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ORIGINAL RESEARCH

Liver Fibrosis is Associated with Clinical Outcomes in Patients with Intracerebral Hemorrhage

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Background: Recent studies have reported the predictive value of liver fibrosis indices for hematoma enlargement in patients with intracerebral hemorrhage (ICH). However, little is known about the precise association between fibrosis and ICH prognosis. Thus, our study was designed to investigate the relevance of liver fibrosis, as evaluated by fibrosis-4 (FIB-4) score and poor outcomes after ICH.

Methods: We used data from a prospective, multi-center and registry-based database. In this study, patients were stratified by the higher cut-off value of a FIB-4 score ≥2.67. The two groups of patients were then compared with regard to baseline characteristics, ICH severity and follow-up outcomes. We performed univariable and multivariable logistic regression analysis to determine the prognostic value of a FIB-4 score ≥2.67 for major disability or death. Kaplan–Meier survival curves were used to analyze the association between different FIB-4 scores and survival rate.

Results: Our present study included 839 patients from 13 hospitals in Beijing. Participants with FIB-4 scores ≥2.67 had a larger baseline hematoma volume and a higher score on the modified Rankin Scale at follow-up (all p values <0.05). In the logistic regression analysis, liver fibrosis defined by a FIB-4 score ≥2.67 was independently associated with poor clinical outcomes at discharge and at 1 year (at discharge: adjusted odds ratio [95% CI] = 1.894 [1.120–3.202], p = 0.0172; at 1 year: adjusted odds ratio [95% CI] = 1.694 [1.021–2.809], p = 0.0412). However, this association was not observed at 3 months. During the follow-up period, patients with a FIB-4 score ≥2.67 also had a significantly lower survival rate according to Kaplan–Meier survival analysis.

Conclusion: Our study suggests that liver fibrosis defined by a FIB-4 score ≥2.67 is associated with poor clinical outcomes and lower survival rates in patients with mild to moderate ICH. These data provide reliable evidence for detecting fibrosis and managing related risk factors to improve prognosis after ICH.

Keywords: liver fibrosis, FIB-4 score, intracerebral hemorrhage, clinical outcomes, survival rate

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a potentially serious liver dysfunction. The overall incidence rate of NAFLD ranges from 23% to 25% and creates substantial burdens on families and society.[1] In the setting of global obesity, the prevalence of NAFLD has increased steadily over recent years, affecting both adults and children.[2] In China, the reported prevalence of NAFLD reached 29.6% over the past two decades.[3] NAFLD is one of the main etiologies of cirrhosis, including excessive fat accumulation (non-alcoholic steatohepatitis, NASH), progression to inflammation and fibrosis, liver cirrhosis, and even carcinoma.[4,5] The pathological grade of liver fibrosis ranges from stage 0 (no fibrosis) to stage 4 (cirrhosis). The presence of fibrosis (stage 1–4) and in particular, advanced fibrosis (AF, stage 3–4), is a critical prognostic marker for liver-related outcomes and overall mortality.[6] Thus, it is vital to identify patients at higher risk of advanced fibrosis to optimize their management.

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Liver biopsy is currently considered as the gold standard for the assessment of fibrosis but is too invasive to use as a routine screening test. More non-invasive tests involve transient elastography (TE) and the enhanced liver fibrosis (ELF) test which exhibit good performance for identifying patients with fibrosis. However, there are some limitations associated with these tests, including price and the requirement for specific training.[7] In addition, several non-invasive scoring systems, including the fibrosis-4 (FIB-4) score, aspartate aminotransferase (AST)-to-platelet ratio index (APRI), BARD score, and NAFLD fibrosis score, have been developed and can be used to exclude patients without AF.[5,8] These assessments are based on simple blood indices and clinical data and thereby avoid unnecessary biopsy and excessive cost. Of the common non-invasive clinical indices, the FIB-4 score probably yields the best diagnostic performance for detecting AF.[9] When a FIB-4 score threshold of 2.67 was used to screen for AF, the sensitivity and specificity was 26.6% and 96.5%, respectively.

Accumulating clinical evidence supports the fact that NAFLD is closely associated with an increased risk of cerebrovascular diseases (CVSD) and stroke-related death.[10–13] Recently, Parikh et al[14] reported the association between liver fibrosis and hematoma volume on admission and subsequent hematoma enlargement (HE) in patients with intracerebral hemorrhage (ICH). ICH is a catastrophic disease with a significant mortality rate during the acute stage and a high disability rate among surviving patients; consequently, there is an urgent need to perform further research related to the prevention and treatment of ICH.[15–18] However, existing research is limited and partly controversial; the underlying mechanisms have yet to be elucidated. Further clinical and preclinical research might provide more reliable evidence with regard to identifying liver fibrosis and controlling risk factors to improve prognosis after ICH. Therefore, this study was designed to determine the association between ICH prognosis and liver fibrosis evaluated by FIB-4 score.

Materials and Methods

Study Design and Population

We used data from a prospective, multi-center and registry-based study. Consecutive patients with ICH were recruited from 13 hospitals in Beijing between January 2014 and September 2016. The study was approved by the Institutional Review Board (IRB) of Beijing Tiantan Hospital, in full accordance with the Declaration of Helsinki. Before participating in the study, all patients or their legal relatives were required to sign an informed consent. All data were collected by qualified researchers from each hospital and finally summarized by the research team of the coordinating center.

The inclusion criteria were as follows: (1) ICH was diagnosed by the WHO standard and confirmed by each hospital's computerized tomography (CT) scan; (2) age ≥18 years old; (3) patient arrived in the emergency room within 72 hours after the onset of symptoms, and (4) patient provided the written consent. Patients were excluded if there were known major comorbidities or late-stage diseases, such as liver failure, end-stage kidney diseases, heart failure and malignant tumors. Additional exclusion criteria were as follows: (1) congenital or obtained coagulation disorders confirmed by imaging or laboratory tests; (2) self-reported alcohol use; (3) missing epidemiological and/or clinical data that was indispensable for calculating FIB-4 score, and (4) missing outcomes at follow-up. A total of 839 patients were finally included in our study after excluding 1125 patients (detailed in Figure 1).

Assessment of Epidemiological, Clinical and ICH Data

We designed a standardized questionnaire for the participants or legal relatives to collect epidemiological data, comorbidity data, the current usage of drugs and other conditions such as smoking and drinking. Hypertension was defined when a patient reported a history of high blood pressure, taking antihypertensive medication, or was found with a systolic blood pressure (SBP) ≥140mmHg or diastolic blood pressure (DBP) ≥90mmHg at baseline. Diabetes mellitus was recorded when a patient reported a history, or accepting hypoglycemic treatment, or was found with a fasting blood glucose (FBG) level ≥7.0 mmol/L at baseline. Dyslipidemia was noted when a patient reported a history of hyperlipidemia or currently using lipid-lowering drugs or was found with a total cholesterol (TC) level ≥6.22 mmol/L or triglyceride (TG) ≥2.26 mmol/L or low-density lipoprotein (LDL) ≥4.14 mmol/L at baseline. Smoking was defined as if a patient smoked more than one cigarette per day for at least one year. To minimize the confounding effects of alcohol consumption, we excluded any patients with self-reported drinking.

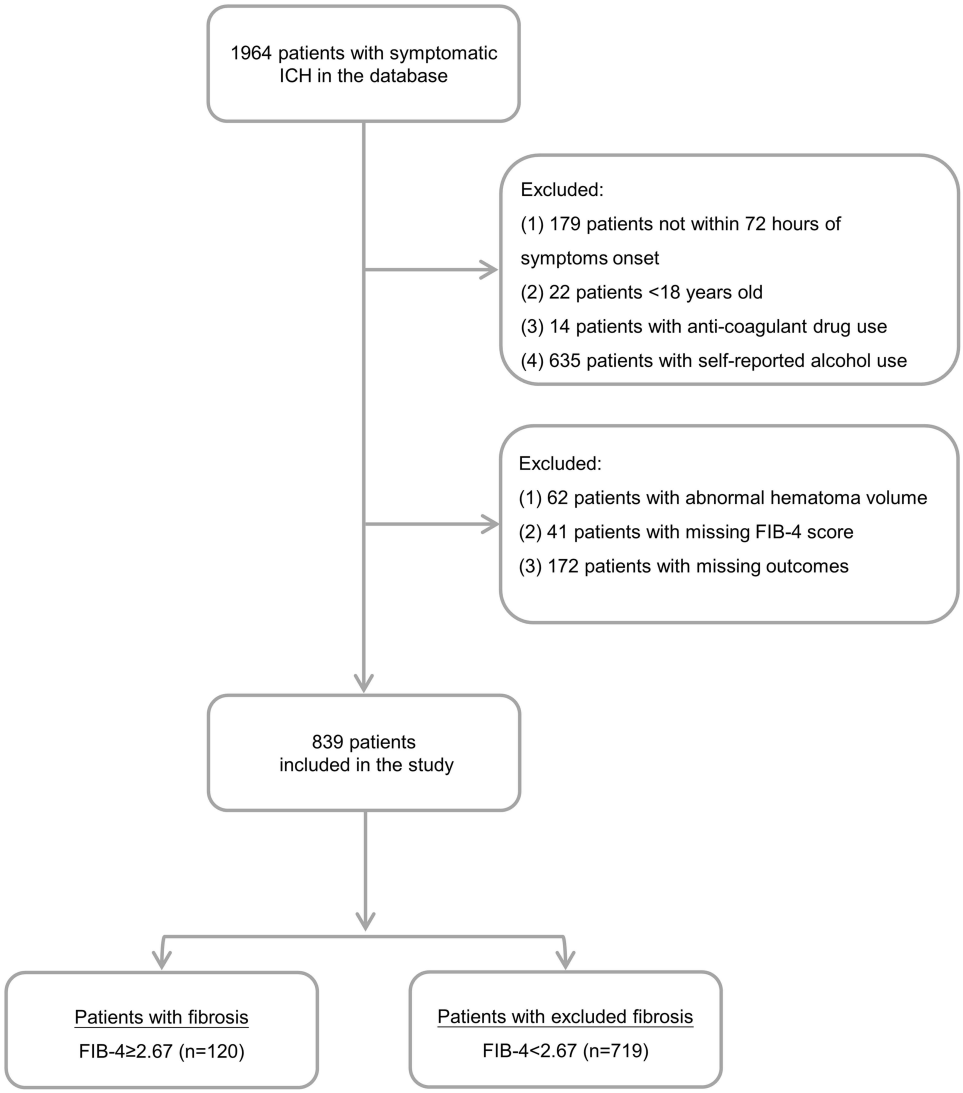

Figure 1 The flowchart of our present study.

Baseline BP was measured in the emergency room. The Glasgow Coma Scale (GCS) and the National Institute of Health Stroke Scale (NIHSS) were used to evaluate the conscious status and neurological deficits. All patients underwent non-contrast computerized tomography (NCCT) on admission to identify the location (lobar, deep, and infratentorial hemorrhage) and volume of ICH hematoma. The coordinating center centrally gathered all digital CT images in uncompressed DICOM formats. All imaging data were separately analyzed by two experienced neurologists who were blinded to the clinical conditions of the patients. The ICH hematoma volumes were calculated using the ABC/2 method.[19] We also recorded if a patient underwent brain surgery during the period of hospitalization, including decompressive craniectomy, craniotomy evacuation of hematoma, hematoma aspiration, and lateral ventriculopuncture drainage.

Assessment of FIB-4 Scores and Other Laboratory Data

Blood samples were taken from superficial veins on admission and measured in qualified clinical laboratories, including AST, alanine aminotransferase (ALT) and platelet counts. In our study, we applied the FIB-4 score for the assessment of liver fibrosis (FIB-4 <1.30, low risk; FIB-4 1.3–2.67, moderate risk; and FIB-4 ≥2.67, high risk).[20,21] The formula to calculate this index is as follows: FIB-4 index = (age× AST [U/L])/(PLT × (ALT [U/L])$^{1/2}$). In the present study, all

participants were stratified by the higher cut-off value of 2.67 for identifying fibrosis. Other laboratory data were also tested on admission, such as international normalized ratio (INR) and activated partial thromboplastin time (APTT).

Follow-Up and Outcomes

A face-to-face interview was conducted at discharge for each patient, while telephone interviews were carried out at 1 month, 3 months and 1 year after the onset of ICH symptoms. In each telephone follow-up, the researchers followed a structural interview protocol that was answered by each patient or their relatives to assess their functional status. Trained research coordinators used modified Rankin Scale (mRS) to assess the functional status at each time-point; these coordinators were blinded to each patient's baseline characteristics. A poor outcome was defined as an mRS score of 3–6, which usually represents a dependently functional status of major disability or death.[22] Major disability among survivors was defined as a mRS score of 3–5. All-cause death was further recorded in detail and analyzed separately.

Statistical Analysis

SAS software (version 9.4; SAS Institute, Cary, NC, USA) was used for statistical analysis. Continuous variables are presented as means ± standard deviation (SD) or medians (interquartile range, IQR), while categorical variables are recorded as counts (%). The Student's *t* test or Kruskal–Wallis test was used to compare continuous variables, while the Chi-square test was performed for categorical variables. To analyze the association between FIB-4 scores and clinical outcomes, we further conducted multivariate logistic regression analysis. Correlations between independent variables were checked for possible collinearity between variables. For each endpoint, two multivariable models were built to correct for covariates which showed significant relevance in the univariable analysis ($p < 0.05$). In model 1, only demographic data was adjusted, including age and sex. Model 2 was adjusted for age, admission DBP, prior dyslipidemia, and baseline hematoma volume. Moreover, a Kaplan–Meier (K-M) curve was generated to estimate the overall probability of survival; the Log Rank test was used to compare the differences. $P < 0.05$ was considered as the threshold of statistical significance.

Results

In total, we recruited 1964 patients; 1785 patients were confirmed as ICH by CT scans within 72 hours of onset. We excluded 22 patients with an age <18 years, 14 patients with anti-coagulant drug use, 635 patients with self-reported alcohol use, 62 patients with abnormal hematoma volumes calculated by CT images, 41 patients with invalid FIB-4 scores, and 172 patients with missing follow-up data. Finally, 839 patients were included in our study.

Of the 839 participants recruited in this study, the median age was 59.0 (49.0–69.0) years old and 52.3% (439) were males. Main liver function indices were generally within the normal range (Table 1). All patients were stratified by the higher cut-off value of the FIB-4 score (FIB-4 ≥2.67 vs FIB-4 <2.67, 120 [14.3%] vs 719 [85.7%]). The baseline characteristics of the two groups are shown in Table 1. The participants with a high risk of fibrosis, defined by a FIB-4 score ≥2.67, were more likely to be older, had a higher DBP, a larger hematoma volume and a more severe condition on admission (all p values <0.05). When comparing the baseline clinical data, we found that patients with a FIB-4 score ≥2.67 had a significantly higher INR value ($p < 0.05$). However, no significant difference was found in comparisons of other baseline ICH data between two groups with different FIB-4 scores, including ICH location, intraventricular extension, and the extension into subarachnoid space. In addition, there was no statistical difference in the distribution of gender, hypertension, diabetes mellitus, and cerebral infarction between the two groups. There was a significantly smaller proportion of patients with a history of dyslipidemia in patients with a FIB-4 score ≥2.67 ($p = 0.0320$). A larger proportion of patients were found to have undergone surgical treatment in the higher FIB-4 group ($p = 0.042$).

Next, we compared ICH prognosis between the two groups (Table 2). Patients with a FIB-4 score ≥2.67 had significantly more severe neurological deficits and conscious status at discharge (all p values <0.05). The distribution of mRS scores with regard to functional outcomes is shown in Figure 2. At each follow-up point, patients with a FIB-4 score ≥2.67 had a significantly higher mRS score (all p values <0.05). There was also a notably higher all-cause mortality rate during hospitalization, at 3 months and 1 year (all p values <0.05). To confirm the association between

Table 1 Baseline Characteristics of Study Participants Stratified by the Level of FIB-4 Score

Characteristic	Study Sample (N=839)	FIB-4 Score ≥2.67 (N= 120)	FIB-4 Score <2.67 (N=719)	P value
Epidemiology				
Age (years)[$]	59.0 (49.0–69.0)	71.0 (61.3–77.5)	57.0 (48.0–66.0)	<0.0001
Male, n (%)	439 (52.3%)	64 (53.3%)	375 (52.1%)	0.8110
Current smoking, n (%)	148 (17.6%)	23 (19.1%)	125 (17.3%)	0.5038
Hypertension, n (%)	579 (68.3%)	80 (66.6%)	499 (69.7%)	0.4923
Diabetes mellitus, n (%)	135 (16.1%)	17 (14.1%)	118 (16.4%)	0.5355
Dyslipidemia, n (%)	70 (8.3%)	4 (3.3%)	66 (9.1%)	0.0320
Prior cerebral infarction, n (%)	117 (14.0%)	12 (10.0%)	105 (14.6%)	0.1778
Prior antiplatelet use, n (%)	133 (15.9%)	18 (15.0%)	115 (15.9%)	0.7365
Clinical data at admission				
SBP (mmHg)[†]	167.7 ± 29.5	164.8 ± 12.8	168.1 ± 29.4	0.3457
DBP (mmHg)[†]	95.7 ± 18.2	90.7 ± 18.5	96.5 ± 18.0	0.0011
GCS[$]	14.0 (9.0–15.0)	12.0 (6.0–14.0)	14.0 (9.0–15.0)	<0.0001
NHISS[$]	10.0 (3.0–19.0)	14.5 (8.0–25.0)	10.0 (4.0–21.0)	0.0001
Imaging data at admission				
Location of hematoma, n (%)				0.4190
Lobar ICH	141 (18.8%)	26 (23.8%)	115 (17.9%)	
Deep ICH	451 (60.1%)	60 (55.0%)	391 (60.9%)	
Infratentorial ICH	80 (10.7%)	12 (11.0%)	68 (10.5%)	
Breaking into ventricle n (%)	296 (39.4%)	51 (46.7%)	245 (38.1%)	0.0861
With SAH, n (%)	125 (16.7%)	19 (17.4%)	106 (16.5%)	0.8274
Hematoma volume, (mL)[$]	16.4 (6.0–39.5)	22.7 (8.2–46.9)	15.8 (5.8–36.9)	0.0211
Laboratory data at admission				
ALT (U/L)[$]	22.2 (15.0–31.3)	19.7 (13.0–32.5)	22.8 (15.5–31.2)	<0.0001
AST (U/L)[$]	21.0 (17.0–28.0)	34.5 (24.9–57.5)	20.2 (16.1–25.4)	0.0843
PLT (10^{12}/L)[$]	213.0 (173.0–256.0)	143.5 (115.0–182.0)	221.0 (182.0–185.0)	<0.0001
APTT (sec)[$]	27.2 (24.1–30.4)	27.8 (25.0–31.2)	27.0 (24.1–30.3)	0.0679
INR[$]	1.0 (0.9–1.0)	1.0 (0.9–1.1)	0.9 (0.9–1.0)	<0.0001
Surgery during hospitalization, n (%)	154 (18.4%)	30 (25.0%)	124 (17.2%)	0.0422

Notes: Continuous variables are expressed as means (± SD)[†]or medians (IQR)[$] as appropriate, and categorical variables are presented as n (%).
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet; APTT, activated partial thromboplastin time; INR, international normalized ratio.

fibrosis and death rate, we further made K-M curves for all patients. A total survival incidence was presented as cumulative incidence. The results indicate that patients with a FIB-4 score ≥2.67 always had a significantly lower rate of survival than patients with a FIB-4 score <2.67 (at discharge, p = 0.0041; at 3 months, p = 0.0064; at 1 year, p = 0.0002. Figure 3).

When comparing the association of clinical outcomes and FIB-4 scores, we found a much larger proportion of patients with a poor prognosis in the group with FIB-4 scores ≥2.67, including death rate, major disability and composite major disability or death at follow-up. Finally, univariable and multivariable logistic regression analyses were performed to verify the independent prediction of fibrosis with regard to poor outcomes (Table 3). In model 1, after adjusting for age and sex, a FIB-4 score ≥2.67 was associated with a higher risk of disability and composite poor outcomes (all p values <0.05). In model 2, even after adjusting for age and other confounders, a FIB-4 score ≥2.67 was still shown to be independently associated with a poor clinical outcome at discharge and 1 year (at discharge: adjusted OR [95% CI] = 1.894 [1.120–3.202], p = 0.0172; at 1 year: adjusted OR [95% CI] = 1.694 [1.021–2.809], p = 0.0412). However, we did not detect the relationship at 3 months (adjusted OR [95% CI] = 1.289 [0.784–2.120], p = 0.3173).

Table 2 Association with ICH Severity and Prognosis Between Two Groups with Different Ranges of FIB-4 Score

Outcomes	FIB-4 score ≥2.67 (n=120)	FIB-4 score <2.67 (n=719)	P value
At discharge			
NIHSS[$]	9.0 (4.0–14.0)	6.0 (2.0–12.0)	0.0082
GCS[$]	14.0 (11.0–15.0)	15.0 (13.0–15.0)	0.0006
mRS score[$]	4.0 (3.0–5.0)	4.0 (1.0–4.0)	<0.0001
Death, n (%)	23 (19.1%)	69 (9.6%)	0.0019
Major disability, n (%)	72 (74.2%)	358 (55.0%)	0.0004
Major disability or death, n (%)	95 (79.1%)	427 (59.3%)	<0.0001
At 3 months			
mRS score[$]	4.0 (2.0–6.0)	3.0 (1.0–4.0)	<0.0001
Death, n (%)	32 (26.6%)	88 (73.3%)	0.0066
Major disability, n (%)	54 (61.3%)	263 (43.7%)	0.0020
Major disability or death, n (%)	86 (71.6%)	381 (52.9%)	0.0001
At 1 year			
mRS score[$]	4.0 (2.0–6.0)	2.0 (1.0–4.0)	<0.0001
Death, n (%)	43 (37.0%)	142 (20.7%)	0.0001
Major disability, n (%)	40 (54.7%)	172 (31.6%)	<0.0001
Major disability or death, n (%)	83 (71.5%)	314 (45.8%)	<0.0001

Notes: Continuous variables are expressed as medians (IQR)[$] as appropriate, and categorical variables are presented as n (%).
Abbreviations: ICH, Intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; mRS, modified Rankin Scale.

Discussion

Our study indicates the association between ICH prognosis and fibrosis as determined by FIB-4 score. On admission, patients with a FIB-4 score ≥2.67 usually had a larger hematoma volume and a more severe condition. At follow-up,

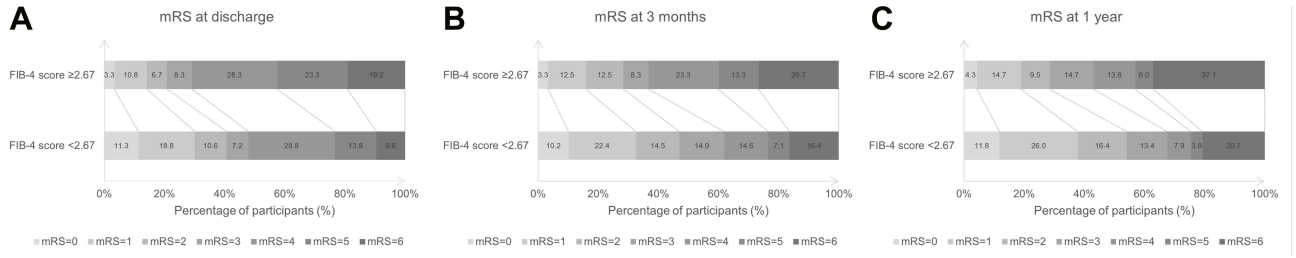

Figure 2 The distributions of the modified Rankin Scale (mRS) score between the two groups at follow-up (FIB-4 score ≥2.67 vs FIB-4 score <2.67). (**A**) at discharge; (**B**) at 3 months; (**C**) at 1 year.

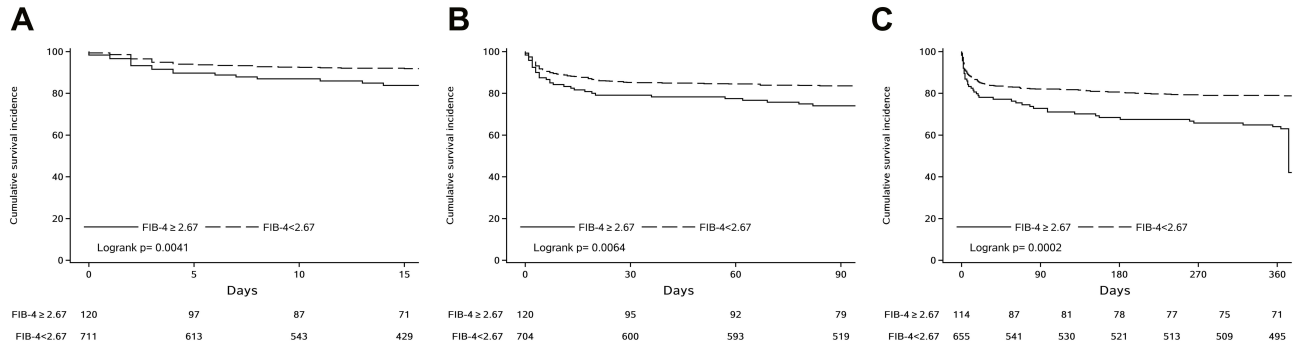

Figure 3 Kaplan–Meier curves of all patients with the total incidence of survival during the follow-up period (FIB-4 score ≥2.67 vs FIB-4 score <2.67). (**A**) at discharge; (**B**) at 3 months; (**C**) at 1 year.

Table 3 Univariable and Multivariable-Adjusted Logistic Regression Analysis of a FIB-4 Score ≥2.67 for Poor Clinical Outcomes

Outcomes	Events, n (%)	Crude		Model 1		Model 2	
		OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
At discharge							
Major disability	430 (57.6%)	2.349 (1.453–3.798)	<0.0001	1.941 (1.178–3.198)	0.0092	1.639 (0.954–2.814)	0.0735
Major disability or death	522 (62.2%)	2.599 (1.632–4.137)	<0.0001	2.160 (1.336–3.493)	0.0017	1.894 (1.120–3.202)	0.0172
At 3 months							
Major disability	317 (46.0%)	2.041 (1.291–3.228)	0.0023	1.396 (0.860–2.266)	0.1775	1.068 (0.622–1.834)	0.8114
Major disability or death	467 (55.7%)	2.244 (1.470–3.426)	0.0002	1.554 (0.995–2.425)	0.0525	1.289 (0.784–2.120)	0.3173
At 1 year							
Major disability	212 (34.4%)	2.614 (1.593–4.288)	0.0001	1.729 (1.022–2.923)	0.0411	1.494 (0.839–2.660)	0.1727
Major disability or death	397 (49.6%)	2.972 (1.932–4.570)	<0.0001	1.906 (1.207–3.009)	0.0056	1.694 (1.021–2.809)	0.0412

Notes: Model 1 was adjusted by age and sex; Model 2 was adjusted by age, admission DBP, prior dyslipidemia, and hematoma volume.
Abbreviations: OR, odds ratio; CI, confidence interval.

a FIB-4 score ≥2.67 was correlated to an increased risk of major disability or death. According to K-M curve analysis, patients with a FIB-4 score ≥2.67 had a lower survival rate during hospitalization, at 3 months and at 1 year. In the multivariable-adjusted logistic analysis, a FIB-4 score ≥2.67 was independently associated with poor outcomes at discharge and 1 year. These results suggest that fibrosis and related risk factors may have an association with secondary injury and functional recovery after ICH, especially in mild to moderate ICH.

As a highly sensitive and cost-effective approach for evaluating liver fibrosis, FIB-4 score has been widely applied for screening in the general population and to predict long-term outcomes. Higher scores may help to identify patients at an increased risk of death from liver disease and non-liver disease. Hepatic fibrosis is a key characteristic in the progression of NAFLD from steatosis to cirrhosis. A growing body of evidence has indicated that there is a strong association between NAFLD and a higher risk of cardiovascular events.[10] In a prospective observational study including 898 outpatients, patients with NAFLD had a 2-fold increased risk of cardiovascular events while patients with fibrosis had a 4-fold increased risk.[23] In another study, Xu et al found that the severity of NAFLD was associated with the occurrence of future ischemic stroke.[24] In addition, liver fibrosis, as determined by transient elastography, was suggested to be an independent predictor for ischemic stroke.[25] Recent studies demonstrated the predictive ability of higher FIB-4 scores for unfavorable outcomes and complications after stroke, including mortality, hemorrhagic transformation and atrial fibrillation.[21,26,27]

More recent studies have focused more on the association between NAFLD and ischemic stroke rather than hemorrhagic events.[28] Only a few studies have investigated the association between liver fibrosis and ICH prognosis, and results are partly controversial. Parikh et al found that liver fibrosis indices, including FIB-4 score and APRI, were associated with hematoma volume on admission, hematoma expansion (HE) and 3-month mortality.[14] Wang et al also reported the association between fibrosis based on clinical indexes and HE in a Chinese cohort.[29] However, Sheng et al[30] did not observe the association with ICH prognosis in a study including 128 patients. Thus, our study aimed to investigate the prognostic value of clinically non-apparent liver fibrosis as determined by a FIB-4 score ≥2.67 for unfavorable outcomes in patients with ICH. Our results are partly consistent with previous studies. There was also a significant difference in ICH severity between two groups with different FIB-4 scores. A FIB-4 score ≥2.67 was correlated to a higher risk of death rate at follow-up. Unlike other studies, a FIB-4 score ≥2.67 was independently associated with composite major disability or death in our study. This difference might be explained by the extended time window, the larger hematoma volumes and the younger age of participants in our study.[14]

Our study also presented a discrepancy in terms of age distribution between the two groups; age is one of the most important determinants of clinical outcome following stroke and ICH. As a serum-based biomarker, the FIB-4 score consists of simple biochemical surrogates (e.g., ALT, AST and PLT) and clinical risk factors (e.g., age) for fibrosis. Age itself is one of the independent indicators for advanced fibrosis.[31] NAFLD and metabolically driven fibrosis occur commonly in the elderly. In a community-based elderly cohort study,[32] the prevalence of NAFLD was 37.2% and 51.4% in the general population and

in participants that were 65–70 years-of-age, respectively. Advanced fibrosis was also detected in 7.8–11.8% of elderly cases and increased with age.

The mechanisms underlying the correlation between liver fibrosis and ICH prognosis are difficult to clarify, as fibrosis is currently recognized as a single part from a complex multisystem disease. Several different explanations need to be considered. Firstly, liver fibrosis shares risk factors with cerebrovascular diseases, such as obesity, diabetes, and hypertension.[25] This association can be interpreted by impaired glucose homeostasis and insulin resistance, including high fasting glucose, high blood pressure, abdominal obesity, and high triglycerides; these factors may all lead to a higher risk of stroke events and unfavorable outcomes.[33] In our study, dyslipidemia was a protective factor for ICH prognosis. In addition, fibrosis is also an independent risk factor for cardiovascular events after controlling for all covariates.[23] Secondly, from the perspective of pathology, the progression of fibrosis that is characterized by increasing activation of hepatic and systemic inflammation response, processes a close association with an increased risk of unfavorable outcomes after ICH.[34,35] Thirdly, other mechanisms underlying fibrosis could account for the possible correlation, such as oxidative stress, subclinical coagulopathy, and endothelial dysfunction, which are frequently detected in patients with fibrosis and may play a potential role in exacerbating secondary injury after ICH.[36–38] Although these implications can explain the association between fibrosis and ICH, it is still a hypothesis that requires more evidence in the further studies.

Herein, we describe the association between ICH prognosis and liver fibrosis, as evaluated by FIB-4 score, thus providing reliable evidence for controlling fibrosis-related risk factors in patients with ICH. Other strengths include the use of data from multiple centers and a prospective database, rigorous recruitment criteria, a relatively large sample, and convincing classification according to a validated cut-off value for fibrosis. However, there are several limitations that must also be considered. Firstly, this study included patients within 72 hours of ICH onset; this relatively longer time window may have led to the omission of patients with severe ICH from the study, especially in the ultra-early stage. Thus, our results mainly apply to patients with mild to moderate ICH. Secondly, we used the FIB-4 score to screen for fibrosis. There were no liver elastography data or biopsy results to confirm the diagnosis of fibrosis and further discriminate the stages of fibrosis. The FIB-4 score has been identified clinically to exclude fibrosis, thus allowing a more focused approach with regard to liver biopsy.[5] In our cohort, the prevalence of advanced fibrosis (14.3%), as defined by a FIB-4 score ≥2.67, was consistent with the population-based incidence. Thirdly, we were unable to obtain serological test data relating to viral hepatitis; the effects of hepatotoxic drugs, such as anti-epileptic drugs, cannot be completely ruled out. We have excluded patients with alcohol use, severe liver diseases and hepatotoxic antineoplastic drugs as much as possible. In addition, the liver function indices of the included patients were within the generally normal range. Although viral hepatitis has been reported to be associated with liver fibrosis, we believe that the proportion of patients is small. Finally, the database did not include data relating to the actual consumption of alcohol. To avoid the confounding effects of excess alcohol consumption, we excluded all patients who reported a history of drinking; this may have reduced our sample size.

Conclusions

In conclusion, our present study suggests that liver fibrosis, as defined by a FIB-4 score ≥2.67, is independently associated with an increased risk of death and poor clinical outcomes in patients with ICH. A FIB-4 score ≥2.67 may serve as a prognostic predictor for ICH. Our data provide reliable evidence for the screening of fibrosis and the control of relevant risk factors to improve prognosis after ICH. It is now urgent that we conduct further studies to clarify the association with ICH prognosis in the pathophysiology of fibrosis.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy/ethical restrictions.

Ethics Statement

The study was approved by the Institutional Review Board (IRB) of Beijing Tiantan Hospital, Captial Medical University. Written informed consents were obtained from all participants or their legal relatives for the publication of any potentially identifiable data or images included in this article.

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Disclosure

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

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