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ORIGINAL RESEARCH

Association Between Liver Fibrosis Markers and Hemorrhagic Transformation Following Endovascular Treatment for Acute Ischemic Stroke: A Chinese Stroke Center Study

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Purpose: To investigate the association between non-invasive liver fibrosis indices and the risk of hemorrhagic transformation (HT) and symptomatic intracranial hemorrhage (sICH) after endovascular therapy (EVT) in patients with anterior circulation large vessel occlusion (LVO) stroke.

Patients and Methods: In this single-center retrospective cohort study, we consecutively enrolled 340 patients with anterior circulation LVO stroke who underwent EVT at a comprehensive stroke center between January 2018 and December 2024. Eight non-invasive liver fibrosis indices were calculated based on fasting laboratory parameters obtained within 24 hours of admission. The primary outcomes were HT and sICH. Multivariable logistic regression and restricted cubic spline analyses were performed to assess the associations.

Results: Of the 340 patients, 161 (47.4%) developed HT, and 69 (20.3%) experienced sICH. After adjusting for confounders, elevated fibrosis-4 index (FIB-4) (adjusted odds ratio [aOR]=1.25, 95% CI: 1.01–1.56; aOR=1.48, 95% CI: 1.12–1.94), the modified FIB-4 (aOR1.07, 95% CI: 1.01–1.15; aOR=1.13, 95% CI: 1.04–1.23), the aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR) (aOR=1.43, 95% CI: 1.03–1.96; aOR=1.91, 95% CI: 1.16–3.12), and the AST to ALT-platelet ratio index (AARPRI) (aOR=1.53, 95% CI: 1.07–2.17; aOR=2.36, 95% CI: 1.45–3.84) were independently associated with increased risks of both HT and sICH. Conversely, the FIB-5 index showed an inverse association (aOR=0.95, 95% CI: 0.91–1.00; aOR=0.91, 95% CI: 0.85–0.98). These indices demonstrated higher predictive values for sICH (AUC: 0.65–0.70) than for HT (AUC: 0.61–0.62). Notably, patients with parenchymal hematoma had significantly greater liver fibrosis indices than those with hemorrhagic infarction or no hemorrhage (all $P<0.05$).

Conclusion: Non-invasive liver fibrosis indices are independently associated with post-EVT hemorrhagic complications in anterior circulation stroke patients and may serve as readily accessible tools for risk stratification.

Keywords: large vessel occlusion, liver fibrosis, hemorrhagic transformation, symptomatic intracerebral hemorrhage, endovascular therapy, stroke

Introduction

Stroke is the second leading cause of death and the third leading cause of disability worldwide, posing a significant public health challenge.[1] Among patients with acute ischemic stroke (AIS), 28–46% present with large vessel occlusion (LVO).[2] These patients are of particular clinical concern because of the rapid progression of their condition, severe neurological deficits, and poor prognosis.[3] In recent years, endovascular therapy (EVT) has emerged as the preferred interventional strategy

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for LVO-AIS in the hyperacute phase, as it enables rapid recanalization of occluded vessels, salvages the ischemic penumbra, and significantly improves functional outcomes.[4] However, approximately half of the patients who undergo EVT develop postreperfusion hemorrhagic transformation (HT), among which symptomatic intracranial hemorrhage (sICH) is closely associated with increased acute-phase mortality and a greater risk of poor long-term functional outcomes.[5–7] Therefore, systematically identifying predictive biomarkers for post-EVT HT and developing precise prevention and treatment strategies are critical issues that need to be addressed in the current stroke research field.

Previous studies have identified multiple risk factors associated with post-EVT hemorrhagic complications, including clinical characteristics (such as atrial fibrillation, high baseline National Institutes of Health Stroke Scale [NIHSS] scores, and prolonged symptom-onset-to-reperfusion time), procedural factors (including number of retrieval attempts), laboratory parameters (such as hyperglycemia), and radiological markers (such as hyperdense artery sign on baseline computed tomography [CT] and poor collateral circulation on computed tomography angiography [CTA]).[8,9] Nevertheless, existing predictive models demonstrate suboptimal performance, and our understanding of the underlying pathophysiological mechanisms remains limited. Therefore, systematically identifying predictive biomarkers for post-EVT HT and elucidating their potential mechanisms have significant clinical value for developing individualized prevention strategies and improving patient outcomes.

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, with a prevalence of 30.1%. Owing to the increasing prominence of risk factors such as obesity and diabetes, the disease burden of MASLD is expected to continue increasing.[10] The pathological spectrum of MASLD ranges from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), and it may progress to liver fibrosis, cirrhosis, and even hepatocellular carcinoma.[11] During the pathological progression of MASLD, liver fibrosis is considered a key stage that may participate in the occurrence and development of stroke through various mechanisms, including endothelial dysfunction, coagulation abnormalities, dyslipidemia, the systemic inflammatory response, and oxidative stress.[12–17]

A growing body of evidence suggests that the severity of liver fibrosis is closely related to poor outcomes in stroke patients, including impaired functional recovery, increased long-term mortality, and increased recurrence rates.[18–21] Liver fibrosis has been shown to promote hematoma expansion in primary intracerebral hemorrhage[20] and is independently associated with an increased risk of sICH after intravenous thrombolysis.[22,23] However, the relationship between liver fibrosis and post-EVT HT remains controversial.[24,25] Some studies have shown that elevated fibrosis-4 (FIB-4) scores can independently predict the risk of post-EVT HT, whereas other studies have not reported similar associations. More importantly, most existing studies rely on a single fibrosis index, which may limit the accurate assessment of liver fibrosis severity. We focused on exploring the independent predictive value of liver fibrosis indices rather than directly developing a composite scoring system, primarily based on two considerations: first, establishing the independent contribution of specific biomarkers is a prerequisite for constructing effective composite models; second, the systemic pathological state reflected by liver fibrosis may represent a unique mechanism not yet incorporated into existing predictive models, thus providing substantial complementary value.

Therefore, the present study is the first to systematically evaluate the associations between eight non-invasive liver fibrosis indices and post-EVT HT and sICH in patients with anterior circulation LVO stroke. Furthermore, we analyzed the dose–response relationships between these indices and hemorrhagic phenotypes (hemorrhagic infarction [HI] vs parenchymal hematoma [PH]). This study aims to clarify the potential value of liver fibrosis indices in risk stratification for post-EVT HT and provide a theoretical basis for developing targeted prevention strategies.

Material and Methods

Study Design and Population

We conducted a single-center retrospective cohort study, consecutively enrolling patients with anterior circulation LVO-AIS who underwent EVT at a comprehensive stroke center between January 1, 2018, and December 31, 2024. The studies involving humans were approved by the Ethics Committee of Zhongshan Hospital of Xiamen University. As the study was retrospective and the data were anonymized, the ethics committee agreed to waive the requirement for informed consent.

The inclusion criteria were age ≥18 years and the presence of anterior circulation LVO (internal carotid artery or middle cerebral artery M1/M2 segment) confirmed by computed tomography angiography or digital subtraction angiography (DSA). Exclusion criteria included: (1) pre-existing intracranial hemorrhage on baseline head CT or magnetic resonance imaging; (2) pre-stroke modified Rankin Scale score >2; (3) history of severe liver disease (viral hepatitis, cirrhosis, primary liver cancer, etc.) or severe renal dysfunction; (4) current use of hepatotoxic drugs; and (5) incomplete clinical laboratory data or imaging records. To reflect real-world clinical practice, we did not exclude patients with a history of chronic alcohol consumption.[24]

Data Collection

Baseline data, including demographic characteristics (age, sex), lifestyle factors (smoking, alcohol consumption), medical history (hypertension, diabetes, hyperlipidemia, atrial fibrillation, previous stroke or transient ischemic attack, coronary heart disease), and vital signs at admission (systolic and diastolic blood pressure), were extracted from the hospital electronic medical record system via a standardized electronic data collection form.

Neurologists who received standardized training assessed the severity of neurological deficits at admission using the National Institutes of Health Stroke Scale (NIHSS) and evaluated the level of consciousness using the Glasgow Coma Scale (GCS).[26,27] The Alberta Stroke Program Early CT Score (ASPECTS) was used to quantitatively assess the baseline infarct volume.[28] Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria. Furthermore, detailed information regarding preoperative anticoagulation therapy was documented, including the use of vitamin K antagonists (warfarin) and non-vitamin K antagonist oral anticoagulants.

We recorded treatment-related details, including intravenous thrombolysis status, key time points (onset-to-puncture time, onset-to-reperfusion time, puncture-to-reperfusion time), and procedural details (number of mechanical thrombectomy attempts, device strategy [stent retriever, aspiration catheter, or combined use], and balloon angioplasty). The modified Thrombolysis in Cerebral Infarction (mTICI) grading system was used to evaluate post-procedural reperfusion status, based on the final DSA results, with mTICI grades 2b-3 defined as successful reperfusion.[29]

All blood samples were collected in the fasting state within 24 hours of admission (between 6:00–8:00 am the following morning). The samples were analyzed using automated analyzers in the hospital's central laboratory. The measured parameters included white blood cell, neutrophil count, lymphocyte count, platelet count (PLT), total protein, albumin (ALB), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C]), fasting blood glucose, urea, creatinine, and uric acid. Thrombocytopenia was defined as a platelet count below 150×10^9/L in accordance with established clinical criteria.

Assessment of Liver Fibrosis

Eight validated non-invasive liver fibrosis indices were calculated using laboratory parameters:[21] FIB-4, modified FIB-4 (mFIB-4), fibrosis-5 (FIB-5), the AST-to-PLT ratio index (APRI), the Forns index, the AST/ALT ratio (AAR), the AST/ALT-PLT ratio index (AARPRI), and liver fibrosis. The specific calculation formulas are presented in Figure 1.

Outcome Measures

All patients underwent head CT examinations at 24 and 72 hours after EVT. HT was classified into four categories according to the Heidelberg Bleeding Classification:[30] HI-1 (punctate hemorrhage at the infarct margin), HI-2 (confluent hemorrhage within the infarct zone without mass effect), PH-1 (hematoma volume ≤30% of the infarcted area without significant mass effect), and PH-2 (hematoma volume >30% of the infarcted area with significant mass effect).

sICH was defined as any intracranial hemorrhage associated with one or more of the following conditions in the absence of other explanations: an increase in the total NIHSS score of ≥4 points compared to baseline, an increase in any single NIHSS item score of ≥2 points compared to baseline, or neurological deterioration requiring endotracheal intubation, decompressive craniectomy, external ventricular drainage, or other significant medical interventions. All imaging assessments were independently performed by two experienced neuroradiologists and one neurologist who were blinded to the clinical data. In case of discrepancies, consensus was reached through discussion.

$$\mathbf{FIB-4} = \frac{\text{Age (years)} \times \text{AST } (\frac{\text{U}}{\text{L}})}{\text{Platelet count } (\frac{10^9}{\text{L}}) \times \sqrt{}\text{ALT } (\frac{\text{U}}{\text{L}})}$$

$$\mathbf{mFIB-4} = \frac{10 \times \text{Age (years)} \times \text{AST } (\frac{\text{U}}{\text{L}})}{\text{Platelet count } (\frac{10^9}{\text{L}}) \times \sqrt{}\text{ALT } (\frac{\text{U}}{\text{L}})}$$

$$\mathbf{FIB-5} = (\text{ALB } (\frac{\text{g}}{\text{L}}) \times 0.3 + \text{PLT } (\frac{10^9}{\text{L}}) \times 0.05) - (\text{ALP } (\frac{\text{U}}{\text{L}}) \times 0.014 + \frac{\text{AST}}{\text{ALT}} \times 6 + 14$$

$$\mathbf{APRI} = \frac{\frac{\text{AST}}{\text{upper limit of normal}}}{\text{PLT } (\frac{10^9}{\text{L}})} \times 100$$

$$\mathbf{Forns\ index} = 7.811 - 3.131 \times \ln (\text{PLT } (\frac{10^9}{\text{L}})) + 0.781 \times \ln(\text{GGT } (\frac{\text{U}}{\text{L}}) + 3.467 \times$$

$$\ln(\text{Age (years)}) - 0.014 \times \text{cholesterol } (\frac{\text{mg}}{\text{dL}})$$

$$\mathbf{ARR} = \frac{\text{AST } (\frac{\text{U}}{\text{L}})}{\text{ALT } (\frac{\text{U}}{\text{L}})}$$

$$\mathbf{AARPRI} = \frac{\text{ARR score}}{\text{PLT } (\frac{10^9}{\text{L}})/150}$$

$$\mathbf{Fibrosis\ index} =- 2.948 + 0.562 \times \text{Forns'index} +- 0.288 \times \text{APRI} + 0.006 \times \text{PLT}(\frac{10^9}{\text{L}})$$

Figure 1 Calculation Formulas for Eight Non-invasive Liver Fibrosis Indices.

Abbreviations: FIB-4, fibrosis-4; mFIB-4, modified fibrosis-4; FIB-5, fibrosis-5; APRI, AST to platelet ratio index; AAR, AST to ALT ratio; AARPRI, AST/ALT-platelet ratio index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet count; ALB, albumin; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase.

Statistical Analyses

Statistical analyses were performed using R software (Version 4.2.2). The Shapiro–Wilk test was used to assess the normality of continuous variables. Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using independent samples *t*-tests. Non-normally distributed continuous variables were expressed as median (interquartile range) and compared using the Mann–Whitney *U*-test. Categorical variables were expressed as counts (percentages) and compared using the chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of liver fibrosis indices for hemorrhagic complications. The area under the curve (AUC), optimal cutoff value (determined by the Youden index), sensitivity, and specificity were calculated.

Covariate selection followed a two-step process: first, variables with statistical significance ($P<0.05$) in univariate analysis were identified as candidate covariates; second, multicollinearity diagnostics were performed on all candidate covariates by calculating variance inflation factor (VIF) and tolerance values, excluding variables that did not meet predetermined criteria (VIF<10 and Tolerance>0.1) (Supplemental Tables 1 and 2). For HT: Model 1 was the unadjusted baseline model; Model 2 adjusted for clinical factors (baseline NIHSS score, GCS score, ASPECTS score, systolic blood pressure, puncture-to-reperfusion time, and number of thrombectomy attempts); Model 3 further adjusted for laboratory parameters (total bilirubin, AST, triglycerides, neutrophil count, lymphocyte count, and platelet count). For sICH: Model 1 was the unadjusted baseline model; Model 2 adjusted for clinical factors (baseline NIHSS score, GCS score, ASPECTS score, preoperative anticoagulation therapy, and number of thrombectomy attempts); Model 3 further adjusted for laboratory parameters (total protein, ALT, AST, total cholesterol, fasting glucose, neutrophil count, lymphocyte count, and platelet count). Restricted cubic spline regression models were used to evaluate potential non-linear associations, with knots placed at the 5th, 35th, 65th, and 95th percentiles. All statistical tests were two-sided, with P<0.05 defined as statistically significant.

Results

Patient Characteristics and Clinical Outcomes

A total of 340 patients with anterior circulation LVO-AIS who underwent EVT were included (Table 1), among whom 161 (47.4%) developed HT and 69 (20.3%) experienced sICH. The median age of the overall population was 67 years (IQR, 57–76 years), and 224 (65.9%) were male. Compared with those in the non-HT group, patients in the HT group had more severe neurological deficits at admission (median NIHSS score: 16 vs 13, P<0.001; median GCS score: 12 vs 13, P=0.047) and lower ASPECTS scores (median: 9 vs 9, P<0.001). The HT group had a longer puncture-to-reperfusion time (P=0.007) and required more mechanical thrombectomy attempts (P=0.002). The two groups were similar in terms of successful reperfusion rates (85.1% vs 86.0%, P=0.805) and proportions of intravenous thrombolysis (41.6% vs 44.1%, P=0.639). Although the HT group had a greater proportion of patients with cardioembolism (51.6% vs 43.0%) and the non-HT group had a greater proportion of patients with large artery atherosclerosis (42.9% vs 52.0%), these differences did not reach statistical significance (P=0.242).

Table 1 Baseline Clinical Characteristics of Patients with Anterior Circulation Large Vessel Occlusion Stroke Stratified by HT Status

Variables	Overall (n = 340)	Non-HT (n = 179)	HT (n = 161)	P Value
Demographics				
Age, years	67 (57, 76)	66 (56, 76)	68 (58, 76)	0.455
Male sex	224 (65.88)	113 (63.13)	111 (68.94)	0.259
Current smoker	129 (37.94)	66 (36.87)	63 (39.13)	0.668
Alcohol consumption	87 (25.59)	38 (21.23)	49 (30.43)	0.052
Medical history				
Hypertension	226 (66.47)	119 (66.48)	107 (66.46)	0.997
Diabetes mellitus	98 (28.82)	48 (26.82)	50 (31.06)	0.389
Hyperlipidemia	78 (22.94)	44 (24.58)	34 (21.12)	0.448
Atrial fibrillation	148 (43.53)	70 (39.11)	78 (48.45)	0.083
Previous stroke/TIA	54 (15.88)	34 (18.99)	20 (12.42)	0.486
Coronary artery disease	45 (13.24)	20 (11.17)	25 (15.53)	0.237
Clinical Presentation				
SBP, mmHg	148 (132, 163)	150 (135, 169)	146 (131, 158)	0.027
DPB, mmHg	87 (77, 97)	87 (77, 100)	87 (77, 93)	0.194
Baseline NIHSS score	15 (12, 19)	13 (11, 18)	16 (13, 20)	<0.001
Baseline GCS score	12 (10, 14)	13.00 (10, 14)	12 (9, 14)	0.047
Baseline ASPECT score	9 (8, 10)	9 (8, 10)	9 (7, 10)	<0.001
Anticoagulation therapy				0.092
No anticoagulation	297 (87.35)	160 (89.39)	137 (85.09)	
Warfarin	29 (8.53)	10 (5.59)	19 (11.80)	
DOACs	14 (4.12)	9 (5.03)	5 (3.11)	
Stroke etiology				0.242
Large-artery atherosclerosis	162 (47.65)	93 (51.96)	69 (42.86)	
Cardioembolism	160 (47.06)	77 (43.02)	83 (51.55)	
Other	18 (5.29)	9 (5.03)	9 (5.59)	

(*Continued*)

Table 1 (Continued).

Variables	Overall (n = 340)	Non-HT (n = 179)	HT (n = 161)	P Value
Procedural Characteristics				
Intravenous thrombolysis	146 (42.94)	79 (44.13)	67 (41.61)	0.639
OPT, min	373 (266, 555)	373 (260, 604)	374 (273, 514)	0.616
PRT, min	76 (48, 99)	70 (40, 97)	80 (55, 101)	0.007
ORT, min	460 (345, 642)	463 (313, 679)	458 (350, 612)	0.946
NOTA	2.00 (1, 2)	1.00 (1, 2)	2.00 (1, 3)	0.002
Successful reperfusion	291 (85.59)	154 (86.03)	137 (85.09)	0.805
Treatment Strategy				0.126
Stent retriever	73 (21.47)	40 (22.35)	33 (20.50)	
Aspiration	21 (6.18)	16 (8.94)	5 (3.11)	
Combined approach	226 (66.47)	112 (62.57)	114 (70.81)	
Balloon angioplasty	61 (17.94)	33 (18.44)	28 (17.39)	0.802
Thrombocytopenia	54 (15.88)	21 (11.73)	33 (20.50)	0.027

Notes: Values are presented as median (IQR) or n (%).

Abbreviations: HT, hemorrhagic transformation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; DOACs, Direct Oral Anticoagulants; OPT, Onset-to-puncture time; PRT, Puncture-to-recanalization time; ORT, Onset-to-recanalization time; NOTA, Number of thrombectomy attempts.

Laboratory Characteristics of Patients with and Without HT

Laboratory tests showed that, compared to the non-HT group, patients in the HT group had significantly higher neutrophil counts (P<0.001), total bilirubin levels (P=0.040), and AST levels (P=0.011), while lymphocyte counts (P<0.001), PLT count (P=0.005) and triglyceride levels (P=0.028) were significantly lower (Table 2). Among the eight liver fibrosis indices evaluated, seven showed significant between-group differences. Notably, FIB-4 (P<0.001), modified FIB-4 (P<0.001), APRI (P<0.001), Forns index (P=0.021), AAR score (P<0.001), and AARPRI (P<0.001) were

Table 2 Laboratory Characteristics of Patients with and Without HT After Endovascular Therapy

Variables	Overall (n = 340)	Non-HT (n = 179)	HT (n = 161)	P Value
White blood cell, $\times10^9$/L	11.5 (9.5, 13.8)	10.5 (8.7, 13.0)	12.4 (10.6, 14.5)	<0.001
Neutrophils, $\times10^9$/L	9.8 (7.8, 11.9)	8.8 (6.9, 11.4)	10.7 (8.9, 12.7)	<0.001
Lymphocytes, $\times10^9$ /L	1.05 (0.74, 1.37)	1.12 (0.85, 1.43)	0.97 (0.68, 1.23)	<0.001
Monocytes, $\times10^9$/L	0.59 (0.43, 0.73)	0.57 (0.43, 0.72)	0.62 (0.45, 0.77)	0.132
Total protein, g/L	65 (62, 70)	65 (62, 70)	64 (62, 69)	0.386
Albumin, g/L	37.2 (34.5, 39.5)	37.3 (35.0, 39.5)	37.0 (33.7, 39.6)	0.742
Total bilirubin, μmol/L	16 (13, 21)	15 (12, 20)	17 (13, 23)	0.040
ALT, U/L	16 (12, 24)	17 (12, 25)	16 (12, 22)	0.217
AST, U/L	24 (19, 32)	24 (18, 30)	25 (21, 34)	0.011
γ-Glutamyl transferase, U/L	28 (19, 46)	29 (19, 46)	28 (20, 45)	0.895
Alkaline phosphatase, U/L	77 (65, 93)	77 (65, 97)	77 (66, 88)	0.333
Triglycerides, mmol/L	1.06 (0.78, 1.42)	1.13 (0.82, 1.47)	1.01 (0.71, 1.31)	0.028
Total cholesterol, mmol/L	4.34 (3.57, 5.05)	4.37 (3.63, 5.06)	4.24 (3.39, 5.04)	0.462
HDL-C, mmol/L	1.17 (1.00, 1.34)	1.17 (1.01, 1.34)	1.16 (0.99, 1.34)	0.965
LDL-C, mmol/L	2.83 (2.22, 3.40)	2.88 (2.30, 3.38)	2.81 (2.06, 3.44)	0.413
FBG, mmol/L	7.5 (6.2, 9.7)	7.3 (6.0, 9.5)	7.7 (6.4, 9.8)	0.133
BUN, mmol/L	5.46 (4.10, 7.20)	5.40 (4.10, 6.85)	5.70 (4.10, 7.70)	0.170

(*Continued*)

Table 2 (Continued).

Variables	**Overall (n = 340)**	**Non-HT (n = 179)**	**HT (n = 161)**	**P Value**
Creatinine, μmol/L	72 (58, 87)	72 (58, 85)	72 (59, 89)	0.343
Uric acid, μmol/L	329 (269, 415)	327 (270, 402)	334 (266, 417)	0.495
Platelet count, ×10^9/L	201 (168, 237)	210 (178, 248)	194 (160, 227)	0.005
FIB-4 index	2.02 (1.35, 3.01)	1.78 (1.17, 2.75)	2.24 (1.48, 3.24)	<0.001
Modified FIB-4	4.8 (3.1, 7.4)	4.2 (2.7, 6.9)	5.3 (3.6, 8.5)	<0.001
FIB-5 index	−3 (−7, 0)	−2 (−5, 1)	−4 (−8, 0)	<0.001
APRI score	0.34 (0.24, 0.48)	0.32 (0.22, 0.43)	0.38 (0.26, 0.53)	<0.001
Forns index	6.03 ± 1.66	5.83 ± 1.70	6.25 ± 1.60	0.021
ARR score	1.48 (1.08, 2.04)	1.35 (1.01, 1.86)	1.68 (1.18, 2.16)	<0.001
AARPRI	1.10 (0.77, 1.56)	1.05 (0.70, 1.39)	1.18 (0.85, 1.82)	<0.001
Fibrosis index	1.81 ± 0.75	1.75 ± 0.77	1.88 ± 0.73	0.111

Notes: Values are presented as median (interquartile range) or mean ± standard deviation, as appropriate.
Abbreviations: HT, hemorrhagic transformation; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BUN, Blood urea nitrogen; FBG, fasting blood glucose; FIB-4, fibrosis-4; FIB-5, fibrosis-5; APRI, aspartate aminotransferase to platelet ratio index; ARR, ALT/AST ratio; AARPR, AST/ALT ratio-platelet ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

significantly higher in the HT group compared to the non-HT group. In contrast, the FIB-5 index was significantly lower in the HT group (P<0.001).

Subgroup analysis stratified by hemorrhage type demonstrated distinct distribution patterns (Figure 2). FIB-4, modified FIB-4, AAR, and AARPRI showed an increasing trend across the non-HT, HI, and PH groups, reaching the highest levels in the PH group (all P<0.05 compared to the non-HT group). Importantly, these indices were also significantly higher in the PH group compared to the HI group. The FIB-5 index exhibited the opposite trend, being lowest in the PH group (P<0.05 compared to both the non-HT and HI groups). Although APRI, Forns index, and Fibrosis index showed similar trends, the differences did not reach statistical significance.

Clinical and Laboratory Characteristics Associated with sICH

Compared to patients without symptomatic intracranial hemorrhage (n=271), those who developed sICH (n=69) had more severe neurological deficits at admission, as indicated by higher NIHSS scores (median: 17 vs 14, P=0.001) and lower GCS scores (median: 11 vs 13, P=0.006). The sICH group had lower baseline ASPECTS scores (median: 8 vs 9, P=0.044) and required more mechanical thrombectomy attempts (median: 2 vs 1, P=0.019). Despite these differences, procedural parameters such as puncture-to-reperfusion time and successful reperfusion rates were similar between the two groups (Table 3). Furthermore, patients who developed sICH had a significantly higher proportion of preoperative warfarin therapy, whereas patients without sICH were more likely to have received no anticoagulation therapy prior to intervention.

The results of the laboratory tests (Table 4 and Figure 3) revealed that patients in the sICH group had significantly lower total protein (P=0.037), PLT (P<0.001), and total cholesterol (P=0.042) levels and higher fasting blood glucose (P=0.002) levels. Except for the FIB-5 index, which was significantly lower (P<0.001), six liver fibrosis indices, FIB-4, modified FIB-4, APRI, Forns index, AAR score, and AARPRI (all P<0.001), were significantly greater in the sICH group. The fibrosis index did not differ significantly between the two groups (P=0.108).

Predictive Value of Liver Fibrosis Indices

ROC curve analysis demonstrated that liver fibrosis indices had moderate predictive value for hemorrhagic complications (Table 5 and Figure 4). In predicting HT, FIB-4 (AUC=0.62, 95% CI: 0.56–0.68), modified FIB-4 (AUC=0.62, 95% CI: 0.56–0.67), and AARPRI (AUC=0.62, 95% CI: 0.57–0.68) showed similar performance. The predictive accuracy for sICH was notably higher, with AARPRI displaying the best discriminative ability (AUC=0.70, 95% CI: 0.62–0.77),

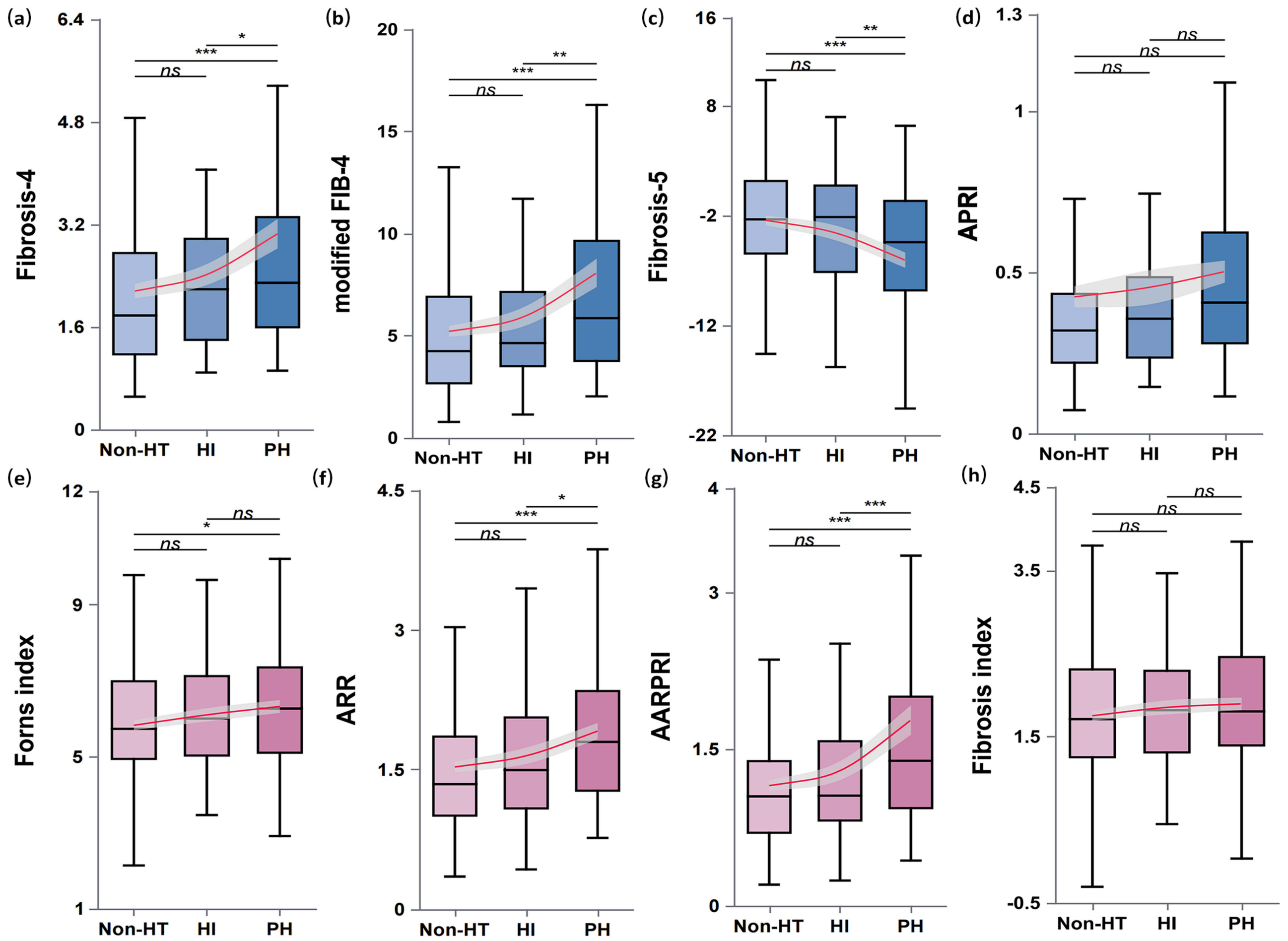

Figure 2 Distribution of Liver Fibrosis Indices Stratified by Hemorrhage Type Box Plots. Box plots showing the distribution of eight liver fibrosis indices across non-hemorrhagic transformation (Non-HT), hemorrhagic infarction (HI), and parenchymal hematoma (PH) groups: (**a**) Fibrosis-4 (FIB-4); (**b**) modified FIB-4; (**c**) Fibrosis-5 (FIB-5); (**d**) AST to Platelet Ratio Index (APRI); (**e**) Forns index; (**f**) AST/ALT Ratio (ARR); (**g**) AST/ALT-Platelet Ratio Index (AARPRI); and (**h**) Fibrosis index. The boxes represent the interquartile range (IQR), with the horizontal line indicating the median. Whiskers extend to 1.5 times the IQR. The red lines represent the trend across hemorrhage severity groups. Statistical significance between groups is indicated as follows: *P<0.05; **P<0.01; ***P<0.001; ns, not significant.

followed by FIB-5 (AUC=0.69, 95% CI: 0.61–0.76), AAR score (AUC=0.68, 95% CI: 0.61–0.75), and modified FIB-4 index (AUC=0.67, 95% CI: 0.59–0.74).

Multivariable Analysis

In the fully adjusted models, AARPRI demonstrated the strongest independent association with both HT and sICH (HT: adjusted OR [aOR]=1.53, 95% CI: 1.07–2.17, P=0.019; sICH: aOR=2.36, 95% CI: 1.45–3.84, P<0.001). The AAR score (HT: aOR=1.43, 95% CI: 1.03–1.96, P=0.030; sICH: aOR=1.91, 95% CI: 1.16–3.12, P=0.010), FIB-4 (HT: aOR=1.25, 95% CI: 1.01–1.56, P=0.044; sICH: aOR=1.48, 95% CI: 1.12–1.94, P=0.006), and modified FIB-4 (HT: aOR=1.07, 95% CI: 1.01–1.15, P=0.030; sICH: aOR=1.13, 95% CI: 1.04–1.23, P=0.003) also showed significant associations. Notably, FIB-5 exhibited significant negative correlations with both outcomes (HT: aOR=0.95, 95% CI: 0.91–1.00, P=0.054; sICH: aOR=0.91, 95% CI: 0.85–0.98, P=0.002). In contrast, the APRI score, Forns index, and Fibrosis index showed no significant associations with HT or sICH risk (all P>0.05) (Table 6).

Non-Linear Association Analysis

RCS regression analysis revealed that liver fibrosis indices were primarily linearly related to hemorrhagic complications (Figures 5 and 6). Only modified FIB-4 showed a significant non-linear association with HT risk (P-nonlinear=0.006). In predicting sICH, all indices maintained linear associations, with no significant non-linear relationships observed.

Table 3 Baseline Clinical Characteristics of Patients with Anterior Circulation Large Vessel Occlusion Stroke Stratified by sICH Status

Variables	Non-sICH (n = 271)	sIHT (n = 69)	P Value
Demographics			
Age, years	67 (57, 75)	67 (57, 78)	0.589
Male sex	180 (66.42)	44 (63.77)	0.678
Current smoker	107 (39.48)	22 (31.88)	0.245
Alcohol consumption	68 (25.09)	19 (27.54)	0.678
Medical history			
Hypertension	183 (67.53)	43 (62.32)	0.413
Diabetes mellitus	73 (26.94)	25 (36.23)	0.128
Hyperlipidemia	65 (23.99)	13 (18.84)	0.364
Atrial fibrillation	112 (41.33)	36 (52.17)	0.105
Previous stroke/TIA	46 (16.97)	8 (11.59)	0.275
Coronary artery disease	32 (11.81)	13 (18.84)	0.124
Clinical Presentation			
SBP, mmHg	149 (133, 164)	144 (125, 156)	0.083
DPB, mmHg	87 (77, 99)	86 (77, 92)	0.119
Baseline NIHSS score	14 (11, 18)	16 (14, 20)	0.001
Baseline GCS score	13 (10, 15)	11 (9, 13)	0.006
Baseline ASPECT score	9 (8, 10)	8 (6, 10)	0.044
Anticoagulation therapy			0.035
No anticoagulation	240 (88.6)	57 (82.6)	
Warfarin	18 (6.6)	11 (15.9)	
DOACs	13 (4.8)	1 (1.4)	
Stroke etiology			0.532
Large-artery atherosclerosis	133 (49.08)	29 (42.03)	
Cardioembolism	124 (45.76)	36 (52.17)	
Other	14 (5.17)	4 (5.80)	
Procedural Characteristics			
Intravenous thrombolysis	121 (44.65)	25 (36.23)	0.207
OPT, min	371 (262, 573)	375 (287, 505)	0.952
PRT, min	75 (45, 99)	80 (56, 101)	0.122
ORT, min	463 (330, 664)	458 (357, 585)	0.949
NOTA	2 (1, 2)	2 (1, 3)	0.019
Successful reperfusion	233 (85.98)	58 (84.06)	0.685
Treatment Strategy			0.964
Stent retriever	59 (21.77)	14 (20.29)	
Aspiration	17 (6.27)	4 (5.80)	
Combined approach	178 (65.68)	48 (69.57)	
Balloon angioplasty	49 (18.08)	12 (17.39)	0.894
Thrombocytopenia	35 (12.92)	19 (27.54)	0.003

Notes: Values are presented as median (IQR) or n (%).

Abbreviations: sICH, symptomatic intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; DOACs, Direct Oral Anticoagulants; OPT, Onset-to-puncture time; PRT, Puncture-to-recanalization time; ORT, Onset-to-recanalization time; NOTA, Number of thrombectomy attempts.

Discussion

In this retrospective cohort study, we systematically evaluated the associations between eight non-invasive liver fibrosis indices and post-EVT hemorrhagic complications. Our findings provide several important insights. First, even after

Table 4 Laboratory Characteristics of Patients with and Without sICH After Endovascular Therapy

Variables	**Non-sICH (n = 271)**	**sIHT (n = 69)**	**P Value**
White blood cell, $\times 10^9$/L	11.1 (9.2, 13.5)	12.6 (11.1, 14.7)	0.001
Neutrophils, $\times 10^9$/L	9.3 (7.4, 11.6)	10.9 (9.7, 13.1)	<0.001
Lymphocytes, $\times 10^9$/L	1.11 (0.82, 1.40)	0.85 (0.61, 1.08)	<0.001
Monocytes, $\times 10^9$/L	0.57 (0.43, 0.72)	0.63 (0.50, 0.81)	0.109
Total protein, g/L	65 (62, 70)	64 (60, 69)	0.037
Albumin, g/L	37.2 (35.1, 39.4)	37.0 (32.5, 39.9)	0.244
Total bilirubin, μmol/L	16 (12, 21)	16 (13, 24)	0.390
ALT, U/L	17 (12, 24)	15 (11, 20)	0.027
AST, U/L	24 (19, 31)	27 (22, 37)	0.011
γ-Glutamyl transferase, U/L	29 (20, 47)	24 (18, 40)	0.080
Alkaline phosphatase, U/L	77 (66, 94)	76 (62, 88)	0.236
Triglycerides, mmol/L	1.07 (0.80, 1.42)	0.99 (0.70, 1.46)	0.254
Total cholesterol, mmol/L	4.36 (3.64, 5.10)	4.14 (3.11, 4.93)	0.042
HDL-C, mmol/L	1.17 (1.01, 1.35)	1.13 (0.93, 1.33)	0.115
LDL-C, mmol/L	2.88 (2.31, 3.42)	2.72 (1.82, 3.22)	0.053
FBG, mmol/L	7.3 (6.0, 9.5)	8.3 (6.9, 11.0)	0.002
BUN, mmol/L	5.40 (4.10, 7.00)	5.80 (4.30, 8.60)	0.055
Creatinine, μmol/L	72 (58, 85)	74 (61, 117)	0.080
Uric acid, μmol/L	327 (271, 402)	351 (265, 439)	0.346
Platelet count, $\times 10^9$/L	207 (176, 243)	178 (140, 210)	<0.001
FIB-4 index	1.86 (1.30, 2.78)	2.72 (1.57, 4.66)	<0.001
Modified FIB-4	4.5 (2.8, 6.9)	6.8 (3.8, 11.4)	<0.001
FIB-5 index	−2 (−6, 1)	−7 (−13, −1)	<0.001
APRI score	0.33 (0.23, 0.44)	0.46 (0.29, 0.70)	<0.001
Forns index	5.92 ± 1.62	6.46 ± 1.76	0.023
ARR score	1.42 (1.04, 1.88)	1.90 (1.32, 2.73)	<0.001
AARPRI	1.06 (0.74, 1.43)	1.61 (0.96, 2.73)	<0.001
Fibrosis index	1.78 ± 0.74	1.95 ± 0.81	0.108

Notes: Values are presented as median (interquartile range) or mean ± standard deviation, as appropriate.

Abbreviations: sICH, symptomatic intracerebral hemorrhage; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BUN, Blood urea nitrogen; FBG, fasting blood glucose; FIB-4, fibrosis-4; FIB-5, fibrosis-5; APRI, aspartate aminotransferase to platelet ratio index; ARR, ALT/AST ratio; AARPR, AST/ALT ratio-platelet ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

adjusting for multiple confounding factors, FIB-4, modified FIB-4, FIB-5, AAR, and AARPRI remained significantly associated with the risk of both HT and sICH. Second, the levels of liver fibrosis indices showed a progressive increase across the non-HT, HI, and PH groups (PH vs HI: $P<0.05$), suggesting that the severity of liver fibrosis may drive the worsening of hemorrhagic phenotypes. Furthermore, although the predictive values of these liver fibrosis indices were similar, the aforementioned indices demonstrated significantly better predictive ability for sICH than for HT.

Growing evidence suggests a strong association between liver fibrosis and cerebrovascular diseases. Numerous studies have shown that the degree of liver fibrosis is closely associated with poor outcomes in AIS patients, including increased short-term mortality, delayed long-term functional recovery, and increased risk of stroke recurrence.[18–21] Moreover, research based on non-invasive liver fibrosis indices has found that the severity of liver fibrosis is significantly correlated with the incidence of HT and sICH after intravenous thrombolysis.[22,23] In intracerebral hemorrhage studies, liver fibrosis has been proven to be closely related to hematoma volume at admission and its subsequent expansion.[31] However, the association between liver fibrosis and post-EVT hemorrhagic complications remains controversial.[24,25] Xu et al[24] based on a cohort study of Asian populations, demonstrated that elevated FIB-4 is an independent risk factor for

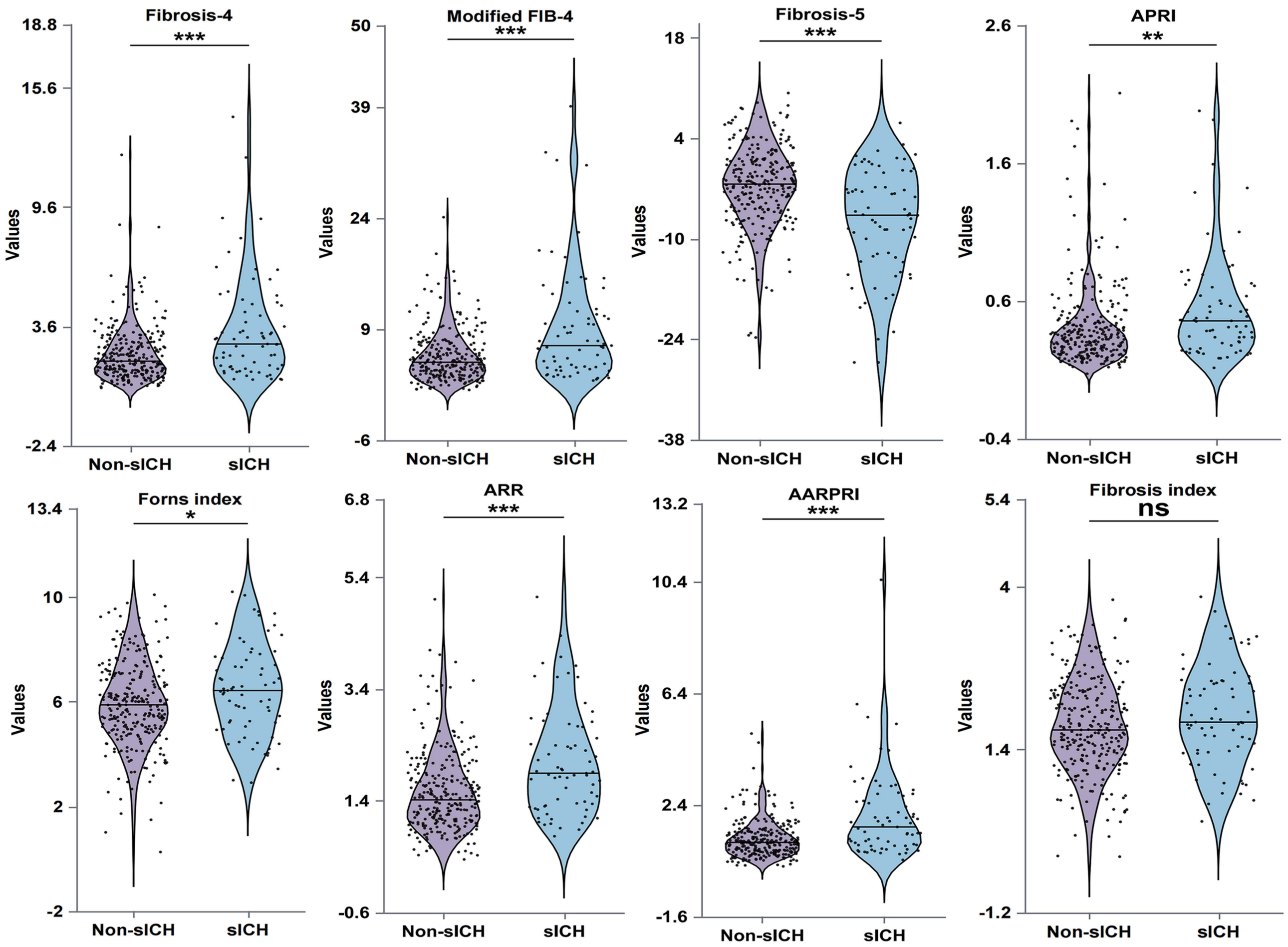

Figure 3 Comparison of Liver Fibrosis Indices Between Patients with and without Symptomatic Intracerebral Hemorrhage. Violin plots with embedded scatter plots comparing the distribution of liver fibrosis indices between patients with and without symptomatic intracerebral hemorrhage (sICH). The width of each violin represents the kernel density estimation of the data distribution. Individual dots represent actual data points. The horizontal lines within the violins indicate the median and quartiles. *P<0.05; **P<0.01; ***P<0.001; ns, not significant.

post-EVT sICH (OR=1.306, 95% CI: 1.127–1.512, P=0.001). In contrast, Höfler et al[25] in a European cohort study, found that although FIB-4 was associated with poor neurological functional outcomes and mortality 3 months after AIS, it was not related to the risk of HT or sICH. Our study supports the notion that liver fibrosis is an independent influence on post-EVT hemorrhagic risk, consistent with evidence from Asian populations. The reasons for the discrepancies in research results may include the following: First, there may be population differences between Asian and European cohorts, but the specific mechanisms still require further in-depth exploration in future studies. Second, the high incidence of HT after EVT may weaken the statistical association between the two. Furthermore, liver fibrosis indices were only significantly associated with the risk of PH (HI vs non-HT group: P>0.05), and previous controversies may have arisen from the failure to differentiate hemorrhage severity.

Liver fibrosis can contribute to the occurrence of post-EVT HT and sICH through multiple pathological mechanisms, including endothelial dysfunction, coagulation-fibrinolysis abnormalities, metabolic disorders, systemic inflammatory responses, and oxidative stress. First, circulating extracellular vesicles released by hepatocytes in MASLD patients can activate vascular endothelial inflammatory responses through signaling pathways such as miRNA-novel-7 and microRNA-1, promoting atherosclerotic plaque instability and microvascular leakage.[12,32–34] The chronic pro-inflammatory microenvironment leads to increased permeability of cerebral microvascular endothelium, resulting in blood-brain barrier (BBB) dysfunction and exacerbating post-ischemic neuronal injury. This BBB disruption-related cerebrovascular endothelial dysfunction has been proven to be a key factor in post-stroke HT.[35] Second, liver fibrosis can

Table 5 Diagnostic Performance of Liver Fibrosis Indices in Predicting Hemorrhagic Complications After Endovascular Therapy

Outcome and Parameter	AUC (95% CI)	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Cut-off Value
Hemorrhagic transformation					
Fibrosis-4	0.62 (0.56–0.68)	0.57 (0.52–0.63)	0.39 (0.32–0.46)	0.78 (0.71–0.84)	1.457
Modified fibrosis-4	0.62 (0.56–0.67)	0.59 (0.53–0.64)	0.40 (0.32–0.47)	0.80 (0.73–0.86)	3.45
Fibrosis-5	0.61 (0.55–0.67)	0.39 (0.34–0.45)	0.25 (0.19–0.31)	0.55 (0.48–0.63)	−5.264
APRI	0.61 (0.54–0.67)	0.59 (0.54–0.65)	0.65 (0.58–0.72)	0.53 (0.45–0.61)	0.373
Forns index	0.57 (0.50–0.63)	0.57 (0.52–0.62)	0.63 (0.55–0.70)	0.51 (0.43–0.59)	6.158
ARR	0.61 (0.55–0.67)	0.61 (0.56–0.66)	0.73 (0.67–0.80)	0.48 (0.40–0.56)	1.748
AARPRI	0.62 (0.57–0.68)	0.61 (0.56–0.66)	0.81 (0.75–0.87)	0.39 (0.32–0.47)	1.468
Fibrosis index	0.54 (0.48–0.61)	0.54 (0.49–0.60)	0.46 (0.39–0.54)	0.63 (0.56–0.71)	1.615
Symptomatic Intracerebral hemorrhage					
Fibrosis-4	0.65 (0.58–0.73)	0.69 (0.64–0.74)	0.73 (0.67–0.78)	0.57 (0.45–0.68)	2.597
Modified fibrosis-4	0.67 (0.59–0.74)	0.70 (0.65–0.75)	0.73 (0.68–0.78)	0.57 (0.45–0.68)	6.363
Fibrosis-5	0.69 (0.61–0.76)	0.26 (0.21–0.31)	0.21 (0.16–0.25)	0.46 (0.35–0.58)	−6.419
APRI	0.65 (0.57–0.72)	0.71 (0.66–0.76)	0.76 (0.71–0.81)	0.52 (0.40–0.64)	0.451
Forns index	0.58 (0.50–0.66)	0.64 (0.58–0.69)	0.66 (0.61–0.72)	0.54 (0.42–0.65)	6.357
ARR	0.68 (0.61–0.75)	0.71 (0.65–0.75)	0.73 (0.68–0.79)	0.59 (0.48–0.71)	1.811
AARPRI	0.70 (0.62–0.77)	0.78 (0.73–0.83)	0.86 (0.82–0.90)	0.48 (0.36–0.60)	1.752
Fibrosis index	0.56 (0.48–0.64)	0.70 (0.65–0.75)	0.79 (0.74–0.84)	0.35 (0.24–0.46)	2.361

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; FIB-4, fibrosis-4 index; FIB-5, fibrosis-5 index; APRI, aspartate aminotransferase to platelet ratio index; AAR, aspartate aminotransferase to alanine aminotransferase ratio; AARPRI, aspartate aminotransferase to alanine aminotransferase-platelet ratio index.

also increase the risk of hemorrhage by affecting coagulation function and metabolic status. Most coagulation factors, such as fibrinogen, thrombin, and coagulation factors V, VII, IX, and X, are synthesized by the liver and undergo post-translational modifications. Hepatocellular injury can lead to abnormal synthesis and function of coagulation factors.[13,36] Furthermore, the progression of liver fibrosis can inhibit the production of thrombopoietin, leading to thrombocytopenia, which is consistent with the decreased platelet count observed in the hemorrhage group in this study.[37] These factors can collectively increase the risk of hemorrhage. Additionally, MASLD is often accompanied by atherogenic dyslipidemia,

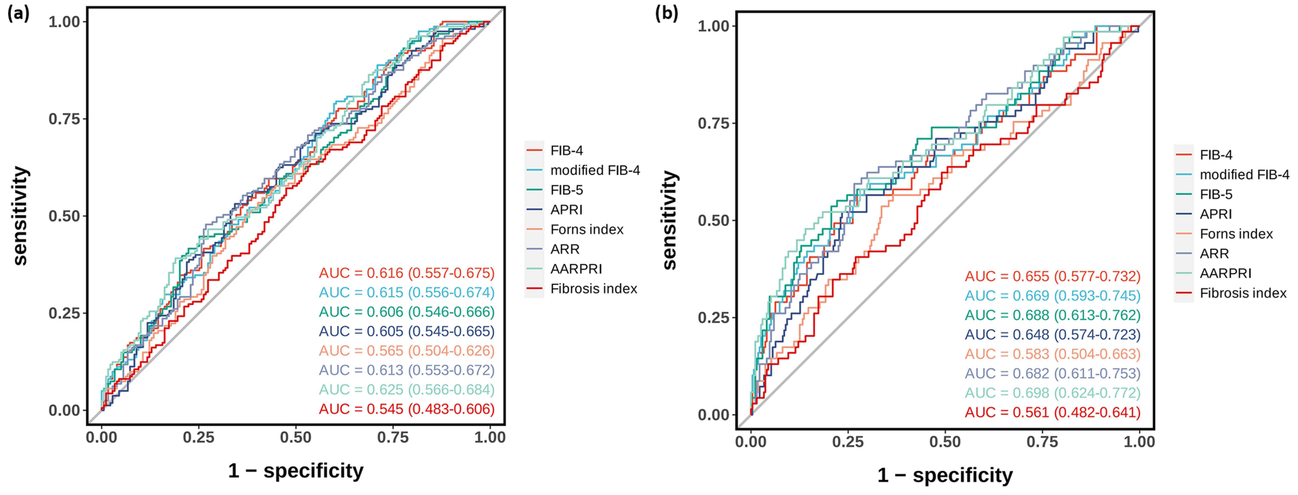

Figure 4 Receiver Operating Characteristic Curves for Liver Fibrosis Indices in Predicting Hemorrhagic Complications. Receiver operating characteristic (ROC) curves showing the predictive performance of liver fibrosis indices for (**a**) hemorrhagic transformation and (**b**) symptomatic intracerebral hemorrhage. The area under the curve (AUC) values with 95% confidence intervals are shown for each index. The diagonal gray line represents the reference line of no discrimination (AUC = 0.5).

Table 6 Multivariable Logistic Regression Analysis of Fibrosis Indices for Predicting HT and sICH

Variables	**Model 1**		**Model 2**		**Model 3**	
	OR (95% CI)	**P Value**	**OR (95% CI)**	**P Value**	**OR (95% CI)**	**P Value**
Hemorrhagic transformation						
FIB-4 index	1.25 (1.08–1.44)	0.002	1.25 (1.09–1.45)	0.002	1.25 (1.01–1.56)	0.044
Modified FIB-4	1.10 (1.04–1.16)	<0.001	1.10 (1.04–1.16)	0.001	1.07 (1.01–1.15)	0.030
FIB-5 index	0.93 (0.90–0.97)	<0.001	0.94 (0.90–0.97)	<0.001	0.95 (0.91–1.00)	0.054
APRI score	1.89 (0.94–3.81)	0.074	1.82 (0.88–3.79)	0.108	2.13 (0.27–16.46)	0.470
Forns index	1.17 (1.02–1.33)	0.022	1.14 (1.00–1.31)	0.057	1.03 (0.83–1.28)	0.805
ARR score	1.57 (1.18–2.08)	0.002	1.57 (1.17–2.11)	0.002	1.43 (1.03–1.96)	0.030
AARPRI	1.76 (1.31–2.35)	<0.001	1.70 (1.27–2.29)	<0.001	1.53 (1.07–2.17)	0.019
Fibrosis index	1.26 (0.95–1.68)	0.113	1.24 (0.92–1.69)	0.160	1.06 (0.72–1.56)	0.773
Symptomatic Intracerebral hemorrhage						
FIB-4 index	1.41 (1.21–1.63)	<0.001	1.40 (1.20–1.63)	<0.001	1.48 (1.12–1.94)	0.005
Modified FIB-4	1.16 (1.09–1.23)	<0.001	1.16 (1.09–1.24)	<0.001	1.13 (1.04–1.23)	0.003
FIB-5 index	0.89 (0.85–0.93)	<0.001	0.89 (0.85–0.93)	<0.001	0.91 (0.85–0.98)	0.018
APRI score	3.45 (1.65–7.21)	<0.001	3.29 (1.52–7.12)	0.003	8.58 (0.65–112.35)	0.102
Forns index	1.22 (1.04–1.44)	0.017	1.21 (1.01–1.44)	0.034	0.89 (0.63–1.27)	0.537
ARR score	2.15 (1.56–2.95)	<0.001	2.20 (1.57–3.09)	<0.001	1.91 (1.16–3.12)	0.010
AARPRI	2.41 (1.74–3.32)	<0.001	2.43 (1.74–3.39)	<0.001	2.36 (1.45–3.84)	<0.001
Fibrosis index	1.36 (0.96–1.94)	0.088	1.32 (0.90–1.92)	0.153	0.87 (0.47–1.60)	0.646

Notes: Model 1: Unadjusted. Model 2: Adjusted for clinical factors (baseline NIHSS score, GCS score, ASPECTS, systolic blood pressure, puncture-to-reperfusion time, and number of thrombectomy attempts for HT; baseline NIHSS score, GCS score, ASPECTS, number of thrombectomy attempts and anticoagulation therapy for sICH). Model 3: Additionally adjusted for laboratory parameters (total bilirubin, AST, triglyceride, neutrophils, lymphocytes and platelet count for HT; total protein, ALT, AST, total cholesterol, fasting blood glucose, platelet count, neutrophils, lymphocytes for sICH).

Abbreviations: HT, hemorrhagic transformation; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; FIB-5, fibrosis-5; APRI, aspartate aminotransferase to platelet ratio index; ARR, ALT/AST ratio; AARPR, AST/ALT ratio-platelet ratio.

manifested as elevated triglycerides, increased small, dense low-density lipoprotein particles, decreased high-density lipoprotein cholesterol, and type 2 diabetes, all of which contribute to increased vascular wall fragility.[14,38]

Liver fibrosis can also participate in the pathological process of HT by inducing systemic inflammatory responses. du Plessis et al[39] found that the severity of MASLD histology positively correlated with the levels of inflammatory mediators. In particular, serum MMP-9 levels were significantly higher in MASH patients compared to controls (12.6±6.5 vs 8.1±3.5,

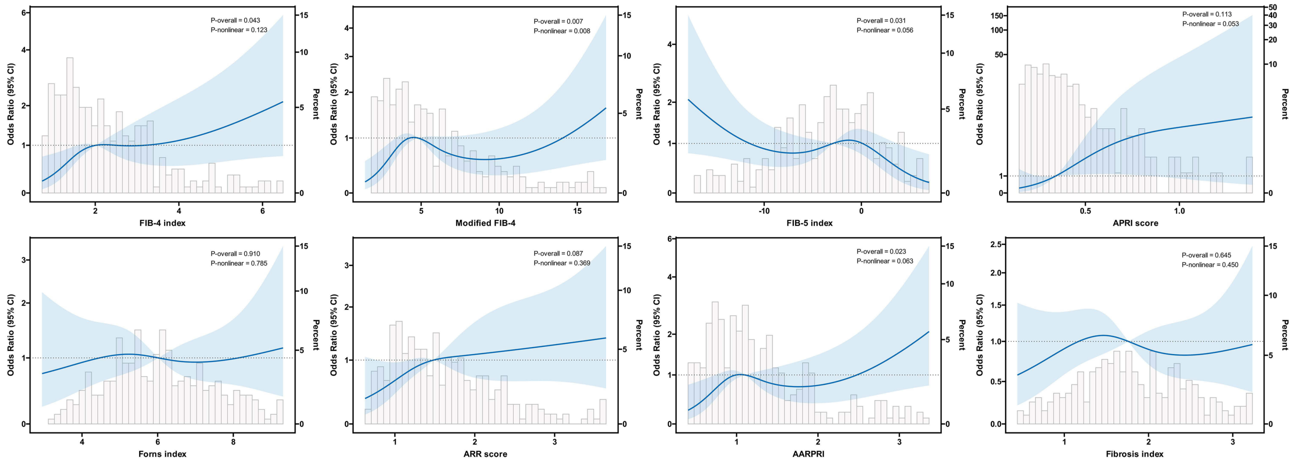

Figure 5 Restricted Cubic Spline Analysis of the Association Between Liver Fibrosis Indices and Hemorrhagic Transformation Risk. Restricted cubic spline curves showing the dose-response relationship between liver fibrosis indices and the risk of hemorrhagic transformation. The solid blue lines represent the estimated odds ratios (ORs), and the shaded areas represent the 95% confidence intervals. Histograms show the distribution of each index in the study population. The reference line (OR = 1) is indicated by the horizontal dotted line. P-overall indicates the significance of the overall association, and P-nonlinear indicates the significance of non-linear components.

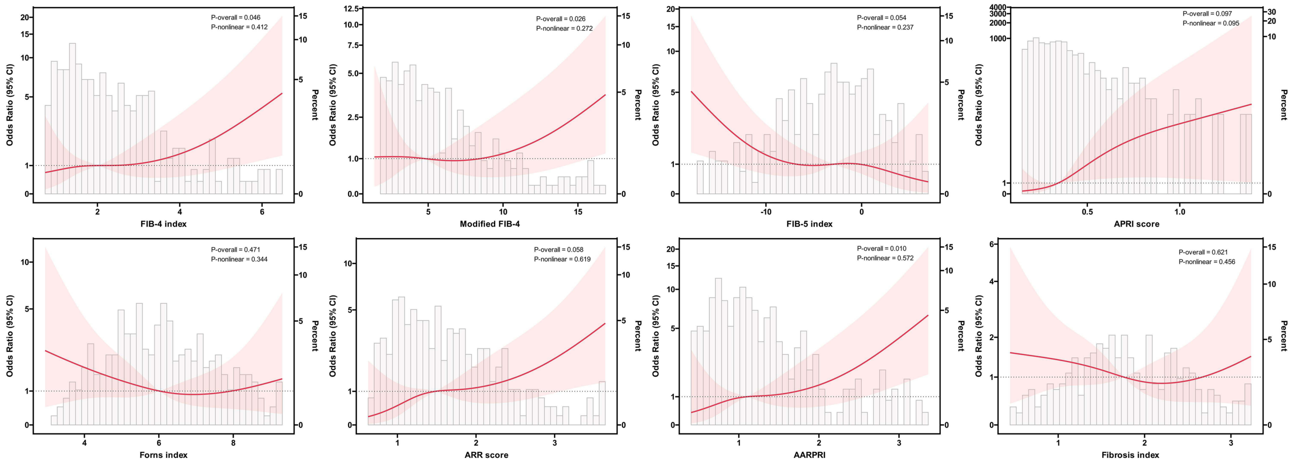

Figure 6 Restricted Cubic Spline Analysis of the Association Between Liver Fibrosis Indices and Symptomatic Intracerebral Hemorrhage Risk. Restricted cubic spline curves showing the dose-response relationship between liver fibrosis indices and the risk of hemorrhagic transformation. The solid blue lines represent the estimated odds ratios (ORs), and the shaded areas represent the 95% confidence intervals. Histograms show the distribution of each index in the study population. The reference line (OR = 1) is indicated by the horizontal dotted line. P-overall indicates the significance of the overall association, and P-nonlinear indicates the significance of non-linear components.

$P<0.01$).[15] MMP-9 is closely related to HT in AIS patients.[40] Previous studies have found that after the occurrence of intracerebral hemorrhage, leukocyte infiltration can activate microglia and recruit peripheral immune cells, accelerating hematoma expansion.[41,42] MASLD can exacerbate this cascade reaction by mobilizing peripheral immune cells.[43] This study found that patients in the PH group had significantly higher liver fibrosis indices compared to the HI and non-HT groups, suggesting that the degree of liver fibrosis may be related to the severity of hemorrhagic lesions. Furthermore, oxidative stress, as a common pathological basis for liver diseases and cardiovascular diseases, can trigger the occurrence of HT by degrading the extracellular matrix and tight junction proteins of the BBB, thereby disrupting BBB integrity.[16,44]

This study has several limitations. First, as a single-center retrospective study, there may be selection bias, and the generalizability of the results needs to be validated. The characteristics of retrospective studies also limit the acquisition and analysis of certain potentially relevant variables (such as detailed medication history and liver imaging data). Furthermore, our dataset lacked body mass index measurements, which represents a significant limitation given the established association between BMI and AIS outcomes. The absence of this anthropometric parameter may have precluded a more comprehensive analysis of potential confounding factors. Second, although the correlation between liver fibrosis and post-EVT hemorrhage has been confirmed, the guiding significance for clinical practice still needs to be further explored. Additionally, the recent emergence of therapeutic interventions for MASLD, including FDA-approved resmetirom and investigational agents, may potentially alter the natural history and severity of liver fibrosis in future patient populations, which could affect the generalizability of our findings to prospective cohorts treated with these novel therapies.Third, this study employed multiple validated non-invasive liver fibrosis indices, but lacked the corroboration of the diagnostic gold standard—liver biopsy. Future studies could combine imaging examinations (such as liver elastography) and serological indicators to improve the accuracy of liver fibrosis diagnosis. Finally, given the heterogeneity of existing research results, the robustness of the association between post-EVT hemorrhage and liver fibrosis needs to be verified, and differences in the included populations may be a potential reason. The relationship between the two needs to be further clarified through multicenter, prospective studies.

Conclusion

This study confirmed the independent association between non-invasive liver fibrosis indices and post-EVT hemorrhagic complications (HT and sICH) in patients with anterior circulation stroke. Multiple liver fibrosis indices had similar predictive values for both hemorrhagic events. Notably, the severity of liver fibrosis may be related to the type of hemorrhagic transformation (PH vs HI). These findings reveal the potential value of liver fibrosis indices in risk stratification for post-EVT HT. In the future, multicenter prospective studies should be conducted to further validate the robustness of this association and explore hemorrhage prevention strategies for high-risk patients.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was conducted with approval from the Ethics Committee of the Zhongshan Hospital of Xiamen University (No.xmzsyyky2022-196). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for Publication

As the study was retrospective and the data were anonymized, the ethics committee agreed to waive the requirement for informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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