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Prognostic Value of Fibrosis-4 in Acute Ischemic Stroke Patients Undergoing Intravenous Thrombolysis

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Purpose: Although recombinant tissue plasminogen activator (rt-PA) treatment is efficient in patients with acute ischemic stroke (AIS), a significant percentage of patients who received rt-PA intravenous thrombolysis (IVT) do not achieve a good prognosis. Therefore, the factors that affect the poor prognosis of patients with IVT are needed. The Fibrosis-4 (FIB-4) index has been used as a liver fibrosis biomarker. We aimed to investigate the relationship between the FIB-4 index and functional outcomes in patients with AIS receiving IVT.

Patients and Methods: This study prospectively included consecutive patients with AIS receiving IVT between April 2015 and May 2022. We collected clinical and laboratory data and calculated the FIB-4 index. Clinical outcome was poor functional outcome (mRS ≥3) at 3 months after IVT. Multivariate logistic regression analysis was used to analyze the association between FIB-4 and outcome. We explored the interactive effect of FIB-4 and dyslipidemia on poor outcomes, and subgroup analysis was performed. Furthermore, an individualized prediction model based on the FIB-4 for functional outcome was established in the dyslipidemia group.

Results: A total of 1135 patients were included, and 41.50% had poor 3-month outcomes. After adjusted by other variants that *P* value <0.05 in univariable analysis, FIB-4 was independently associated with poor outcomes (OR=1.420; 95% CI: 1.113–1.812; *P*=0.004). There was a significant interaction between FIB-4 and dyslipidemia on poor outcome (*P*=0.036), and the independent association between FIB-4 and poor outcome was maintained in the dyslipidemia subgroup (OR=1.646; 95% CI: 1.228–2.206; *P*=0.001). Furthermore, in the dyslipidemia group, the FIB-4-based prediction model had good predictive value (the AUC of the training and validation sets were 0.767 and 0.708, respectively), good calibration (*P*-values for the Hosmer–Lemeshow test >0.05), and clinical usefulness.

Conclusion: FIB-4 is an independent risk factor for poor outcomes in IVT patients with dyslipidemia, which can be used as a simple predictor of their prognosis.

Keywords: Fibrosis-4, acute ischemic stroke, intravenous thrombolysis, prognosis, dyslipidemia

Introduction

Stroke is the second-leading cause of death worldwide, with ischemic stroke (IS) accounting for the majority of cases.[1,2] Recombinant tissue plasminogen activator (rt-PA) has been approved as a reperfusion treatment for patients with acute ischemic stroke (AIS) and can greatly improve survival and functional outcome.[3] Nonetheless, a significant percentage of patients who receive rt-PA intravenous thrombolysis (IVT) have a poor prognosis.[4] Therefore, there is a need for definitive indicators to predict the prognosis of AIS patients receive IVT treatment. Early assessment of risk factors for poor prognosis allows for the stratification of outcomes and more appropriate treatment management.

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Liver fibrosis is present in a large percentage of the general population[5,6] as well as a significant proportion of stroke patients.[7] Several studies have demonstrated that liver fibrosis plays an important role in both intracerebral hemorrhage and IS.[8,9] Growing evidence showed that the proportion of stroke patients increased with the elevated levels of liver fibrosis, and people with higher liver fibrosis levels had a higher risk of stroke even after adjusting for traditional cardiovascular risk factors.[10,11] Previous studies have shown that liver fibrosis is associated with the risk of IS[12] and is independently associated with long-term prognosis after IS.[7,13] Research of Fandler-Höfler et al reported that poor outcome after IS occurred in approximately 41.8% of the general population, but the presence of poor outcome after IS was found to be much higher (67.4%) among patients with liver fibrosis.[14] In addition, liver fibrosis and stroke have common pathophysiological mechanisms, such as dyslipidemia.[15,16] As one of the risk factors for stroke, dyslipidemia can lead to disturbances in intrahepatic lipid metabolism, and ultimately leads to liver fibrosis.[17,18] Therefore, the association between liver fibrosis and stroke warrants further investigation.

Liver fibrosis is frequently asymptomatic, and patients have normal aminotransferase levels.[19] Liver biopsy is the gold standard for assessing liver fibrosis. However, it is an invasive procedure with possible complications.[20] The Fibrosis-4 (FIB-4) index, calculated from age and blood test results, is considered a reliable non-invasive marker of liver fibrosis and has been clinically validated.[21,22] A recent study found that the FIB-4 is associated with symptomatic intracranial hemorrhage (sICH) and mortality after IVT.[23] The relationship between liver fibrosis and functional outcomes in patients undergoing IVT should be explored. Therefore, in the present study, we aimed to investigate the association between the FIB-4 index and prognosis in patients with AIS receiving IVT.

Materials and Methods

Study Population

We enrolled consecutive patients with AIS who received rt-PA IVT at First Hospital of Jilin University between April 2015 and May 2022. Patients were excluded if they met the following criteria: 1) had a final diagnosis of a stroke mimic; 2) received mechanical thrombectomy after IVT; 3) had a modified Rankin Scale (mRS) score >2 before the onset of the disease; 4) had self-reported or were diagnosed with severe liver disease; and 5) had incomplete laboratory tests or follow-up data. Patients with a clinical diagnosis of AIS confirmed on brain imaging and fulfilling local criteria for thrombolysis treatment administered within 4.5 hours of symptom onset receive low-dose (0.6 mg/kg; maximum dose is 60 mg; 15% intravenously injected within the first 1 min, 85% infused with infusion pump infusion for 1 hour) or standard-dose (0.9 mg/kg; maximum dose is 90 mg; 10% intravenously injected within the first 1 min, 90% infused with infusion pump infusion for 1 hour) intravenous rt-PA according to the Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders.[24]

Data Collection

The following data were prospectively collected and recorded in a well-established database: demographic and medical history including age, sex, cigarette smoking, alcohol consumption, atrial fibrillation, coronary heart disease, hypertension, diabetes mellitus, dyslipidemia, previous stroke, and previous use of statin. Dyslipidemia was defined as having at least one of the following criteria: total cholesterol (TC) ≥5.18 mmol/L, triglycerides (TG) ≥1.70 mmol/L, low-density lipoprotein cholesterol (LDL) ≥3.37 mmol/L, and high-density lipoprotein cholesterol (HDL) <1.04 mmol/L or receiving antidyslipidemic therapy.[25] Clinical data included baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP), baseline blood glucose, low-dose (0.6 mg/kg) thrombolysis, onset-to-needle time (ONT), platelet count, baseline National Institutes of Health Stroke Scale (NIHSS) score and sICH. Stroke subtypes were categorized as large artery atherosclerosis, small vessel occlusion, cardioembolism, or undetermined etiology.[26] The laboratory data obtained included the platelet count at admission and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels from fasting liver tests within 24 h of stroke onset. FIB-4 value was calculated using the following equation:

$$FIB-4=\frac{\text{age (years)}*\text{aspartate aminotransferase}\left(\frac{Units}{Liter}\right)}{\text{platelet count}\left(\frac{10^9}{Liter}\right)*\sqrt{\text{alanine aminotransferase}\left(\frac{Units}{Liter}\right)}}$$

The clinical outcome was a poor functional outcome at 3 months after IVT, defined as mRS ≥3.

Statistical Analysis

The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Categorical variables are expressed as frequencies and percentages. Continuous variables are presented as means ± standard deviation or median and interquartile range (IQR). Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U*-test, depending on the normality of distribution. Pearson χ^2 test was used for categorical variables.

Odds ratio (OR) and 95% confidence interval (CI) for the association between the FIB-4 and clinical outcome were analyzed using binary logistic analysis. The model in entire study population was adjusted by age, hypertension, baseline SBP, baseline NIHSS score, and stroke subtypes. The model in subgroup with dyslipidemia was adjusted by age, hypertension, diabetes mellitus, baseline blood glucose, baseline NIHSS score, and stroke subtypes. The model in subgroup without dyslipidemia was adjusted by age, baseline SBP, baseline NIHSS score, and stroke subtypes.

Furthermore, we explored the possible interactive effect between FIB-4 and poor outcomes in subgroups, including sex, alcohol consumption, atrial fibrillation, diabetes mellitus, and dyslipidemia. We use binary logistic analysis to perform a multiplicative interaction analysis between FIB-4 and covariates (including sex, alcohol consumption, atrial fibrillation, diabetes mellitus, and dyslipidemia). $P<0.05$ was considered statistically significant. Stratified analysis was performed based on statistically significant interactions. An individualized predictive model for functional outcomes was developed based on the FIB-4 index. The study population was randomly assigned to the training and validation sets in a 7:3 ratio. Variables with $P<0.05$ in the univariate analysis were included in the multivariate logistic regression analysis. A nomogram was constructed to predict personalized poor outcome probability based on the results of the multivariate analysis using a backward selection method in the training set. Discriminative performance was assessed using the receiver operating characteristic (ROC) curve and area under the curve (AUC), and calibration of the prediction model was assessed using the Hosmer–Lemeshow test. In addition, the clinical usefulness of the nomogram models was determined using decision curve analysis (DCA) to quantify the net benefit. Discrimination, calibration, and DCA were performed on both the training and validation sets.

Statistical analyses were performed using Stata 15.0. A two-sided *P* value <0.05 was considered statistically significant.

Results

Participant Characteristics

A total of 1135 patients who received rt-PA IVT were analyzed in our study. Figure 1 presents a flowchart of the study. The median age of the cohort was 63 years, and 72.25% of the patients were male. About 78.77% of the patients received standard-dose thrombolysis, and 21.23% received low-dose thrombolysis. At three months post-stroke, 41.50% of patients had poor outcomes. The median FIB-4 value was 1.660 (IQR, 1.205–2.249) of all patients. Clinical characteristics were stratified by the FIB-4 score (quartile 4 versus quartiles 1–3) to display the baseline characteristic distribution according to liver fibrosis levels, as shown in Table 1.

The Association of FIB-4 and Prognosis

Table 2 shows the clinical characteristics of patients stratified according to favorable and poor outcomes. FIB-4 levels were significantly higher in the poor outcome group than in the favorable outcome group [1.814 (IQR, 1.336–2.475) vs 1.564 (IQR, 1.154–2.049), $P<0.001$]. Patients with poor outcomes tended to have higher age, NIHSS score, SBP, glucose level, and a higher proportion of hypertension and diabetes mellitus. FIB-4 was significantly associated with a 3-month poor outcome in univariate analysis ($P<0.001$).

The results of univariable analysis in the entire study group are shown in Supplementary Table 1, indicating that the FIB-4 had a significant association with poor outcome (OR = 1.410, 95% CI: 1.239–1.605, $P<0.001$). Multiple logistic

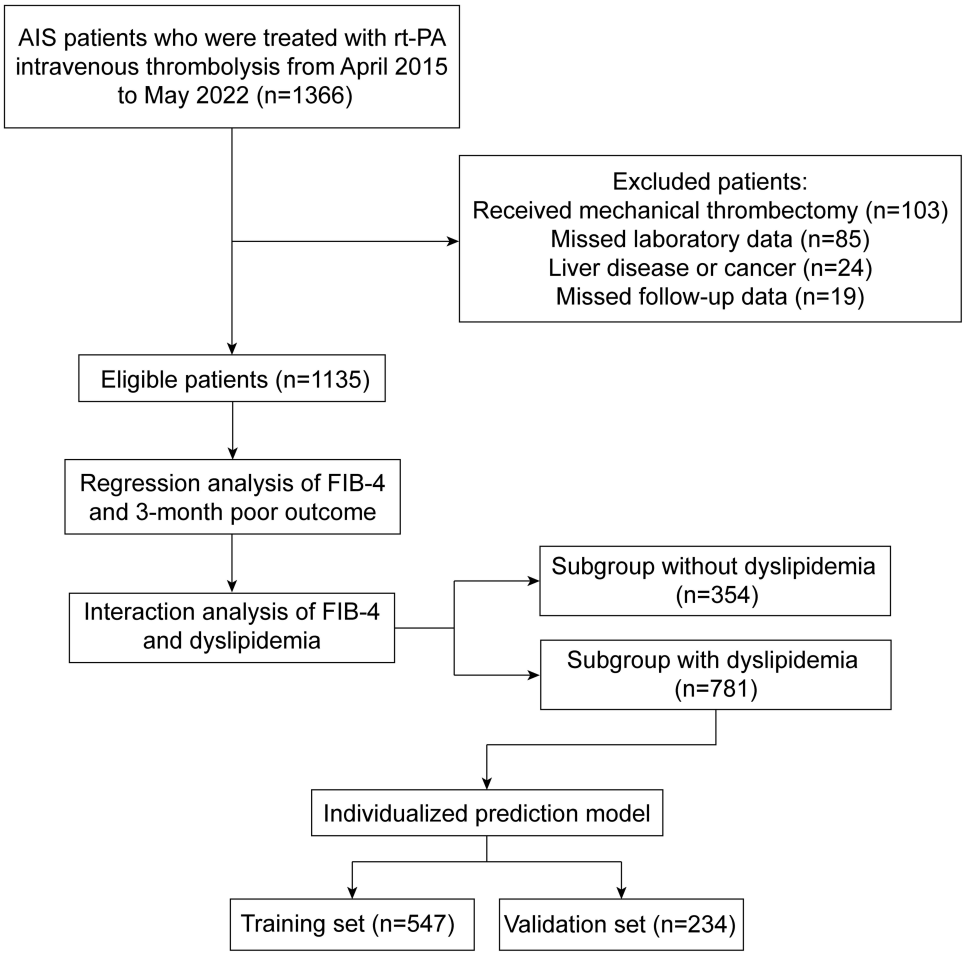

Figure 1 The flow chart of patient selection.
Abbreviations: AIS, acute ischemic stroke; rt-PA, recombinant tissue plasminogen activator; FIB-4, Fibrosis-4.

regression showed stable and significant independent associations of FIB-4 with 3-month poor outcome in model adjusted by other variants that *P* value <0.05 in univariable analysis, including age, hypertension, baseline SBP, baseline NIHSS score, and stroke subtypes (OR=1.420; 95% CI: 1.113–1.812; *P*=0.004) (Table 3; Figure 2).

Table 1 Clinical Characteristics of Patients, Stratified by FIB-4 Levels

	Total (n=1135)	FIB-4 (Q1–3) (n=852)	FIB-4 (Q4) (n=283)	t/Z/χ2	P
Age, years (IQR)	63 (54–70)	60 (53–66)	74 (67–78)	−17.584	<0.001
Male, n (%)	820 (72.25)	630 (73.94)	190 (67.14)	4.908	0.027
Cigarette smoking, n (%)	565 (49.78)	452 (53.05)	113 (39.93)	14.633	<0.001
Alcohol consumption, n (%)	471 (41.50)	373 (43.78)	98 (34.63)	7.327	0.007
Hypertension, n (%)	578 (50.93)	433 (50.82)	145 (51.24)	0.015	0.904
Diabetes mellitus, n (%)	221 (19.47)	168 (19.72)	53 (18.73)	0.133	0.715
Coronary heart disease, n (%)	220 (19.38)	146 (17.14)	74 (26.15)	11.042	0.001
Atrial fibrillation, n (%)	157 (13.83)	82 (9.62)	75 (26.50)	50.768	<0.001
Previous stroke, n (%)	185 (16.30)	141 (16.55)	44 (15.55)	0.156	0.693
Previous use of statin, n (%)	34 (3.00)	28 (3.29)	6 (2.12)	−0.997	0.319
Dyslipidemia, n (%)	781 (68.81)	618 (72.54)	163 (57.60)	22.088	<0.001
Low-dose thrombolysis, n (%)	241 (21.23)	147 (17.25)	94 (33.22)	32.363	<0.001

(*Continued*)

Table 1 (Continued).

	Total (n=1135)	FIB-4 (Q1–3) (n=852)	FIB-4 (Q4) (n=283)	$t/Z/\chi 2$	*P*
Baseline SBP, mmHg (IQR)	154 (140–167)	153 (139–168)	156 (141–167)	−1.054	0.292
Baseline DBP, mmHg (IQR)	89 (81–98)	90 (82–99)	87 (78–96)	−3.988	<0.001
Baseline blood glucose, mmol/L (IQR)	7.5 (6.4–9.1)	7.5 (6.4–9.1)	7.7 (6.6–9.2)	−1.243	0.214
Baseline NIHSS score	8 (5–12)	8 (5–11)	10 (5–14)	−5.007	<0.001
ONT, min (IQR)	185 (144–231)	188 (147–232)	178 (138–227)	−1.824	0.068
Subtypes				47.096	<0.001
Large-artery atherosclerosis, n (%)	394 (34.71)	298 (34.98)	96 (33.92)		
Small-vessel occlusion, n (%)	427 (37.62)	349 (40.96)	78 (27.56)		
Cardioembolism, n (%)	157 (13.83)	85 (9.98)	72 (25.44)		
Undetermined etiology, n (%)	157 (13.83)	120 (14.08)	37 (13.07)		
Platelet count, 10^9/L (IQR)	202 (171–234)	214 (184–246)	162 (141–192)	−15.232	<0.001
AST, units/L (IQR)	22.0 (18.5–26.5)	21.2 (17.9–25.3)	25.1 (21.1–31.7)	−9.150	<0.001
ALT, units/L (IQR)	17.2 (12.4–23.9)	17.9 (13.4–25.5)	14.1 (10.3–20.1)	−6.832	<0.001
TG	1.38 (0.97–2.01)	1.48 (1.05–2.12)	1.13 (0.83–1.65)	−6.899	<0.001
TC	4.87 (4.18–5.64)	4.93 (4.25–5.73)	4.62 (4.06–5.33)	−3.818	<0.001
LDL	3.01 (2.46–3.53)	3.06 (2.51–3.61)	2.77 (2.39–3.38)	−3.902	<0.001
HDL	1.20 (1.02–1.42)	1.19 (1.01–1.40)	1.22 (1.04–1.52)	−2.796	0.005
FIB-4	1.66 (1.21–2.25)	1.43 (1.10–1.78)	2.86 (2.50–3.57)	−25.234	<0.001
sICH, n (%)	10 (0.88)	5 (0.59)	5 (1.77)	−1.839	0.066
Poor outcome, n (%)	471 (41.50)	323 (37.91)	148 (52.30)	18.110	<0.001
mRS				36.640	<0.001
0	155 (13.66)	125 (14.67)	30 (10.60)		
1	316 (27.84)	243 (28.52)	73 (25.80)		
2	193 (17.00)	161 (18.90)	32 (11.31)		
3	200 (17.62)	150 (17.61)	50 (17.67)		
4	157 (13.83)	108 (12.68)	49 (17.31)		
5	49 (4.32)	32 (3.76)	17 (6.01)		
6	65 (5.73)	33 (3.87)	32 (11.31)		

Abbreviations: FIB-4, Fibrosis-4; IQR, inter quartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ONT, onset to needle time; AST, aspartate aminotransferase. ALT, alanine aminotransferase; TG, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale.

Table 2 Clinical Characteristics of Patients, Stratified by Favorable Outcome and Poor Outcome

	Favorable Outcome (n=664)	Poor Outcome (n=471)	$t/Z/\chi^2$	*P*
Age, years (IQR)	62 (53–69)	64 (56–72)	−4.516	<0.001
Male, n (%)	486 (73.19)	334 (70.91)	0.714	0.398
Cigarette smoking, n (%)	341 (51.36)	224 (47.56)	1.590	0.207
Alcohol consumption, n (%)	272 (40.96)	199 (42.25)	0.188	0.665
Hypertension, n (%)	314 (47.29)	264 (56.05)	8.464	0.004
Diabetes mellitus, n (%)	115 (17.32)	106 (22.51)	4.726	0.030
Coronary heart disease, n (%)	117 (17.62)	103 (21.87)	3.182	0.074
Atrial fibrillation, n (%)	83 (12.50)	74 (15.71)	2.384	0.123
Previous stroke, n (%)	98 (14.76)	87 (18.47)	2.783	0.095
Previous use of statin, n (%)	20 (30.12)	14 (29.72)	−0.039	0.969
Dyslipidemia, n (%)	468 (70.48)	313 (66.45)	2.083	0.149
Low-dose thrombolysis, n (%)	138 (20.78)	103 (21.87)	0.194	0.660
Baseline SBP, mmHg (IQR)	152 (138–166)	156 (142–169)	−2.928	0.003

(*Continued*)

Table 2 (Continued).

	Favorable Outcome (n=664)	Poor Outcome (n=471)	$t/Z/\chi^2$	*P*
Baseline DBP, mmHg (IQR)	89 (81–98)	90 (81–98)	0.169	0.866
Baseline blood glucose, mmol/L (IQR)	7.4 (6.3–9)	7.7 (6.7–9.3)	−3.161	0.002
Baseline NIHSS score (IQR)	7 (4–10)	11 (7–14)	−13.252	<0.001
ONT, min (IQR)	184 (139–231)	187 (152–231)	−1.229	0.219
Platelet count, 10^9/L (IQR)	209 (175–278)	202 (164–268)	−2.505	0.012
Subtypes			75.460	<0.001
Large-artery atherosclerosis, n (%)	170 (25.60)	224 (47.56)		
Small-vessel occlusion, n (%)	311 (46.84)	116 (24.63)		
Cardioembolism, n (%)	87 (13.10)	70 (14.86)		
Undetermined etiology, n (%)	96 (14.46)	61 (12.95)		
FIB-4	1.564 (1.154–2.049)	1.814 (1.336–2.475)	−5.350	<0.001
sICH, n (%)	0 (0.00)	10 (2.12)	−3.770	<0.001

Abbreviations: IQR, inter quartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ONT, onset to needle time; FIB-4, Fibrosis-4; sICH, symptomatic intracranial hemorrhage.

Table 3 Associations Between FIB-4 Level and Poor Outcome and the Stratified Analysis by Dyslipidemia

	Univariable Analysis		Multivariable Analysis	
FIB-4	**Unadjusted**		**Adjusted**	
Groups	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Entire study population (n=1135)	1.410 (1.239–1.605)	<0.001	1.420 (1.113–1.812)	0.004
Subgroup with dyslipidemia (n=781)	1.590 (1.328–1.902)	<0.001	1.646 (1.228–2.206)	0.001
Subgroup without dyslipidemia (n=354)	1.203 (0.996–1.452)	0.055	0.963 (0.592–1.566)	0.879

Notes: Multivariable analysis was adjusted by other variants that *P* value < 0.05 in univariable analysis. The model in entire study population was adjusted by age, hypertension, baseline SBP, baseline NIHSS score, and stroke subtypes. The model in subgroup with dyslipidemia was adjusted by age, hypertension, diabetes mellitus, baseline blood glucose, baseline NIHSS score, and stroke subtypes. The model in subgroup without dyslipidemia was adjusted by age, baseline SBP, baseline NIHSS score, and stroke subtypes.
Abbreviations: FIB-4, Fibrosis-4; OR, odds ratio; 95% CI, 95% confidence interval.

We further used binary logistic analysis to explore the possible interactive effect between FIB-4 and poor outcomes in subgroups, including sex, alcohol consumption, atrial fibrillation, diabetes mellitus, and dyslipidemia. We found that there is a significant interaction between the FIB-4 index and dyslipidemia on functional outcomes after thrombolysis (*P*=0.036), while no significant interaction with sex (*P*=0.614), alcohol consumption (*P*=0.249), diabetes mellitus (*P*=0.592), or atrial fibrillation (*P*=0.889) (Supplementary Table 2). The FIB-4 may contribute differently to patient functional outcomes depending on the presence of dyslipidemia. We stratified the study population according to the presence or absence of dyslipidemia. The results of univariable and multivariable analysis in subgroup with and without dyslipidemia are shown in Supplementary Tables 3 and 4 separately. In subgroup with dyslipidemia, the univariable analysis indicated that the FIB-4 had a significant association with poor outcome (OR=1.590, 95% CI: 1.328–1.902, *P*<0.001). The FIB-4 value was independently associated with poor outcomes in patients with dyslipidemia in multivariable analysis (OR=1.646; 95% CI: 1.228–2.206; *P*=0.001). There was no significant association between FIB-4 value and poor outcomes in patients without dyslipidemia (all *P*>0.05) (Table 3; Figure 2).

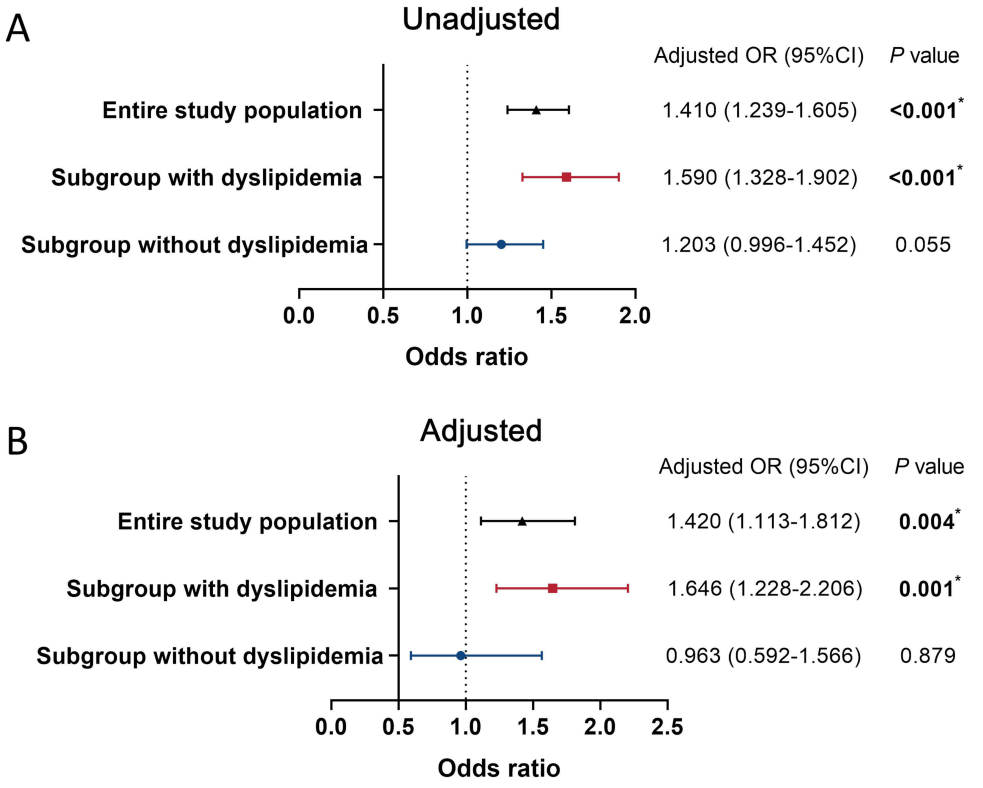

Figure 2 Association between FIB-4 level and 3-month poor outcome after thrombolysis in univariable analysis and multivariable analysis. (**A**) Univariable analysis; (**B**) Multivariable analysis.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval. *P<0.05.

Individualized Prediction Model

Based on the results of stratified analyses, we established an individualized prediction model for poor outcomes in a population with dyslipidemia. The characteristics of the populations randomly assigned to the training (n=547) and validation (n=234) sets were not significantly different (Table 4). In the univariate analysis, the age, hypertension,

Table 4 Characteristics of Patients with Dyslipidemia in the Training and Validation Sets

	Validation Set (n=234)	Training Set (n=547)	$t/Z/\chi^2$	*P*
Age, years (IQR)	62 (54–69)	62 (54–70)	−0.602	0.547
Male, n (%)	162 (69.23)	409 (74.77)	2.560	0.110
Cigarette smoking, n (%)	107 (45.73)	285 (52.10)	2.665	0.103
Alcohol consumption, n (%)	101 (43.16)	234 (42.78)	0.010	0.921
Hypertension, n (%)	123 (52.56)	304 (55.58)	0.600	0.439
Diabetes mellitus, n (%)	49 (20.94)	121 (22.12)	0.134	0.714
Coronary heart disease, n (%)	38 (16.24)	87 (15.90)	0.014	0.907
Atrial fibrillation, n (%)	35 (14.96)	60 (10.97)	2.440	0.118
Previous stroke, n (%)	38 (16.24)	89 (16.27)	0.0001	0.991
Previous use of statin, n (%)	17 (7.26)	8 (1.46)	−0.366	0.714
Low-dose thrombolysis, n (%)	54 (23.08)	107 (19.56)	1.238	0.266
Baseline SBP, mmHg (IQR)	157 (140–169)	155 (142–168)	0.504	0.615
Baseline DBP, mmHg (IQR)	91 (83–99)	89 (81–98)	1.940	0.052
Baseline blood glucose, mmol/L (IQR)	7.5 (6.5–9.1)	7.7 (6.5–9.6)	−1.532	0.126
Baseline NIHSS score (IQR)	8 (5–11)	8 (5–12)	−0.643	0.520

(*Continued*)

Table 4 (Continued).

	Validation Set (n=234)	Training Set (n=547)	$t/Z/\chi^2$	*P*
ONT, min (IQR)	184 (144–227)	185 (140–230)	0.080	0.936
Platelet count, 10^9/L (IQR)	208 (204–212)	210 (203–218)	−0.087	0.930
Subtypes			3.385	0.336
Large-artery atherosclerosis, n (%)	79 (33.76)	196 (35.83)		
Small-vessel occlusion, n (%)	91 (38.89)	207 (37.84)		
Cardioembolism, n (%)	35 (14.96)	60 (10.97)		
Undetermined etiology, n (%)	29 (12.39)	84 (15.36)		
FIB-4 (IQR)	1.588 (1.126–2.157)	1.589 (1.169–2.102)	−0.046	0.963
sICH, n (%)	5 (2.14)	4 (0.73)	−0.953	0.340
Poor outcome, n (%)	93 (39.74)	220 (40.22)	0.015	0.901

Abbreviations: IQR, inter quartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ONT, onset to needle time; FIB-4, Fibrosis-4; sICH, symptomatic intracranial hemorrhage.

diabetes mellitus, baseline blood glucose, baseline NIHSS score, stroke subtypes, and FIB-4 value had a *P* value <0.05, indicating a poor outcome in the training set. These variables were subsequently included in the multivariate logistic regression analysis. Finally, the final nomogram was comprised of FIB-4 value, hypertension, diabetes mellitus, baseline NIHSS score and stroke subtypes (Figure 3).

The discriminative performance of the model was evaluated using the AUC of the training set (AUC, 0.767; 95% CI: 0.727–0.807). The model was then tested using the AUC of the validation set (AUC, 0.708; 95% CI: 0.642–0.775) (Figure 4). The *P*-values for the Hosmer–Lemeshow test were 0.709 and 0.646 in the training and validation sets, respectively, indicating good calibration. DCA estimates the net benefit of the model based on the difference between the number of true and false-positive results. As shown in Figure 5, using the nomogram for 3-month poor outcome prediction was clinically useful.

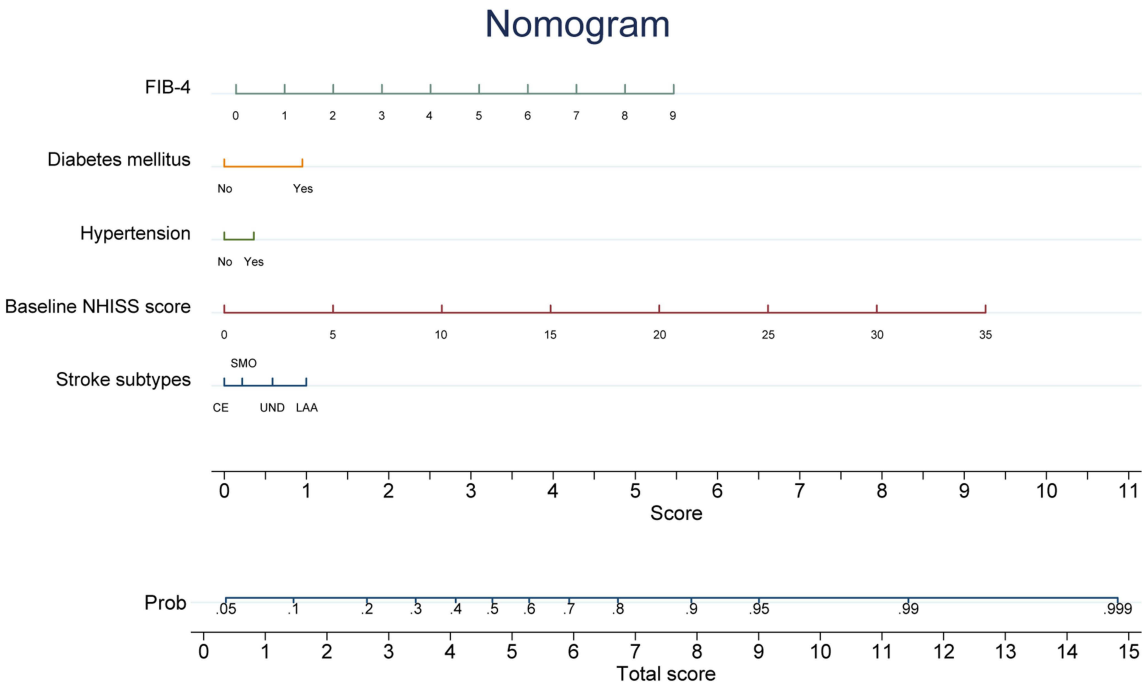

Figure 3 Nomogram to predict 3-month poor outcome.
Abbreviations: FIB-4, Fibrosis-4; NIHSS, National Institutes of Health Stroke Scale; CE, cardioembolism; SMO, small-vessel occlusion; UND, undetermined etiology; LAA, large-artery atherosclerosis.

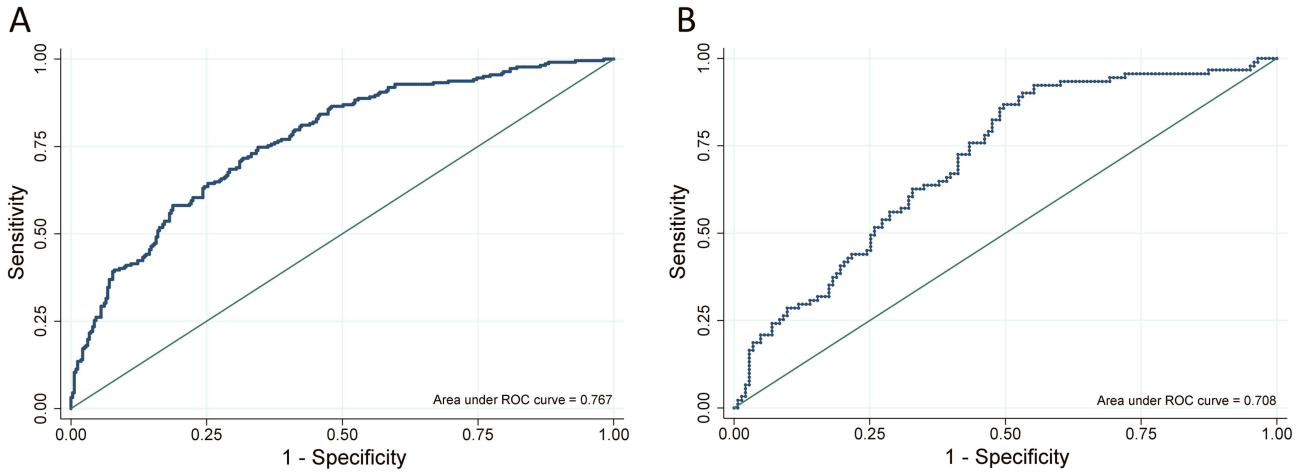

Figure 4 ROC curves for the nomogram in training and validation sets. (**A**) Training set; (**B**) Validation set.
Abbreviation: ROC, receiver operating characteristics.

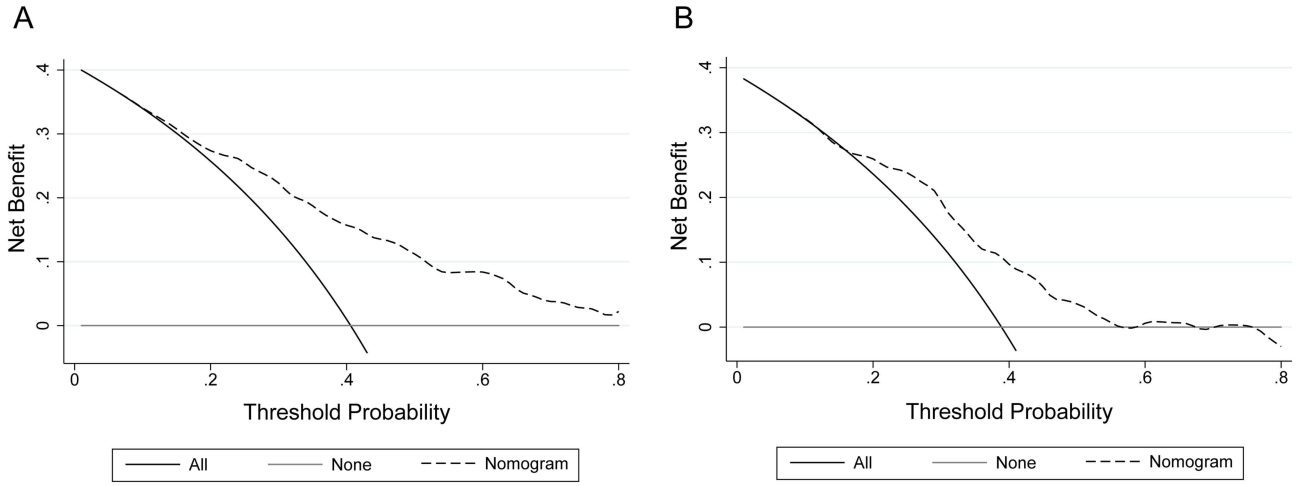

Figure 5 DCA of the nomogram in training and validation sets. (**A**) Training set; (**B**) Validation set.
Abbreviation: DCA, decision curve analysis.

Discussion

Our study demonstrated that the FIB-4 index was independently associated with poor functional outcomes in IVT patients with dyslipidemia and can be used as a simple predictor of prognosis in this patient population. Furthermore, our results suggest that the FIB-4 may be regarded as a possible intervention target to improve the outcome of patients with dyslipidemia who receive IVT.

The FIB-4 index is a clinically validated indicator of liver fibrosis,[27] and can predict liver-related adverse outcomes and all-cause mortality in patients with liver disease.[28] Recent studies have focused on the relationship of the FIB-4 with cerebrovascular disease. Parikh et al demonstrated that the FIB-4 index is associated with adverse outcomes in intracerebral hemorrhage.[8] Regarding IS, previous studies have suggested that FIB-4 is an independent predictor of unfavorable long-term prognosis.[13] In addition, a recent study on large-vessel occlusion stroke found that FIB-4 was independently associated with unfavorable outcomes after thrombectomy.[29] Recently, Toh et al found that FIB-4 is a risk factor for sICH and 3-month mortality after IVT.[23] Moreover, a study by Norata et al confirmed the predictive value of FIB-4 for poor prognosis 3 months after IVT in a sample of 264 cases from Italy.[30] Our study comprehensively examined

the FIB-4 index for predicting outcomes in patients with stroke who underwent IVT. The present study confirmed the prognostic ability of the FIB-4 index in a larger sample cohort and using three logistic regression models, which demonstrated that the results were stable.

Furthermore, our study is the first to identify a significant interaction between FIB-4 and dyslipidemia in patients with a poor prognosis after IVT. Stratified analysis of this finding revealed a modifying effect of dyslipidemia on FIB-4 on prognosis after IVT. Dyslipidemia is a common metabolic risk factor of liver fibrosis[15] and IS.[16] Besides, dyslipidemia is widespread in IS patients[31] and is closely related to liver fibrosis.[32] Several possible mechanisms have been proposed to explain this connection. Previous studies have shown that liver fibrosis is associated with systemic inflammation,[33] oxidative stress,[34] endothelial dysfunction,[35] insulin resistance,[36] and hypercoagulable state.[37,38] Dyslipidemia has been shown to exacerbate the above mechanisms,[39–43] which may synergistically contribute to poor prognosis after IVT in stroke patients.[44–48] According to our results, dyslipidemia altered the prognostic value of liver fibrosis in patients with IS after IVT. Hence, owing to the strong association of dyslipidemia with liver fibrosis and stroke, it is necessary to further investigate the prognostic significance of liver fibrosis in patients with dyslipidemia and IS after IVT. Besides, with the improvement of emergency green channel comprehensive management strategy in China, the time of emergency medical test is shortened, which makes the potential clinical predictive value of FIB-4 index more significant.

In this study, we identified an association between FIB-4 and poor prognosis, and the predictive power was maintained only in the dyslipidemia subgroup. Therefore, we developed an individualized predictive model for patients with dyslipidemia. The model is based on the FIB-4 level, stroke subtypes, baseline NIHSS score, and SBP, where each item represents its respective score, and the sum of the scores gives an individualized probability of poor prognosis for each patient in the lower part of the nomogram. The model was then tested for discrimination, calibration, and clinical utility in both the training and validation sets with satisfactory results. The prediction of poor prognosis early after thrombolysis can be interpreted in patients and treated aggressively at an early stage, with the early identification of risk factors for poor prognosis.

Our study has some limitations. First, this was a single-center retrospective study; therefore, there may have been selection bias. Second, we did not perform more tests of other liver indicators; therefore, the association between additional indicators of liver fibrosis and stroke patients undergoing IVT remained unclear. Third, the prediction model was not validated at other institutions. Prospective studies using liver imaging should be conducted to validate our findings.

Conclusion

FIB-4 was an independent risk factor for poor outcome in patients with dyslipidemia undergoing IVT, which suggests that the FIB-4 level could be further regarded as a possible intervention target to improve the outcomes of dyslipidemia patients who receive IVT.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was conducted according to the principles of the Declaration of Helsinki. Written informed consent for this study was obtained from all study participants or their direct relatives, which was approved by the Ethics Committee of the First Hospital of Jilin University (2015-156).

Consent for Publication

All participants consented to publish.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors report no conflicts of interest in this work.

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