Liver Fibrosis Indices and Hemorrhagic Transformation After Ischemic Stroke

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Abstract

Background: Hemorrhagic transformation (HT) is recognized as a common compilation of acute ischemic stroke. The aim of this study was to investigate whether liver fibrosis indices are related to HT. Methods: We included ischemic stroke patients within 7 days of symptom onset. We calculated 3 liver fibrosis indices including the Aspartate Aminotransferase - Platelet Ratio Index (APRI), the Fibrosis - 4 (FIB - 4) score, and the Nonalcoholic Fatty Liver Disease Fibrosis Score (NFS) . Primary outcome was HT and secondary outcomes were symptomatic HT or parenchymal hemorrhage. We used multivariate logistic regression to assess the association between liver fibrosis indices and outcomes. Results: Among 2033 patients with ischemic stroke, the median APRI, FIB - 4 and NFS were significantly higher in HT cases compared with controls (APRI: 0.37 vs. 0.31; FIB-4: 2.44 vs. 1.86; 0.13 vs. -0.30, respectively; all P <0.001). After adjustment for potential confounders, the OR (95%CI) of HT for those in the highest tertile of APRI was 1.53 (1.05 - 2.24) compared with patients in the lowest tertile (P for trend = 0.038). FIB - 4 (OR 1.28, 95% CI 0.82 - 2.01; P for trend = 0.07) and NFS (OR 1.31, 0.71 - 2.44; P for trend = 0.068) were not associated with HT. Indices were not associated with the secondary outcomes. Conclusions: In patients with ischemic stroke, high APRI was associated with increased risks of HT, suggesting that APRI might be a prognostic biomarker for HT after acute ischemic stroke.

Introduction

Hemorrhagic transformation (HT) is recognized as a common compilation of acute ischemic stroke.[1] HT, especially symptomatic HT or parenchymal hematoma (PH), not only contributes to poor prognosis but also limits access to appropriate therapies.[2] In China, the rate of thrombolysis is very low (< 10%), partly due to fears of intracerebral hemorrhage after thrombolysis.[3] Therefore, it is very important to explore risk factors of HT, which would help to identify high-risk individuals and select appropriate treatment.

Recent evidence suggests that non-alcoholic fatty liver disease (NAFLD) is associated with increased incidence of ischemic stroke.[4–6] In addition, accumulating data indicates that ischemic stroke patients with NAFLD had worse functional outcome compared with those without NAFLD.[7, 8] NAFLD can progress to liver fibrosis, which is also an independent risk factor of ischemic stroke and its long-term outcomes.[4, 6, 9] Liver fibrosis and HT shared similar mechanisms, including inflammation, oxidative stress and endothelial dysfunction. Few studies on a possible association between HT and liver fibrosis exist; it is uncertain whether liver fibrosis affects HT development. To date, liver biopsy is the most effective method for the evaluation of liver fibrosis.[10] However, not all stoke patients can perform a liver biopsy to assess the liver fibrosis unless necessary. The Aspartate Aminotransferase-Platelet Ratio Index (APRI), the Fibrosis – 4 score (FIB – 4), and the Nonalcoholic Fatty Liver Disease Fibrosis Score (NFS) are the three commonly used noninvasive liver fibrosis indices, which have been suggested in current guidelines.[11]

Thus, we conducted this study to assess the association between liver fibrosis indices and HT.

Materials And Methods

Study Participants

We performed this study based on the data of the Chengdu Stroke Registry, which prospectively and consecutively recruited stroke patients from the Department of Neurology at West China Hospital, Sichuan University.[12] The ischemic stroke was diagnosed on the clinical manifestations and then confirmed by radiological findings. For the present analysis, we included ischemic stroke patients within 7 days of stroke onset from January 2016 to September 2018. Patients were excluded if they: 1) presented hemorrhagic transformation in initial computed tomography (CT) or magnetic resonance imaging (MRI); 2) did not performed follow-up CT or MRI scan during hospital; 3) did not offer blood samples. The protocol of this study was approved by the Biomedical Research Ethics Committee of West China Hospital, Sichuan University, and conformed to local and international ethical criteria. Written informed consent was given by each patient before the procedure.

Data Collection

Based on a pre-designed standardized form, we collected demographic characteristics (age, sex and body mass index), medication histories (antiplatelets, lipid-lowering agents and anticoagulants), medical histories (hypertension, diabetes mellitus, hyperlipidemia and atrial fibrillation), lifestyle risk factors (current smoking and drinking), clinical features (stroke severity and baseline blood pressure), laboratory data [glucose, platelet, total bilirubin, albumin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and therapies after admission (antiplatelets, thrombolysis, thrombectomy, lipid-lowering agents and anticoagulants). The baseline stroke severity was evaluated by trained neurologists assessed using National Institutes of Health Stroke Scale (NIHSS) score.[13] The potential stroke etiology was identified by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system.[14] Fasting blood samples were collected within 24 h of hospital admission and delivered to the laboratory department of our hospital. All laboratory data were analyzed via automatic biochemical analyzer. An initial head CT was performed on admission for all patients, then follow-up head MRI was finished within 7 days after admission. When patients showed clinical deterioration, repeated CT would be undergone.

Measurement of Liver Fibrosis Indices

Liver fibrosis indices including APRI, FIB – 4 and NFS. The calculation formulas are as follows[15]: APRI = [(AST/upper limit of normal)/platelet count] × 100; FIB-4 = (age × AST) / [platelet count × (alanine aminotransferase) ^1/2]; NFS=-1.675 + 0.037 × age + 0.094 × body mass index + 1.13 × impaired fasting glucose or diabetes (Yes = 1, No = 0) + 0.99 × AST / ALT – 0.013 × platelet count – 0.66 × albumin (AST: IU/L; platelet: 10^9; age: years; body mass index: kilograms/square meter; glucose: mmol/L; albumin: g/dL).

Outcome Assessment

The primary outcome measure was HT, which was defined as imaging evidence of hemorrhagic infarction or parenchymal hemorrhage. The secondary outcome measures were symptomatic HT or parenchymal hemorrhage (PH). Symptomatic HT was defined as any intracranial hemorrhage associated with neurological deterioration.[16] PH was defined as intracranial hemorrhage with mass effect according to the European Cooperative Acute Stroke Study II criteria.[17] HT was independently evaluated by two researchers who were blind to clinical data. Any disagreement was resolved through discussion.

Statistical Analysis

Categorical variables were presented as frequencies with percentages, and Chi-square test or Fisher's exact test was applied to compare categorical variables. Continuous variables were described as means with the standard deviations or median with interquartile ranges, and Student's t test or Mann–Whitney U test was applied to compare continuous variables.

Unadjusted and adjusted odds ratio (OR) and 95% confidence interval (CI) was calculated. We created two multivariate logistic regression models to evaluate the relationships between each fibrosis index and HT. Model 1 included age and sex. Model 2 included variables in model 1 plus other possible confounding factors. If significant association was found, we would conduct stratified logistic regression analyses used to explore potential indicators that may modify the relationship between liver fibrosis indices and HT. The significance of interaction was tested by the likelihood ratio test. We further used logistic regression model with restricted cubic splines to explore the pattern and magnitude of the association between liver fibrosis indices (continuous variable) and HT with three knots (at the 10th, 50th, 90th percentiles), adjusting for covariates in model 2 if possible. Additionally, we calculated net reclassification index (NRI) and integrated discrimination improvement (IDI) to assess the incremental prognostic value of liver fibrosis indices beyond conventional risk factors if possible.[18]

All statistical analyses were performed using SPSS 26.0 (IBM, Chicago, IL, USA), R (http://www.R-project.org, The R Foundation) and Stata 15.0 (STATA, College Station, TX, USA). Two-sided values of $P < 0.05$ were considered statistically significant.

Results

Study participants and characteristics

During the study period, 2206 patients with ischemic stroke patients met the study criteria, of whom 173 (7.8%) were excluded: 85 patients had HT on admission, 67 patients did not undergo a second CT or MRI scan and 21 patients lacked blood samples. Finally, 2033 patients were included in this study. The mean age was 64.6 years and 1284 (63.2%) subjects were males. Baseline characteristics are shown in Table 1 and Table S1.

Table 1

Baseline characteristics of participants according to hemorrhagic transformation

	Non-HT group (n = 1803)	HT group (n = 230)	P-value
Demographics			
Age (years)	64 ± 14	68 ± 14	< 0.001
Male, n (%)	1171 (64.95%)	113 (49.13%)	< 0.001
Medication histories			
Antiplatelets, n (%)	192 (10.65%)	25 (10.87%)	0.919
Lipid-lowering agents, n (%)	123 (6.82%)	17 (7.39%)	0.748
Anticoagulants, n (%)	72 (3.99%)	12 (5.22%)	0.38
Medical histories			
Hypertension, n (%)	1013 (56.18%)	114 (49.57%)	0.057
Diabetes mellitus, n (%)	414 (22.96%)	51 (22.17%)	0.789
Hyperlipidemia, n (%)	68 (3.77%)	7 (3.04%)	0.711
Atrial fibrillation, n (%)	165 (9.15%)	69 (30.00%)	< 0.001
Current smoking, n (%)	779 (43.21%)	83 (36.09%)	0.04
Current drinking, n (%)	509 (28.23%)	51 (22.17%)	0.053
Clinical features			
NIHSS on admission, median (IQR)	5 (2–10)	12 (7–18)	< 0.001
SBP (mmHg)	146 ± 23	139 ± 23	< 0.001
DBP (mmHg)	86 ± 15	84 ± 16	0.042
Glucose (mmol/L)	6.77 (5.75–8.80)	7.75 (6.45–9.34)	< 0.001
Platelet (× 109/L)	173(134–213)	152 (117–194)	< 0.001
Total bilirubin (umol/L)	12 (8.9–16.9)	13.25 (9.67–17.92)	0.004
ALT (IU/L)	18 (13–27)	18 (13–27)	0.788
AST (IU/L)	21 (17–27)	23 (18–30)	0.003
APRI	0.31 (0.22–0.46)	0.37 (0.27–0.60)	< 0.001

NHISS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI: the Aspartate Aminotransferase-Platelet Ratio Index; FIB-4: the Fibrosis-4 score; NFS: the Nonalcoholic Fatty Liver Disease Fibrosis Score; TOAST: the Trial of ORG 10172 in Acute Stroke Treatment. *n = 1011.

	Non-HT group (n = 1803)	HT group (n = 230)	P-value
FIB-4	1.86 (1.23–2.79)	2.44 (1.50–3.85)	< 0.001
NFS	-0.30 (− 1.23–0.59)	0.13 (− 0.72–1.03)	< 0.001
Therapies after admission			
Antiplatelet, n (%)	1704 (94.51%)	196 (85.22%)	< 0.001
Thrombolysis, n (%)	79 (4.38%)	27 (11.74%)	< 0.001
Thrombectomy, n (%)	78 (4.33%)	24 (10.43%)	< 0.001
Anticoagulants, n (%)	213 (11.81%)	33 (14.35%)	0.267
Lipid-lowering agents, n (%)	1702 (94.40%)	201 (87.39%)	< 0.001
TOAST classification			
Large-artery atherosclerosis, n (%)	596 (33.06%)	72 (31.30%)	< 0.001
Small-artery occlusion, n (%)	479 (26.57%)	3 (1.30%)	
Cardioembolic, n (%)	319 (17.69%)	111 (48.26%)	
Other etiology, n (%)	345 (19.13%)	40 (17.39%)	
Undetermined etiology, n (%)	64 (3.55%)	4 (1.74%)	

NHISS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI: the Aspartate Aminotransferase-Platelet Ratio Index; FIB-4: the Fibrosis-4 score; NFS: the Nonalcoholic Fatty Liver Disease Fibrosis Score; TOAST: the Trial of ORG 10172 in Acute Stroke Treatment. *n = 1011.

Table 2

Multivariable logistic regression analysis between liver fibrosis indices and hemorrhagic transformation

	Unadjusted		Model 1		Model 2	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
ARRI						
Tertiles 1	Reference		Reference		Reference	
Tertiles 2	1.51 (1.05–2.18)	0.028	1.45 (1.00–2.10)	0.050	1.32 (0.89–1.95)	0.163
Tertiles 3	2.05 (1.44–2.91)	< 0.001	1.98 (1.39–2.83)	< 0.001	1.53 (1.05–2.24)	0.027
P for trend	< 0.001		< 0.001		0.038	
FIB − 4						
Tertiles 1	Reference		Reference		Reference	
Tertiles 2	1.16 (0.80–1.69)	0.445	1.00 (0.67–1.51)	0.993	0.83 (0.54–1.27)	0.389
Tertiles 3	2.16 (1.53–3.03)	< 0.001	1.71 (1.13–2.60)	0.011	1.28 (0.82–2.01)	0.275
P for trend	< 0.001		0.001		0.07	
NFS						
Tertiles 1	Reference		Reference		Reference	
Tertiles 2	1.67 (1.01–2.75)	0.045	1.26 (0.74, 2.14)	0.404	1.27 (0.71, 2.29)	0.422
Tertiles 3	2.05 (1.26–3.32)	0.004	1.35 (0.77, 2.37)	0.298	1.31 (0.71, 2.44)	0.388
P for trend	0.005		0.356		0.068	

OR: odds ratio; CI: confidence interval; APRI: the Aspartate Aminotransferase-Platelet Ratio Index; FIB-4: the Fibrosis-4 score; NFS: the Nonalcoholic Fatty Liver Disease Fibrosis Score; Model 1: adjusted for age, sex; Model 2: adjusted for covariates from Model 1 and further adjusted for NHISS, National Institutes of Health Stroke Scale, atrial fibrillation, smoking, drinking, systolic blood pressure, diastolic blood pressure, glucose, antiplatelets, thrombolysis, thrombectomy, lipid-lowering agents after admission and the Trial of ORG 10172 in Acute Stroke Treatment classification.

A total of 230 patients (11.3%) experienced HT, of whom 33 exhibited symptomatic HT and 103 developed PH. Compared with patients who did not develop HT, those who developed HT were more likely to be older, females, and had higher prevalence of atrial fibrillation, baseline NIHSS score, glucose, total bilirubin, AST, proportion of thrombolysis, and thrombectomy, but had lower prevalence of smoking, drinking, systolic and diastolic blood pressure, platelet, proportion of antiplatelet and lipid-lowering agents after admission (All $P < 0.05$).

Association of liver fibrosis indices with risk of hemorrhagic transformation

Levels of APRI, FIB-4 and NFS were significantly higher in HT cases compared with controls (APRI: 0.37 vs. 0.31; FIB − 4: 2.44 vs. 1.86; 0.13 vs. -0.30, respectively; all $P < 0.001$). Compared with patients in the lowest tertile, the OR (95%CI) of HT for those in the highest tertile of APRI was 1.53 (1.05–2.24) after adjustment for potential confounders in model 2 (P for trend = 0.038). However, there was no significant association of FIB − 4 in tertiles with HT in model 2 (OR 1.28, 95% CI 0.82–2.01; P for trend = 0.07). Similar results were obtained for NFS in tertiles (OR 1.31, 0.71–2.44; P for trend = 0.068).

The multivariable-adjusted spline regression model suggested a linear relationship between APRI, FIB − 4, NFS and HT (Fig. 1). We further explored the association between liver fibrosis indices and symptomatic HT or PH. No liver fibrosis indices were independently associated with symptomatic HT or PH after adjusting for confounders (Table S2).

Subgroup analyses on the association between APRI and hemorrhagic transformation

In subgroup analyses stratified by sex, age, atrial fibrillation, smoking, drinking, baseline NIHSS score, systolic blood pressure, diastolic blood pressure, glucose, antiplatelets, lipid-lowering agents, reperfusion therapy (thrombolysis or thrombectomy) and stroke subtype,, no significant interaction between APRI and these interesting factors on HT was observed (all P for interaction > 0.05; Fig. 2).

Incremental prognostic value of APRI in patients with ischemic stroke

We evaluated reclassification to explore whether any of liver indices could add the predictive values to conventional risk factors (Table 3). Individually, adding each liver fibrosis index to the basic model improved risk reclassification for HT. FIB − 4 provided the greatest incremental predictive ability over the basic model (NRI 21.6%, P = 0.002; IDI 0.9%, P = 0.011).

Table 3
Reclassification and discrimination statistics for hemorrhagic transformation by liver fibrosis indices

	NRI		IDI	
	Estimate (95% CI), %	P value	Estimate (95% CI), %	P value
Conventional model	Reference	-	Reference	-
Conventional model + APRI	17.3 (3.6–31.0)	0.013	0.5 (-0.1–1.1)	0.058
Conventional model + FIB − 4	21.6 (7.9–35.3)	0.002	0.9 (0.3–1.5)	0.011
Conventional model + NFS	12.1 (-6.7–30.9)	0.001	0.1 (-0.3–0.5)	0.419

NRI, Net reclassification index; IDI, integrated discrimination improvement; APRI: the Aspartate Aminotransferase-Platelet Ratio Index; FIB-4: the Fibrosis-4 score; NFS: the Nonalcoholic Fatty Liver Disease Fibrosis Score; Conventional model included age, sex, National Institutes of Health Stroke Scale, atrial fibrillation, smoking, drinking, systolic blood pressure, diastolic blood pressure, glucose, antiplatelets, thrombolysis, thrombectomy, lipid-lowering agents after admission and the Trial of ORG 10172 in Acute Stroke Treatment classification

Discussion

In this study, we assessed the association between three non-invasive indices of liver fibrosis (APRI, FIB − 4 and NFS) and HT in patients with acute ischemic stroke. The present study of 2033 patients demonstrated high APRI was independently associated with increased risk of HT after adjustment for potential confounders. Subgroup analyses further confirmed these findings. Moreover, the addition of liver fibrosis indices to conventional prognostic factors could significantly improve the risk prediction for HT after ischemic stroke.

Although it is well known that liver fibrosis is associated with cardiovascular diseases[19–22], only a few studies have assessed the relationship between liver fibrosis and stroke specifically. The study by Kim et al. showed a significant positive association between acute ischemic stroke and liver fibrosis. [6] In addition, a Korean study involving 395 patients with ischemic stroke or transient ischaemic attack showed that liver fibrosis was an independent predictor of mortality during long-term follow-up.[9] Recently, a cohort study using data from the Virtual International Stroke Trials Archive–Intracerebral Hemorrhage indicated that two liver fibrosis indices-APRI and FIB-4 were associated with increased risk of mortality in patients with acute intracerebral hemorrhage.[15] To our knowledge, the association of liver fibrosis indices with HT after ischemic stroke has not been reported previously. In the present study, we found that higher APRI was associated with increased risk of HT after ischemic stroke.

Because of an excessive concern over the bleeding risk after thrombolysis among stroke patients, families and physicians[3], it is necessary for us to explore novel and effective biomarkers for HT. Liver fibrosis indices could significantly improve the predictive power for HT beyond established traditional risk factors (NRI: 17.3% for APRI, 21.6% for FIB-4, and 12.1% for NFS, respectively), suggesting that liver

fibrosis indices at baseline may be a potential biomarkers in the prediction of HT in patients with acute ischemic stroke. Therefore, we speculated that liver fibrosis indices might be useful in risk stratification of HT after acute ischemic stroke and could help the selection of high-risk patients in clinical practice. If patents have high APRI levels at admission, they may be at high risk of HT and should cautiously receive therapies with bleed risks. Further studies are needed to justify our findings.

The possible explanations for the positive relationship between liver fibrosis and the risk of HT could be considered in several ways. There are common risk factors between liver fibrosis and HT. Liver fibrosis is associated with atherosclerosis[23], diabetes[24], dyslipidemia[25] and arterial stiffness[26], which are associated with HT[27, 28]. Moreover, liver fibrosis is associated with inflammation, oxidative stress and endothelial dysfunction[29], which also participate in the occurrence and development of HT.[1, 30] In our study, the association of liver fibrosis with HT remained still significant in multivariate analysis adjusting for common potential confounders. Future investigation is warranted to explore underlying mechanism.

This study has several limitations that should be mentioned. First, because liver imaging or liver biopsy data are not available in our study, we explored the association between three noninvasive liver fibrosis indices and HT. Therefore, these findings, to some extent, might not reflect the real relationship between liver fibrosis and HT. However, these indices have been proved to have better predictive value for identifying liver fibrosis.[31, 32] Second, alcohol use is an important confounder for liver fibrosis[33], but it is difficult to determine the accurate alcohol consumption in clinical practice. Therefore, we perform subgroup analyses to explore potential interactions, but we could not find significant interaction effect by alcohol consumption. Third, we assessed the relationship between NFS and HT based on 1011 stroke patients because body mass index was not available for other 1022 individuals, which may lead to the potential selection bias.

Conclusions

Among patients with acute ischemic stroke, high APRI was associated with increased risks of HT, suggesting that APRI might be a prognostic biomarker for HT after acute ischemic stroke. Further studies are needed to validate our findings and to determine the underlying mechanisms.

Declarations

Abbreviations

HT: hemorrhagic transformation; APRI: the Aspartate Aminotransferase - Platelet Ratio Index; FIB-4: the Fibrosis-4 score; NFS: the Nonalcoholic Fatty Liver Disease Fibrosis Score; PH: parenchymal hematoma; NAFLD: non-alcoholic fatty liver disease; CT: computed tomography; MRI: magnetic resonance imaging; NIHSS: National Institutes of Health Stroke Scale; TOAST: the Trial of ORG 10172 in Acute Stroke Treatment; OR: odds ratio; CI: confidence interval; NRI: net reclassification index; IDI: integrated discrimination improvement.

Ethics approval and consent to participate

This study was approved by the Biomedical Research Ethics Committee of West China Hospital, Sichuan University, and conformed to local and international ethical criteria. Informed consent was obtained from patients or their next of kin.

Consent for publication

Not applicable.

Availability of data and materials

The data used in this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

ML designed the study, supervised and offered guidance to all authors, and revised the manuscript. YC and KQ collected the clinical data. YW collected the imaging data, performed statistical analysis and drafted the manuscript. QS collected the imaging data and critical revision of the manuscript. JL was involved in statistical analysis and critical revision of the manuscript. All authors read and approved the final manuscript.

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References

1. Wang W, Li M, Chen Q, Wang J. Hemorrhagic Transformation after Tissue Plasminogen Activator Reperfusion Therapy for Ischemic Stroke: Mechanisms, Models, and Biomarkers**.** Mol Neurobiol. 2015;52**:**1572-9.

2. Alvarez-Sabin J, Maisterra O, Santamarina E, Kase CS. Factors influencing haemorrhagic transformation in ischaemic stroke. Lancet Neurol. 2013;12:689-705.
3. Wu S, Wu B, Liu M, Chen Z, Wang W, Anderson CS, Sandercock P, Wang Y, Huang Y, Cui L, et al. Stroke in China: advances and challenges in epidemiology, prevention, and management. Lancet Neurol. 2019;18:394-405.
4. Baratta F, Pastori D, Angelico F, Balla A, Paganini AM, Cocomello N, Ferro D, Violi F, Sanyal AJ, Del Ben M. Nonalcoholic Fatty Liver Disease and Fibrosis Associated With Increased Risk of Cardiovascular Events in a Prospective Study. Clin Gastroenterol Hepatol. 2019.
5. Kwak MS, Kim KW, Seo H, Chung GE, Yim JY, Kim D. Non-obese fatty liver disease is associated with lacunar infarct. Liver Int. 2018;38:1292-9.
6. Kim SU, Song D, Heo JH, Yoo J, Kim BK, Park JY, Kim DY, Ahn SH, Kim KJ, Han KH, Kim YD. Liver fibrosis assessed with transient elastography is an independent risk factor for ischemic stroke. Atherosclerosis. 2017;260:156-62.
7. Lombardi R, Fargion S, Fracanzani AL. Brain involvement in non-alcoholic fatty liver disease (NAFLD): A systematic review. Dig Liver Dis. 2019;51:1214-22.
8. Abdeldyem SM, Goda T, Khodeir SA, Abou Saif S, Abd-Elsalam S. Nonalcoholic fatty liver disease in patients with acute ischemic stroke is associated with more severe stroke and worse outcome. J Clin Lipidol. 2017;11:915-9.
9. Baik M, Kim SU, Kang S, Park HJ, Nam HS, Heo JH, Kim BK, Park JY, Kim DY, Ahn SH, et al. Liver Fibrosis, Not Steatosis, Associates with Long-Term Outcomes in Ischaemic Stroke Patients. Cerebrovasc Dis. 2019;47:32-9.
10. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55:2005-23.
11. Newsome PN, Cramb R, Davison SM, Dillon JF, Foulerton M, Godfrey EM, Hall R, Harrower U, Hudson M, Langford A, et al. Guidelines on the management of abnormal liver blood tests. Gut. 2018;67:6-19.
12. Liu J, Zheng L, Cheng Y, Zhang S, Wu B, Wang D, Zhang S, Tao W, Wu S, Liu M. Trends in Outcomes of Patients With Ischemic Stroke Treated Between 2002 and 2016: Insights From a Chinese Cohort. Circ Cardiovasc Qual Outcomes. 2019;12:e005610.
13. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989;20:864-70.
14. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE, 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35-41.
15. Parikh NS, Kamel H, Navi BB, Iadecola C, Merkler AE, Jesudian A, Dawson J, Falcone GJ, Sheth KN, Roh DJ, et al. Liver Fibrosis Indices and Outcomes After Primary Intracerebral Hemorrhage. Stroke.

2020.

16. National Institute of Neurological D, Stroke rt PASSG. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581-7.
17. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet. 1998;352:1245-51.
18. Greenland S. The need for reorientation toward cost-effective prediction: Comments on 'Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond' by M. J. Pencinaet al.,Statistics in Medicine (DOI: 10.1002/si. Statistics in Medicine. 2008;27:199-206.
19. Kovalic AJ, Satapathy SK. The Role of Nonalcoholic Fatty Liver Disease on Cardiovascular Manifestations and Outcomes. Clin Liver Dis. 2018;22:141-74.
20. Han E, Lee YH. Non-Alcoholic Fatty Liver Disease: The Emerging Burden in Cardiometabolic and Renal Diseases. Diabetes Metab J. 2017;41:430-7.
21. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol. 2016;65:589-600.
22. Mellinger JL, Pencina KM, Massaro JM, Hoffmann U, Seshadri S, Fox CS, O'Donnell CJ, Speliotes EK. Hepatic steatosis and cardiovascular disease outcomes: An analysis of the Framingham Heart Study. J Hepatol. 2015;63:470-6.
23. Huang Y, Bi Y, Xu M, Ma Z, Xu Y, Wang T, Li M, Liu Y, Lu J, Chen Y, et al. Nonalcoholic fatty liver disease is associated with atherosclerosis in middle-aged and elderly Chinese. Arterioscler Thromb Vasc Biol. 2012;32:2321-6.
24. Tada T, Toyoda H, Sone Y, Yasuda S, Miyake N, Kumada T, Tanaka J. Type 2 diabetes mellitus: A risk factor for progression of liver fibrosis in middle-aged patients with non-alcoholic fatty liver disease. J Gastroenterol Hepatol. 2019;34:2011-8.
25. Perazzo H, Munteanu M, Ngo Y, Lebray P, Seurat N, Rutka F, Couteau M, Jacqueminet S, Giral P, Monneret D, et al. Prognostic value of liver fibrosis and steatosis biomarkers in type-2 diabetes and dyslipidaemia. Aliment Pharmacol Ther. 2014;40:1081-93.
26. Li N, Zhang GW, Zhang JR, Jin D, Li Y, Liu T, Wang RT. Non-alcoholic fatty liver disease is associated with progression of arterial stiffness. Nutr Metab Cardiovasc Dis. 2015;25:218-23.
27. Yaghi S, Willey JZ, Cucchiara B, Goldstein JN, Gonzales NR, Khatri P, Kim LJ, Mayer SA, Sheth KN, Schwamm LH. Treatment and Outcome of Hemorrhagic Transformation After Intravenous Alteplase in Acute Ischemic Stroke: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2017;48:e343-e61.
28. Acampa M, Camarri S, Lazzerini PE, Guideri F, Tassi R, Valenti R, Cartocci A, Martini G. Increased arterial stiffness is an independent risk factor for hemorrhagic transformation in ischemic stroke undergoing thrombolysis. Int J Cardiol. 2017;243:466-70.

29. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest. 2005;115:209-18.
30. Jickling GC, Liu D, Stamova B, Ander BP, Zhan X, Lu A, Sharp FR. Hemorrhagic transformation after ischemic stroke in animals and humans. J Cereb Blood Flow Metab. 2014;34:185-99.
31. Xiao G, Zhu S, Xiao X, Yan L, Yang J, Wu G. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology. 2017;66:1486-501.
32. Chalasani N, Abdelmalek MF, Loomba R, Kowdley KV, McCullough AJ, Dasarathy S, Neuschwander-Tetri BA, Terrault N, Ferguson B, Shringarpure R, et al. Relationship between three commonly used non-invasive fibrosis biomarkers and improvement in fibrosis stage in patients with non-alcoholic steatohepatitis. Liver Int. 2019;39:924-32.
33. Alexander M, Loomis AK, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, Pasqua A, Lapi F, Rijnbeek P, Mosseveld M, et al. Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults. BMJ. 2019;367:l5367.

Supplementary Files Legend

Table S1. 1 Baseline characteristics of included patients with Nonalcoholic Fatty Liver Disease Fibrosis Score data according to the subcategorized groups of hemorrhagic transformation

Table S2. Multivariate logistic regression analysis between liver fibrosis indices and the secondary outcomes

Figures

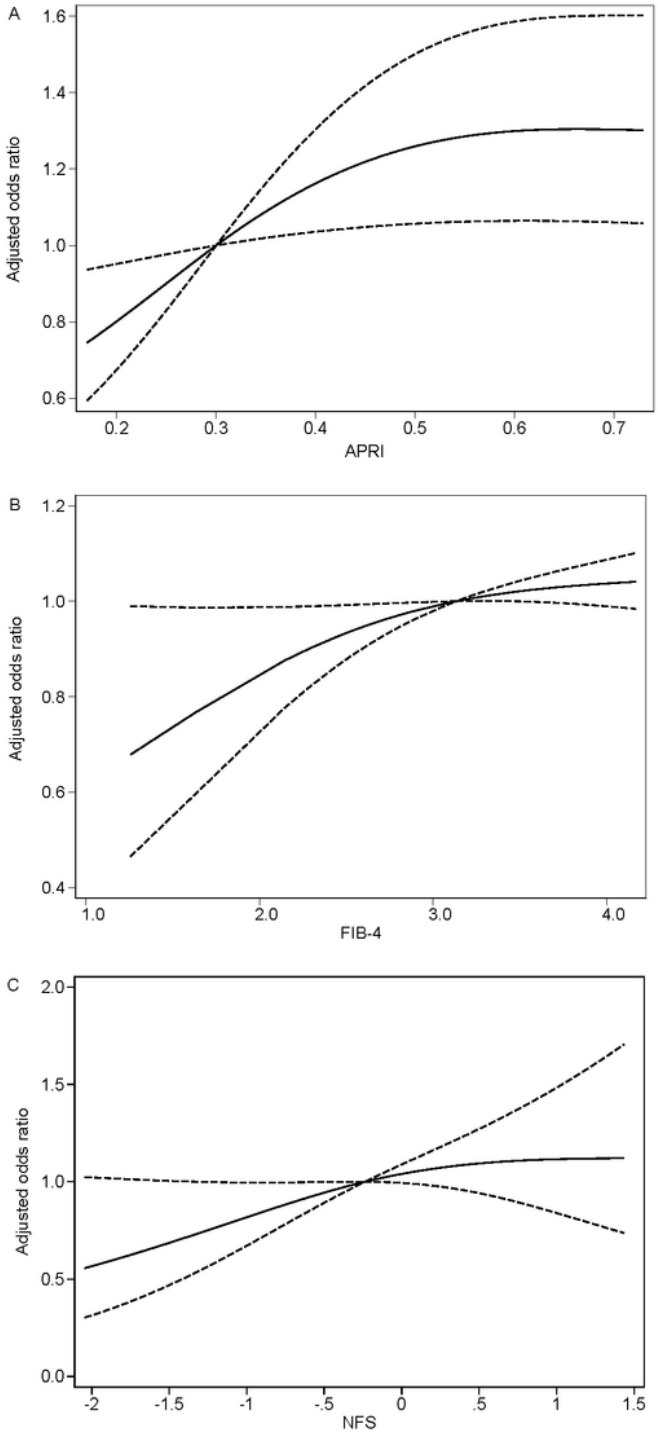

Figure 1

Multivariate adjusted odds ratios and 95% confidence intervals of hemorrhagic transformation associated with the Aspartate Aminotransferase - Platelet Ratio Index (APRI), the Fibrosis-4 score (FIB - 4), and the Nonalcoholic Fatty Liver Disease Fibrosis Score (NFS). Odds ratios and 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 50th, and 95th percentiles of the distribution of APRI, FIB - 4 and NFS. Odds ratios were adjusted for age, sex, atrial fibrillation, baseline

National Institutes of Health Stroke Scale score, smoking, drinking, systolic and diastolic blood pressure, glucose, antiplatelets, thrombolysis, thrombectomy, lipid-lowering agents and the Trial of Org 10172 in Acute Stroke Treatment classification. (A) APRI. (B) FIB - 4. (C) NFS.

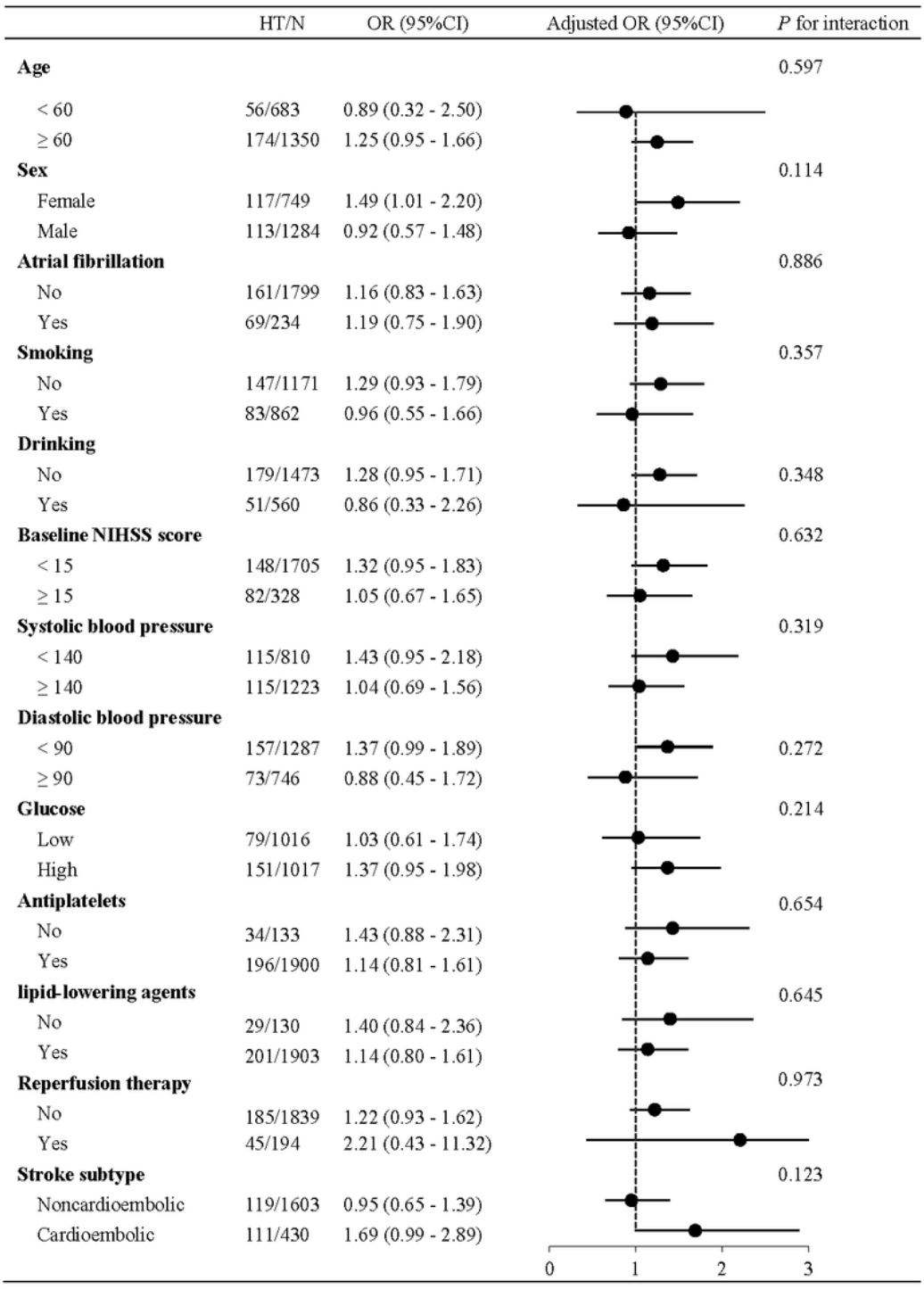

Figure 2

Stratified logistic regression analysis to identify variables that modify the relationship between APRI and HT. Above model adjusted for age, sex, atrial fibrillation, baseline National Institutes of Health Stroke

Scale score, smoking, drinking, systolic and diastolic blood pressure, glucose, antiplatelets, lipid-lowering agents reperfusion therapy (thrombolysis/ thrombectomy) and stroke subtype. In each case, the model is not adjusted for the stratification variable. APRI, Aspartate Aminotransferase - Platelet Ratio Index; HT, hemorrhagic transformation; NIHSS, National Institutes of Health Stroke Scale score;

Supplementary Files

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- TableS1.doc
- TableS2.doc