrhosis, or bile duct disease), five patients on hemodialysis, and two patients with congenital heart disease were excluded. Additionally, four patients were excluded during follow-up because of loss of contact. Finally, in the present study, 343 patients (249 males, mean age 64 ± 10 years) were registered. All subjects provided written informed consent. The Fukushima Medical University Ethics Committee has approved the study protocol (approval number 2020-311).

2.3 | Clinical comorbidities, echocardiography, and laboratory data

Data on clinical comorbidities, echocardiography, and laboratory tests were obtained 1 day before PVI. Echocardiography was recorded by experienced echocardiographers with standard techniques at our hospital. In the echocardiographic parameters, LA diameter, right atrial end-systolic area, and left ventricular ejection fraction were evaluated. In the laboratory test, platelet count and estimated glomerular filtration rate, as well as the levels of AST, and ALT were assessed.

2.4 | PVI procedure for AF

The PVI procedure was performed using RFCA or CBA as described previously.[12–14] Antiarrhythmic drugs were discontinued for a minimum of five half-lives before the procedure. Regarding PVI using

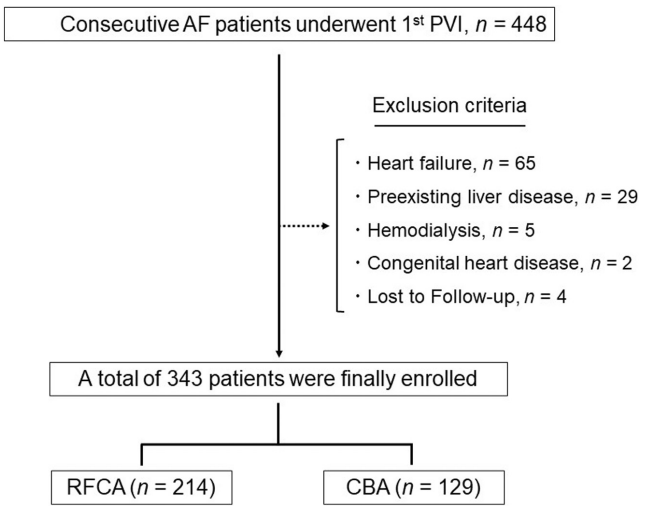

FIGURE 1 Patient flow diagram. AF, atrial fibrillation; CBA, cryoballoon ablation; FIB4, fibrosis-4; PVI, pulmonary vein isolation; RFCA, radiofrequency catheter ablation.

RFCA, the creation of LA geometry was performed using a 20-pole catheter (LassoNaV or PentaRay, Biosense Webster, Inc., Diamond Bar, CA), followed by PVI using ThermoCool SmartTouch SF ablation catheter (Biosense Webster) under the CARTO system guidance (Biosense Webster). A point-by-point RFCA was performed using an ablation index module (Biosense Webster).[12–14] If AF was sustained following PVI, electrical cardioversion was used to restore sinus rhythm. The completion of PVI was determined as the creation of a bidirectional conduction block between the left atrium and PVs. After the completion of PVI, detailed voltage mapping was performed as described previously.[14] The CARTO confidence module was used to collect mapping points automatically using the following setups: cycle length filtering, ±30 ms; local activation time stability, <3 ms; position stability, <2 mm; and density, <1 mm. An LA geometry was created using fast anatomical mapping, and the color interpolation threshold for mapping points was set at 5. In the present study, LVA is defined as a region with a bipolar peak-to-peak voltage amplitude of <0.5 mV that covers >5 cm^2 of the left atrium.[14] Ablation of LVAs or nonPV foci, and isolation of superior vena cava were added at the operator's judgment based on the background of each patient.

In PVI using CBA, following a transseptal puncture, a fourth-generation cryoballoon (Arctic Front Advance, Medtronic, Minneapolis, MN) was inserted into the PV ostium over a 10-polar spiral mapping catheter (Achieve, Medtronic), and the complete PV ostium occlusion was confirmed using contrast medium injection. A 180–240 s freezing with a minimum temperature of −60°C was performed in each vein for the risk reduction of PV stenosis,[15] and no additional CBA was done after the PVI. The completion of PVI was determined as the creation of a bidirectional conduction block between the left atrium and PVs.[13]

Cavotricuspid isthmus ablation was added at the operator's judgment based on the background of each patient after PVI using RFCA or CBA.

2.5 | Assessment of the FIB4 index

The FIB4 index was calculated as follows: age (years) × AST (U/L)/[ALT (U/L)$^{1/2}$ × platelet count (10^9/L)].[9] A FIB4 index of ≥1.3 has been proposed as a reliable indicator for liver fibrosis in patients with nonalcoholic fatty liver disease,[16] and assessment of the FIB4 index is recommended for the initial screening of liver fibrosis by general physicians.[17] The patients were classified into two groups according to their FIB4 index: the high FIB4 index group of ≥1.3 and the low FIB4 index group of <1.3. Clinical data were compared between the two groups of patients who received RFCA or CBA.

2.6 | Clinical follow-up

Following the ablation procedure, the patients were observed at 1, 3, 6, and 12 months. Depending on the physician's judgment, antiarrhythmic medications were additionally provided following the procedure and discontinued 3 months after the procedure in all patients with paroxysmal AF. Patients who were unable to attend outpatient follow-up at our institution were observed by their referring physicians and were also addressed over the telephone regarding recurrent arrhythmias and symptoms. The definition of AF recurrence was determined as any atrial tachyarrhythmia lasting more than 30 s on a 12-lead electrocardiogram or 24-h Holter recording during 3–12 months postablation.

2.7 | Statistical analysis

Mean values ± SD were used to represent normally distributed data, and medians and interquartile ranges were used to represent non-normally distributed data. In categorical data, absolute values and percentages were provided. In the normally distributed data, to evaluate the differences between the two groups, an independent sample *t*-test was used. In the non-normally distributed data, the Mann–Whitney *U* test was used to compare the differences between the two groups. The chi-square or Fisher's exact test was used to evaluate categorical data. In patients who underwent RFCA, logistic regression analysis was used to elucidate the association between clinical parameters and LA LVAs. In the logistic regression analysis, we chose the following clinical factors, which are known as predictors of LVAs (female gender, hypertension, diabetes, estimated glomerular filtration rate, nonparoxysmal AF, and LA diameter).[18] In patients who underwent CBA, the Kaplan–Meier method and a log-rank test were utilized to evaluate the event-free survival of patients with AF recurrence. Cox proportional hazard regression analysis was used to elucidate the association between the FIB4 index and AF recurrence. In the Cox regression analysis, the variables were chosen in the same way as the logistic regression analysis. The area under the curve was calculated to assess the prediction ability regarding LVAs and AF recurrence using the receiver operating characteristic curve analysis. Additionally, DeLong tests were conducted to compare the prediction ability between the FIB4 index and CHA_2DS_2-VASc score. Statistical significance was defined as *p* values of <.05. Statistical analyses were carried out using IBM SPSS statistics version 28.0 (IBM, Armonk, NY, USA) and Python version 3.10.12 (Python Software Foundation, Wilmington, DE, USA).

3 | RESULTS

3.1 | Association of the FIB4 index with LA LVAs in RFCA using electroanatomic mapping

A comparison of clinical features between high and low FIB4 indices in RFCA is summarized in Table 1. Age, female gender, and the prevalence of diabetes were higher in the high FIB4 index group than in the low FIB4 index group. The number of patients with

TABLE 1 The comparison of clinical characteristics between high and low FIB4 indices in RFCA.

Total ($n=214$)	Low FIB4 index ($n=79$)	High FIB4 index ($n=135$)	p value
Age (years)	56.3 ± 8.0	68.1 ± 8.3	<.001
Female gender *n* (%)	13 (16.4%)	39 (28.8%)	.041
Body mass index (kg/m^2)	24.0 (22.5–27.2)	23.4 (21.6–26.7)	.080
Hypertension *n* (%)	41 (51.8%)	83 (61.4%)	.171
Diabetes *n* (%)	7 (8.8%)	34 (25.1%)	.004
Hyperlipidemia *n* (%)	55 (69.6%)	81 (60.0%)	.158
Stroke/TIA *n* (%)	4 (5.0%)	13 (9.6%)	.300
Nonparoxysmal AF *n* (%)	42 (53.1%)	68 (50.3%)	.693
Echocardiography			
LA diameter (mm)	39.0 (36.0–44.0)	43.0 (38.0–49.0)	<.001
RA end-systolic area (cm^2)	16.0 (14.0–20.0)	19.0 (17.0–23.0)	<.001
LVEF (%)	64.0 (60.0–66.0)	62.0 (59.0–66.0)	.184
Laboratory data			
eGFR (mL/min/1.73 m^2)	61.7 (56.2–68.2)	57.7 (49.8–65.3)	.007
Platelet count (10^9/L)	242.0 (217.0–285.0)	204.0 (176.0–229.0)	<.001
AST (U/L)	20.0 (17.0–23.0)	24.0 (20.0–29.0)	<.001
ALT (U/L)	22.0 (17.0–31.0)	19.0 (16.0–27.0)	.129
BNP (pg/mL)	23.3 (12.3–54.8)	58.5 (26.3–116.4)	<.001
Additional ablation			
CTI ablation *n* (%)	25 (31.6%)	48 (35.5%)	.560
SVC isolation *n* (%)	11 (13.9%)	28 (20.7%)	.213
NonPV foci ablation *n* (%)	3 (3.7%)	12 (8.8%)	.179
LVA ablation *n* (%)	2 (2.5%)	19 (14.0%)	.007

Abbreviations: AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CTI, cavotricuspid isthmus; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4; LA, left atrial; LVA, low-voltage area; LVEF, left ventricular ejection fraction; PV, pulmonary vein; RA, right atrial; RFCA, radiofrequency catheter ablation; SVC, superior vena cava; TIA, transient ischemic attack.

nonparoxysmal AF was comparable in both groups. In echocardiography, the values of LA diameter and right atrial end-systolic area were higher in the high FIB4 index group compared with the low FIB4 index group, but no significant difference was found in left ventricular ejection fraction. In laboratory data, AST was higher, and the estimated glomerular filtration rate and platelet count were lower in the high FIB4 index group than in the low FIB4 index group. In the present study, type IV collagen 7S was measured as a serum liver fibrosis marker,[17] and it was higher in the high FIB4 index group than in the low FIB4 index group (4.1 ± 1.1 vs. 3.8 ± 0.8 ng/mL, $p=.015$).

The procedural results of RFCA are displayed in Table 1. All patients obtained complete isolation on both sides of the PV. Additional ablation of LVAs was higher in the high FIB4 index group than in the low FIB4 index group ($p=.007$), but no significant differences were found in other additional ablations.

The presence of LA LVAs was found in 41 patients (19.1%), and it was higher in the high FIB4 index group than in the low FIB4 index group (24.4% vs. 10.1%, $p=.011$). In patients with LA LVAs, the quantitative size of LVAs was larger in the high FIB4 index group than in the low FIB4 index group [median 7.4 cm^2 (interquartile range 5.2–16.9) vs. median 5.1 cm^2 (interquartile range 5.0–7.3), $p=.041$], as demonstrated in Figure 2A. In the correlation analysis (Figure 2B), the quantitative size of LVAs showed a positive correlation with the FIB4 index ($R=.642$, $p<.001$).

We performed logistic regression analysis to clarify the association of the FIB4 index with the presence of LVAs (Table 2). In univariate analysis, nonparoxysmal AF, LA diameter, right atrial end-systolic area, and a FIB4 index ≥1.3 were significantly related to the presence of LVAs. In multivariate analysis, a FIB4 index ≥1.3 was independently correlated with the presence of LVAs after adjusting for nonparoxysmal AF, LA diameter, and right atrial end-systolic area (odds ratio, 2.508; $p=.039$).

In the prediction ability regarding LA LVAs, the area under the curve of the FIB4 index and CHA_2DS_2-VASc score was 0.66 and 0.58, respectively. DeLong test revealed that there was no significant difference between the FIB4 index and CHA_2DS_2-VASc score ($p=.997$).

Since age is a part of the FIB4 index, an interaction between a FIB4 index ≥1.3 and the prevalence of older age (>65 years) for the presence of LA LVAs was assessed by the logistic regression analysis. As a result, the interaction p-value was .555 (Table S1).

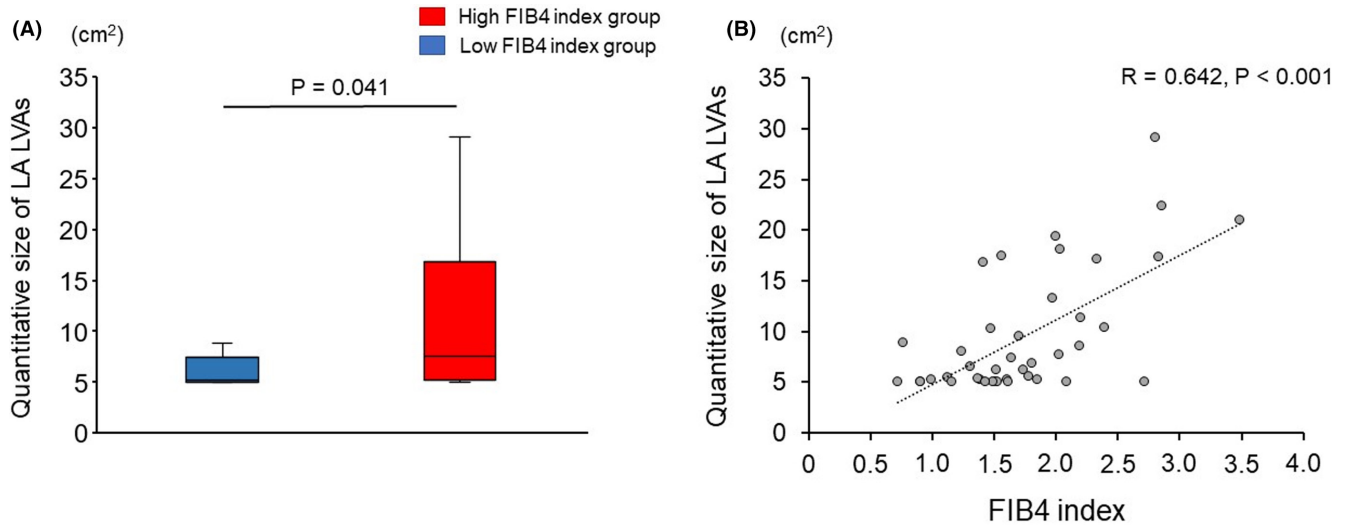

FIGURE 2 Relationship between the FIB4 index and quantitative size of LA LVAs in patients with LA LVAs ($n = 41$). (A) Difference in quantitative size of LVAs between the high and low FIB4 index groups. (B) Correlation of the FIB4 index and quantitative size of LVAs. FIB4, fibrosis-4; LA, left atrial; LVAs, low-voltage areas.

TABLE 2 Logistic regression analysis for the presence of low-voltage areas.

	Univariate OR (95% CI)	*p* value	Multivariate OR (95% CI)	*p* value
Female gender	1.842 (0.880–3.857)	.105		
Body mass index (kg/m^2)	1.038 (0.945–1.140)	.440		
Hypertension	0.806 (0.406–1.598)	.537		
Diabetes	0.676 (0.263–1.734)	.415		
Nonparoxysmal AF	2.745 (1.315–5.730)	.007	2.257 (1.013–5.029)	.047
eGFR (mL/min/1.73 m^2)	1.001 (0.974–1.028)	.961		
LA diameter (mm)	1.080 (1.027–1.135)	.003	1.043 (0.983–1.107)	.165
RA end-systolic area (cm^2)	1.099 (1.031–1.171)	.004	1.029 (0.951–1.113)	.476
FIB4 index ≥1.3	2.871 (1.252–6.583)	.013	2.508 (1.046–6.011)	.039

Abbreviations: AF, atrial fibrillation; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4; LA, left atrial; OR, odds ratio; RA, right atrial.

3.2 | Association of the FIB4 index with AF recurrence in CBA without additional LVA ablation

The comparison of clinical features between high and low FIB4 indices in CBA is summarized in Table 3. Age was higher in the high FIB4 index group than in the low FIB4 index group. In echocardiography, the value of right atrial end-systolic area was higher in the high FIB4 index group compared with the low FIB4 index group, but no significant differences were found in other variables. In laboratory data, AST was higher, and the estimated glomerular filtration rate and platelet count were lower in the high FIB4 index group than in the low FIB4 index group.

All patients obtained complete isolation on both sides of the PV, and no additional touch-up RFCA was necessary for complete isolation. The number of cavotricuspid isthmus ablation was comparable in both groups (Table 3).

The recurrence of AF occurred in 17 patients (13.1%), and the recurrence rate was higher in the high FIB4 index group than in the low FIB4 index group (20.2% vs. 5.0%, $p = .017$). As shown in Figure 3, the high FIB4 index group had a higher AF recurrence rate compared with the low FIB4 index group in the Kaplan–Meier analysis (log-rank $p = .012$).

We performed Cox regression analysis to clarify the association of the FIB4 index with AF recurrence (Table 4). In univariate analysis, female gender, nonparoxysmal AF, and a FIB4 index ≥1.3 were significantly related to AF recurrence. In multivariate analysis, a FIB4 index ≥1.3 was independently correlated with AF recurrence after adjusting for the female gender and nonparoxysmal AF (hazard ratio, 3.796; $p = .037$).

In the prediction ability regarding AF recurrence, the area under the curve of the FIB4 index and CHA_2DS_2-VASc score was 0.64 and 0.69,

TABLE 3 The comparison of clinical characteristics between high and low FIB4 indices in CBA.

Total ($n=129$)	Low FIB4 index ($n=60$)	High FIB4 index ($n=69$)	p value
Age (years)	58.8 ± 11.7	71.0 ± 8.2	<.001
Female gender *n* (%)	16 (26.6%)	26 (37.6%)	.183
Body mass index (kg/m^2)	23.7 (21.1–26.7)	23.3 (20.1–25.2)	.127
Hypertension *n* (%)	35 (58.3%)	44 (63.7%)	.527
Diabetes *n* (%)	8 (13.3%)	13 (18.8%)	.477
Hyperlipidemia *n* (%)	45 (75.0%)	44 (63.7%)	.169
Stroke/TIA *n* (%)	4 (6.6%)	8 (11.5%)	.379
Nonparoxysmal AF *n* (%)	2 (3.3%)	3 (4.3%)	1.000
Echocardiography			
LA diameter (mm)	37.0 (33.0–41.7)	39.0 (35.0–44.0)	.157
RA end-systolic area (cm^2)	15.0 (13.0–18.7)	18.0 (14.0–20.0)	.006
LVEF (%)	66.0 (61.0–68.0)	64.0 (60.0–68.0)	.564
Laboratory data			
eGFR (mL/min/1.73 m^2)	66.6 (58.1–71.6)	61.7 (52.7–69.8)	.037
Platelet count (10^9/L)	260.0 (243.0–289.7)	215.0 (186.0–249.0)	<.001
AST (U/L)	20.0 (17.0–24.0)	24.0 (21.0–28.0)	<.001
ALT (U/L)	21.5 (16.2–31.5)	20.0 (15.0–27.0)	.239
BNP (pg/mL)	17.7 (11.0–44.4)	37.3 (17.9–81.6)	<.001
Additional ablation			
CTI ablation *n* (%)	16 (26.6%)	27 (39.1%)	.134

Abbreviations: AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CBA, cryoballoon ablation; CTI, cavotricuspid isthmus; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4; LA, left atrial; LVEF, left ventricular ejection fraction; RA, right atrial; TIA, transient ischemic attack.

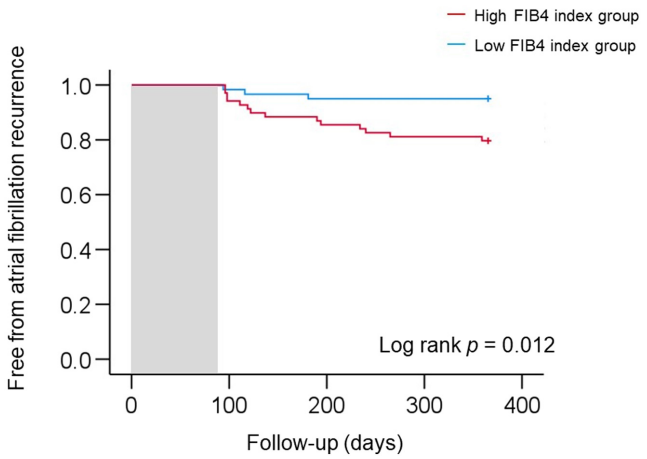

FIGURE 3 Association of the fibrosis-4 index with atrial fibrillation recurrence in patients treated with cryoballoon ablation ($n=129$).

respectively. DeLong test revealed that there was no significant difference between the FIB4 index and CHA_2DS_2-VASc score ($p=.998$).

Since age is a part of the FIB4 index, an interaction between a FIB4 index ≥1.3 and the prevalence of older age (>65 years) for AF recurrence was assessed by Cox proportional hazard regression analysis. As a result, the interaction p-value was .381 (Table S2).

4 | DISCUSSION

In this work, we examined the association of the FIB4 index with LA LVAs using electroanatomic mapping. Furthermore, we verified the efficacy of the FIB4 index in assessing risk for AF recurrence after PVI in patients who underwent CBA without using electroanatomic mapping. The key findings were that: (1) the FIB4 index was positively correlated to the quantitative size of LA LVAs, and a FIB4 index ≥1.3 was significantly related to the presence of LA LVAs and (2) a FIB4 index ≥1.3 was a reliable indicator of AF recurrence after PVI using CBA without additional LVA ablation. Preprocedural assessment of the FIB4 index may provide crucial information on the presence of LA LVAs and the selection of suitable devices for AF ablation.

4.1 | The FIB4 index and LA LVAs

Cardiovascular disease is often associated with multiple organ dysfunctions. AF frequently complicates chronic kidney disease, and the estimated glomerular filtration rate is a useful indicator of renal dysfunction associated with LA remodeling in AF.[18,19] Also, AF and liver disease coexist because of complex cardio-hepatic interactions.[7,8] The FIB4 index is calculated from the patient's age, AST, ALT, and platelet count,[9] and a FIB4 index of ≥1.3 has been

TABLE 4 Cox regression analysis for associations of the FIB4 index with AF recurrence.

	Univariate HR (95% CI)	*p* value	Multivariate HR (95% CI)	*p* value
Female gender	3.201 (1.218–8.415)	.018	2.784 (1.048–7.399)	.040
Hypertension	3.113 (0.894–10.834)	.074		
Diabetes	1.095 (0.315–3.812)	.886		
Nonparoxysmal AF	7.957 (2.255–28.076)	.001	7.263 (1.989–26.520)	.003
eGFR (mL/min/1.73 m^2)	0.966 (0.931–1.002)	.065		
LA diameter (mm)	1.065 (0.993–1.142)	.079		
RA end-systolic area (cm^2)	1.018 (0.913–1.135)	.752		
FIB4 index ≥1.3	4.317 (1.240–15.027)	.022	3.796 (1.085–13.286)	.037

Abbreviations: AF, atrial fibrillation; CI, confidence interval; eGFR, estimated glomerular filtration rate; FIB4, fibrosis-4; HR, hazard ratio; LA, left atrial; RA, right atrial.

suggested as a reliable indicator for liver fibrosis in patients with nonalcoholic fatty liver disease.[16] However, the relationship between the FIB4 index and liver fibrosis has not been clarified in patients with AF. Type IV collagen 7S is useful for the assessment of subclinical liver fibrosis.[17] In patients with heart failure, it has been demonstrated that type IV collagen 7S is associated with both liver fibrosis assessed by shear wave elastography in abdominal sonography[20] and the FIB4 index.[21] Therefore, in the present study, type IV collagen 7S was measured as a serum liver fibrosis marker. Consequently, type IV collagen 7S was higher in the high FIB4 index group than in the low FIB4 index group. Further study is required to elucidate the association between high FIB4 index and liver fibrosis in patients with AF. Currently, the FIB4 index is considered a useful indicator for the severity of cardiac overload and cardiovascular risk in heart failure.[21,22] Therefore, patients with heart failure were excluded from this work, and the association of the FIB4 index with LA remodeling in AF was investigated. In the present study, the high FIB4 index group had lower eGFR and platelet count levels, higher AST levels, but similar ALT levels when compared to the low FIB4 index group. Our results were concordant with previous reports.[9,23]

Atrial remodeling, including atrial fibrosis, is an essential arrhythmogenic substrate for the incidence and perpetuation of AF.[24] Although late gadolinium enhancement on cardiac magnetic resonance imaging can reveal atrial fibrosis before the ablation procedure,[25] the utility of this method is limited in a thin-walled atrium and patients with renal dysfunction or cardiac implantable electronic devices. The extent of atrial remodeling is determined by LVAs on electroanatomic mapping,[3] and the DR-FLASH score (based on diabetes mellitus, hypertension, renal dysfunction, female gender, age >65 years, persistent form of AF, and LA diameter >45 mm) has been proposed as the noninvasive indicator of LVAs before ablation procedures.[18] However, the usefulness of the FIB4 index as a predictor of LVAs has not yet been verified. In the present study, the FIB4 index was positively correlated to the quantitative size of LA LVAs ($R = .642$, $p < .001$), suggesting that liver fibrosis and LA remodeling might be closely associated with each other. Furthermore, the multivariate logistic regression analysis showed a significant association of a FIB4 index ≥1.3 with the presence of LVAs independent of nonparoxysmal AF, LA diameter, and right atrial end-systolic area. This finding indicates that the FIB4 index is a simple and noninvasive preprocedural predictor of the presence of LA LVAs. Although age is a part of the FIB4 index, an interaction between a FIB4 index ≥1.3 and the prevalence of older age (>65 years) for the presence of LA LVAs was not found ($p = .555$).

4.2 | The FIB4 index and AF recurrence

It is considered that LVAs on electroanatomic mapping play important roles in identifying the pathogenesis of AF,[3] and the ablation of LA LVAs in addition to PVI contributes to reducing the recurrence rate of nonparoxysmal AF.[26] Additionally, nonPV triggers, related to the recurrence of AF, are presumed to arise from LA LVAs in paroxysmal AF.[27] Therefore, the prediction of LA LVAs before the procedure is useful to determine the ablation strategy for any type of AF.

It was reported that advanced liver fibrosis, assessed by the FIB4 index, was related to AF recurrence after catheter ablation in patients with nonalcoholic fatty liver disease.[28] However, the causes of AF recurrence have not yet been clarified in patients with advanced liver fibrosis. In patients with AF, it is considered that the overexpression of transforming growth factor-β, an activator of tissue fibrosis, maybe a common underlying mechanism of advances in both liver fibrosis and LA remodeling.[29,30] Therefore, LA LVAs may be one of the causes of AF recurrence after PVI in patients with advanced liver fibrosis. In the present study, the association of the FIB4 index with AF recurrence was assessed in patients who underwent PVI using CBA to avoid the influence of additional LVA ablation. Accordingly, in multivariate Cox models, a FIB4 index ≥1.3 was found to be an independent predictor for AF recurrence, with a hazard ratio of 3.796. These results suggest that liver fibrosis might be related to the presence of LA LVAs and AF recurrence after PVI using CBA without additional LVA ablation.

In this work, the association between additional LVA ablation and AF recurrence could not be assessed in patients who underwent RFCA because not all patients with LA LVAs received additional ablation. Further study is required on the effects of additional LVA ablation on AF recurrence in patients with a high FIB4 index.

4.3 | Clinical implication

Our study results revealed that the FIB4 index was a reliable indicator of the existence of LA LVAs on electroanatomic mapping and AF recurrence after PVI using CBA. Balloon-based ablation has been established as a durable PVI approach. However, when substrate modification targeting LVAs is performed beyond PVI, additional approaches with RFCA are generally required. Therefore, preprocedural assessment of the FIB4 index provides useful information in determining appropriate devices for AF ablation.

4.4 | Limitations

There are some limitations to the present study. First, this study was carried out with data from a relatively small number of participants from a single institution. Second, because of the lack of abdominal sonography data, the severity of liver fibrosis or the etiology of high FIB4 index could not be evaluated in the study population. Third, age is an important predictor of atrial fibrosis, AF occurrence, and recurrence after catheter ablation. We assessed interactions between a FIB4 index ≥1.3 and the prevalence of older age (>65 years) regarding the prediction of LVAs and AF recurrence. As a result, interaction *p* values were not significant in LVAs and AF recurrence. However, it was difficult to clarify the predictive value of the FIB-4 index by matching all groups regarding age because of the small sample size. Finally, the characteristics of high and low FIB4 index groups were different between the patients who underwent RFCA and CBA. In the present study, the selection between RFCA and CBA was performed at the operator's judgment. For the correction of selection bias, we conducted multivariate analyses to investigate the associations of the FIB4 index with both LA LVAs and AF recurrence.

5 | CONCLUSIONS

The FIB4 index, an indicator of liver fibrosis, was significantly associated with LA LVAs on electroanatomic mapping. Furthermore, a FIB4 index ≥1.3 was an independent predictor of AF recurrence in patients who underwent CBA without additional LVA ablation. Preprocedural assessment of the FIB4 index may be useful for determining the appropriate strategy and suitable devices.

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CONFLICT OF INTEREST STATEMENT

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ETHICS STATEMENT

The Fukushima Medical University ethics committee accepted the study protocol (approval number: 2020-311).

INFORMED CONSENT

All participants in the study provided informed consent.

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SUPPORTING INFORMATION

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

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