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ORIGINAL RESEARCH

Association Between Liver Fibrosis and Risk of Incident Stroke and Mortality: A Large Prospective Cohort Study

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BACKGROUND: There is a well-established relationship between liver conditions and cardiovascular diseases. However, uncertainty persists regarding the contribution of liver fibrosis to major stroke types including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage at the population level.

METHODS: In this large prospective cohort study, participants without previous stroke or coronary heart disease at baseline from the UK Biobank were included. We identified participants at high probability of advanced liver fibrosis using the Fibrosis-4 index >2.67 or aspartate aminotransferase to platelet ratio index ≥1.0. Multivariable Cox proportional hazard regression analyses were conducted to estimate hazard ratios (HRs) for liver fibrosis with the incidence of major stroke types, stroke-related death, and all-cause death.

RESULTS: Among 379 953 participants (mean age, 56.2 [SD, 8.1] years; 44.6% men), 7396 (1.9%) had a Fibrosis-4 index >2.67 at baseline. During a median follow-up of 12.75 (interquartile range, 12.03–13.48) years, 7143 (1.9%) incident stroke cases were documented. Advanced liver fibrosis assessed by the Fibrosis-4 index was associated with an increased risk of ischemic stroke (HR, 1.94 [95% CI, 1.70–2.22]), intracerebral hemorrhage (HR, 2.14 [95% CI, 1.63–2.81]), subarachnoid hemorrhage (HR, 1.90 [95% CI, 1.27–2.84), stroke-related death (HR, 2.20 [95% CI, 1.73–2.80]), and all-cause death (HR, 2.59 [95% CI, 2.46–2.73]). Using the aspartate aminotransferase to platelet ratio index as an alternative score, liver fibrosis was correlated with magnified risk of intracerebral hemorrhage (HR, 3.76 [95% CI, 2.38–5.93]) and subarachnoid hemorrhage (HR, 3.05 [95% CI, 1.51–6.13]) compared with ischemic stroke (HR, 1.58 [95% CI, 1.17–2.14]). Restricted cubic spline analysis showed nonlinear associations of the Fibrosis-4 index and aspartate aminotransferase to platelet ratio index with stroke incidence and all-cause death.

CONCLUSIONS: Liver fibrosis is associated with increased risk of incident stroke and death among people without previous stroke or cardiovascular events, with particularly greater risk of intracerebral hemorrhage and subarachnoid hemorrhage. Noninvasive indices of liver fibrosis may serve as an easily accessible marker to detect individuals facing elevated risk of stroke and death in the primary prevention settings.

Key Words: liver fibrosis ■ death ■ population-based study ■ stroke

Stroke represents a major global health challenge as the second leading cause of death and the third-leading cause of disability.[1] The identification and control of risk factors of stroke are crucial for primary and secondary prevention strategies to reduce the incidence of stroke at the population level.

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CLINICAL PERSPECTIVE

What Is New?

- In this large population-based prospective cohort study, individuals with high risk of advanced liver fibrosis assessed by noninvasive blood-based indices were associated with an increasing risk of future ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and death.
- There is a nonlinear relationship between the Fibrosis-4 index or aspartate aminotransferase to platelet ratio index and stroke incidence and all-cause death.

What Are the Clinical Implications?

- Using noninvasive scores of liver fibrosis may be valuable for evaluating future risk of stroke and death.

Nonstandard Abbreviations and Acronyms

APRI	aspartate aminotransferase to platelet ratio index
IS	ischemic stroke
ICH	intracerebral hemorrhage

Liver cirrhosis, characterized by extensive hepatic fibrogenesis, has emerged as a substantial public health issue, evidenced by a 47% increase in death over the past decade. It ranks as the second-leading cause of lost working years in European regions.[2–4] The assessment of liver fibrosis is frequently overlooked in stroke management, likely due to the high prevalence of compensated cases and an underestimated prevalence of unknown liver diseases with advanced liver fibrosis.[5,6] Accumulating evidence suggests that liver fibrosis acts as an independent risk factor for cardiovascular events, even in the subclinical stage when abnormal liver enzyme profiles and liver-related symptoms are absent. Noninvasive blood-based scores such as the Fibrosis-4 index and the aspartate aminotransferase (AST) to platelet ratio index (APRI) incorporating alanine aminotransferase, AST, and platelet count, are instrumental in detection of individuals at high risk of liver fibrosis in large populations.[7]

There are few data on the association between liver fibrosis and future stroke risk at the population level. Mechanistically, liver fibrosis is closely associated with exposure to cardiovascular risk factors including hypertension, diabetes, obesity, and dyslipidemia.[8] Conversely, progressive hepatic fibrosis frequently leads to impaired coagulation activity and reduced platelet count, which subsequently increase the risk of hemorrhagic events.[2] However, there are limited data establishing a connection between advanced liver fibrosis and stroke incidence, as well as delineating the association of liver fibrosis with different types of stroke.

Leveraging data from a large-scale UK prospective cohort, we sought to investigate the correlation of liver fibrosis with stroke incidence, major stroke types, stroke-related death, and all-cause death.

METHODS

Study Population

The study population consisted of participants recruited by the UK Biobank, a population-based prospective cohort that enrolled >500 000 individuals aged between 40 and 69 years across England, Scotland, and Wales from 2006 to 2010. All participants were invited to complete an extensive touchscreen questionnaire and nurse-led verbal interview, physical measurements, and biological sample collection. The UK Biobank study was approved by the North West Multicentre Research Ethics Committee (REC reference: 21/NW/0157). Written informed consent was obtained from all participants. This study was conducted under UK Biobank application number 100889. UK Biobank data are accessible to all qualified researchers upon application.

In the current analysis, we initially included all UK Biobank participants and then excluded participants with incomplete data required for calculating the Fibrosis-4 index and APRI, those lost to follow-up, and those with prevalent myocardial infarct or stroke at the baseline visit. Additionally, we excluded individuals with missing covariate data to facilitate a complete case analysis. We also excluded individuals with signs of possible acute hepatitis (defined as AST or alanine aminotransferase levels ≥250 IU/L) or severe thrombocytopenia (platelet count <50 000/μL) at the baseline assessment to mitigate potential impacts of these diseases on liver fibrosis risk assessment (Figure 1).[9]

Exposures and Outcomes

The main exposure was probable advanced liver fibrosis identified by the Fibrosis-4 index, a simple formula incorporating age, platelet count, alanine aminotransferase, and AST levels. In the UK Biobank, venous blood samples were collected for complete blood count analysis using a Coulter LH750 analyzer, and liver biochemistry tests were performed on a Beckman Coulter AU5800. The formula for calculating the Fibrosis-4 index is as follows:

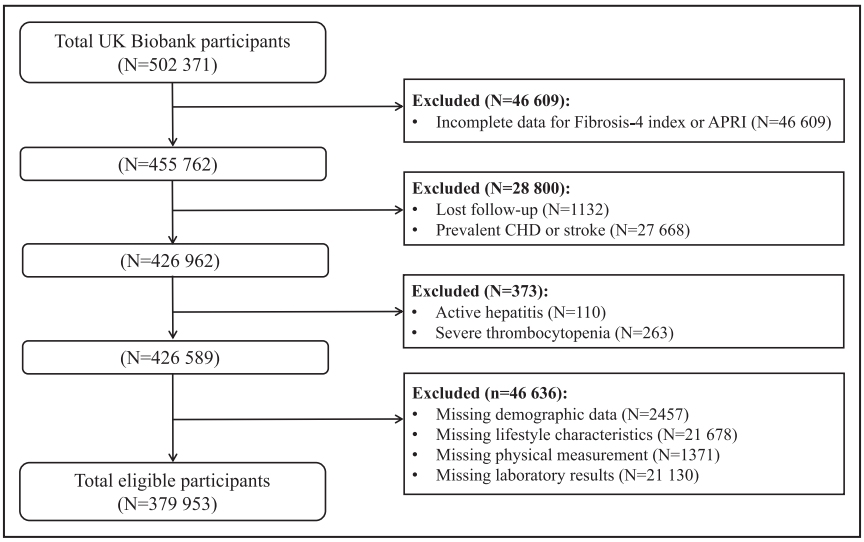

Figure 1. Study flowchart.
APRI indicates aspartate aminotransferase to platelet ratio index; and CHD, coronary heart disease.

$$\text{Fibrosis}-4=\left(\text{age}\ [\text{years}]\times\text{AST}\ [\text{U/L}]\right)\div\left(\text{platelets}\ [10^9/\text{L}]\times\sqrt{\text{alanineaminotransferase}\ [\text{U/L}]}\right)$$

Participants with a Fibrosis-4 index >2.67 were categorized as having high probability of advanced hepatic fibrosis, whereas those with a Fibrosis-4 index <2.67 were identified as having low to intermediate risk. We also used APRI, another simple formula based on AST level and platelet count to assess the probability of advanced liver fibrosis recommended by the recent guidelines.[7] The cutoff value of APRI to determine high risk of advanced fibrosis is ≥1.0.[7] The cutoff values were consistent with previous literature to rule in high probability of advanced liver fibrosis and to predict future cardiovascular and dementia events.[9–13] The sensitivity, specificity, positive predictive value, and negative predictive value for the Fibrosis-4 index >2.67 to diagnose advanced fibrosis demonstrated by biopsy was 28%, 97%, 78%, and 77%, respectively, among individuals with nonalcoholic fatty liver disease, the most common type of chronic liver disease.[17] Additionally, the Fibrosis-4 index and APRI demonstrated good accuracy, with c-statistics ranging from ≈0.7 to 0.9 for identifying advanced liver fibrosis across various liver conditions, including viral hepatitis, alcoholic liver disease/alcoholic cirrhosis, and nonalcoholic fatty liver disease.[14–17] A recent European large-scale longitudinal study demonstrated that the Fibrosis-4 index is correlated with a 17-fold higher risk, and APRI is associated with a 45-fold higher risk of developing clinically significant liver conditions in the general population, highlighting their value as easily accessible and low-cost alternatives for screening individuals at elevated risk of impaired liver and cerebrovascular health.[18] Using the blood-based scores enables us to explore the link between liver fibrosis and stroke incidence in the unselected general population commonly with mixed underlying pathogeneses.[19]

The primary outcome of our study is fatal or nonfatal incident stroke and stroke types including ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). We also assessed the association of liver fibrosis with stroke-related death and all-cause death. Incident stroke and stroke types were ascertained by algorithmically defined outcomes developed by the UK Biobank Adjudication Group (Table S1). Multiple data sources were used, including hospital inpatient data (Hospital Episode Statistics for England, Morbidity Records for Scotland, and the Patient Episode Database for Wales) and death registry data (National Health Service Digital, National Health Service Central Register, and National Records). Stroke-related death was determined if any stroke event was recorded as the primary cause of death or death identified within 30 days after any stroke onset.[10,20]

Covariates

We extracted demographic, behavioral, clinical, and physical measurement and laboratory characteristics at baseline previously reported to be correlated with outcomes as per literature review.[21,22] Self-reported race was dichotomized into White and non-White race. The Townsend deprivation index is an area-based index of multiple derivation derived from residential post code in the United Kingdom. Behavioral characteristics including smoking status (categorized as never, former, or current), alcohol intake frequency (classified as never,

special occasions only, 1–3 times per month, once or twice per week, 3 or 4 times per week, and daily or almost daily), physical activity (quantified by days of moderate to vigorous exercise >10 minutes per week),[21] and diet intake habits collected via structured touchscreen questionnaires. A healthy diet in this study was defined as achieving at least 5 food intake goals of each diet component aligned with recent dietary recommendations for cardiovascular health and previous UK Biobank studies (Table S2).[23,24] Hypertension was identified by self-reported diagnosis by doctors or use of antihypertensive medications.[18] Diabetes was defined as self-reported diagnosis, glycated hemoglobin ≥6.5%, or use of antidiabetic medications as per previously published algorithm.[25] During the verbal interview, participants self-reported any prevalent chronic liver conditions, including infective or noninfective hepatitis, liver cirrhosis, and hepatic carcinoma. C-reactive protein levels were measured using immunoturbidimetric–high-sensitivity analysis on a Beckman Coulter AU5800. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula incorporating serum creatinine, age, sex, and race. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2.[26,27] Body mass index reflecting general adiposity and waist–hip ratio indicating central adiposity were measured at baseline assessment centers. Both measures were included in this analysis because these 2 adiposity distribution patterns were previously demonstrated to herald divergent correlation with ischemic and hemorrhagic stroke.[22]

Statistical Analysis

Baseline characteristics were compared between individuals categorized as high and low/intermediate risk of liver fibrosis. Continuous variables were expressed as mean (SD) or median (interquartile range), while categorical variables were presented as numbers (percentages). Kaplan–Meier analyses were conducted to compare the cumulative incidence risk of outcomes between individuals with and without high risk of hepatic fibrosis. Multivariable Cox proportional hazard models were conducted to calculate the hazard ratio (HR) and 95% CI between high risk of fibrosis assessed by Fibrosis-4 index and outcomes adjusted for sex, race, and Townsend deprivation index, smoking status, alcohol use frequency, physical activity, diet status, hypertension, diabetes, chronic kidney disease, use of antihypertensive or cholesterol-lowering agents, body mass index, waist–hip ratio, cholesterol, and C-reactive protein in the fully adjusted model. Follow-up duration in years was determined from the date of baseline assessment to the date of earliest incident outcome, death, or the end of follow-up data coverage (November 30, 2021). Schoenfeld residual tests were performed to visually examine proportionality hazards, and no violation was observed.

Several sensitivity analyses were performed to test the robustness of our results. First, we fit the Fibrosis-4 index and APRI into restricted cubic spline analysis with 4 knots to investigate potential nonlinear relationships between serum indices and risk of stroke outcomes. Second, we restricted the study population to participants without any prevalent clinically known chronic liver conditions at baseline including infectious or noninfectious liver disease, alcoholic liver disease, any prevalent liver failure, and hepatocarcinoma to explore the associations between subclinical liver injury and stroke. Third, we further conducted multivariable analyses by replacing hypertension, diabetes, and chronic kidney disease with systolic blood pressure, glycated hemoglobin, and estimated glomerular filtration rate as continuous variables. Fourth, we also investigated the relationship between progressive fibrosis and stroke by categorizing participants into 3 groups, including those who reported diagnosed liver cirrhosis, those with high Fibrosis-4 or APRI scores but no previous diagnosis, and those with neither diagnosis nor high noninvasive fibrosis scores. Finally, we combined the Fibrosis-4 index and APRI to further stratifying the probability of advanced fibrosis and assessed the associations between fibrosis and incident stroke. A 2-sided *P* value <0.05 was considered statistically significant. All statistical analyses were performed using R software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

RESULTS

Of the 502 371 participants, a total of 379 953 individuals (mean age, 56.2 [SD, 8.1] years; 55.4% women) remained in the final analysis after excluding individuals with incomplete laboratory data for calculating the Fibrosis-4 index or APRI (n=46 609); those who were lost to follow-up (n=1132); those with prevalent stroke or coronary heart disease (n=27 668), active hepatitis, or severe thrombocytopenia (n=373); and those with missing demographic, lifestyle, or clinical characteristics for analysis (n=46 636). The characteristics of participants with missing data appeared similar to the included participants, except that they had a higher Townsend deprivation index and a slightly lower proportion of individuals of White race (Table S3). A total of 7398 (1.9%) of 379 953 individuals were identified as having high risk of liver fibrosis defined as a Fibrosis-4 index >2.67. Baseline characteristics of study participants according to probability of advanced liver fibrosis were displayed in Table 1. Participants with an

Table 1. Baseline Characteristics of Participants Stratified by the Fibrosis-4 Index

	Total (N=379 953)	Low/intermediate risk (N=372 557)	High risk (N=7396)
Sociodemographic characteristics			
Age, y	56.2±8.1	56.1±8.1	62.3±6.0
Male sex	169 547 (44.6)	164 775 (44.2)	4772 (64.5)
White race	363 344 (95.6)	356 287 (95.6)	7057 (95.4)
Townsend deprivation index, quintiles			
1 (least deprived)	80 407 (21.2)	78 914 (21.2)	1493 (20.2)
2	78 617 (20.7)	77 091 (20.7)	1526 (20.6)
3	76 480 (20.1)	75 026 (20.1)	1454 (19.7)
4	75 637 (19.9)	74 130 (19.9)	1507 (20.4)
5 (most deprived)	68 812 (18.1)	67 396 (18.1)	1416 (19.1)
Lifestyle characteristics			
Smoking status			
Never	212 159 (55.8)	208 417 (55.9)	3742 (50.6)
Former	129 624 (34.1)	126 640 (34.0)	2984 (40.3)
Current	38 170 (10.0)	37 500 (10.1)	670 (9.1)
Alcohol intake			
Never	27 012 (7.1)	26 407 (7.1)	605 (8.2)
Special occasions only	41 330 (10.9)	40 574 (10.9)	756 (10.2)
1–3 times/mo	42 483 (11.2)	41 818 (11.2)	665 (9.0)
1–2 times/wk	99 252 (26.1)	97 612 (26.2)	1640 (22.2)
3–4 times/wk	90 765 (23.9)	89 150 (23.9)	1615 (21.8)
Daily or almost daily	79 111 (20.8)	76 996 (20.7)	2115 (28.6)
Days of moderate to vigorous physical activity >10 min			
0	45 644 (12.0)	44 843 (12.0)	801 (10.8)
1–2	54 050 (14.2)	53 188 (14.3)	862 (11.7)
3–7	280 259 (73.8)	274 526 (73.7)	5733 (77.5)
Healthy diet	61 752 (16.3)	60 174 (16.2)	1578 (21.3)
Clinical characteristics			
Hypertension	98 388 (25.9)	95 636 (25.7)	2752 (37.2)
Diabetes	18 376 (4.8)	17 736 (4.8)	640 (8.7)
Chronic kidney disease	7186 (1.9)	6835 (1.8)	351 (4.7)
On antihypertensive	71 692 (18.9)	69 423 (18.6)	2269 (30.7)
On lipid-lowering agent	49 025 (12.9)	47 377 (12.7)	1648 (22.3)
Laboratory characteristics			
Alanine aminotransferase, U/L	19.97 (15.32–27.15)	19.95 (15.33–27.08)	21.30 (15.06–33.03)
AST, U/L	24.30 (20.90–28.60)	24.20 (20.90–28.50)	33.10 (27.00–48.02)
Platelet count, 10^9/L	249 (214.6–287.9)	250.0 (216.5–288.7)	155.0 (126.5–182.9)
eGFR, mL/min per 1.73 m^2	93.3 (83.6–100.4)	93.4 (83.7–100.5)	89.1 (77.9–95.6)
C-reactive protein, mg/L	1.30 (0.64–2.68)	1.29 (0.64–2.68)	1.34 (0.64–2.85)
Total cholesterol, mmol/L	5.72 (5.00–6.47)	5.72 (5.01–6.47)	5.42 (4.66–6.20)
Glycated hemoglobin, mmol/L	35.10 (32.60–37.60)	35.10 (32.60–37.60)	35.30 (32.70–38.10)
Physical measurement			
Body mass index	26.6 (24.0–29.7)	26.6 (24.0–29.7)	26.4 (23.8–29.6)
Waist–hip ratio	0.87 (0.80–0.93)	0.87 (0.80–0.93)	0.90 (0.83–0.96)

Categorical variables are displayed as number and percentage. Continuous variables are displayed as mean±SD or median (interquartile range). High risk of liver fibrosis was defined as score of Fibrosis-4 index >2.67.

AST indicates aspartate aminotransferase; eGFR, estimated glomerular filtration rate.

elevated Fibrosis-4 index were older; were more likely to be men; and exhibited higher rates of hypertension, diabetes, and alcohol intake, along with elevated levels of C-reactive protein but lower cholesterol concentrations. Additionally, participants with high probability of advanced fibrosis exhibited higher prevalence of clinically known liver conditions (Table S4).

During a median follow-up period of 12.75 (interquartile range, 12.03–13.48) years, a total of 7143 stroke events occurred including 5593 cases of IS, 1237 incident cases of ICH, 784 incident cases of SAH. A total of 447 (6.3%) had >1 incident stroke events; 28 618 participants died within the follow-up period, among whom 1421 were recorded as stroke related. The incidence rate of IS was 27.5 (95% CI, 24.0–31.0) per 10 000 person-years among individuals with high risk of advanced fibrosis identified using the Fibrosis-4 index versus 11.5 (95% CI, 11.2–11.8) among those with low/intermediate risk of advanced fibrosis. The incidence rate of ICH was 6.4 (95% CI, 4.7–8.0) per 10 000 person-years in those with high risk of advanced fibrosis versus 2.5 (95% CI, 2.4–2.7) per 10 000 person-years among those without high risk of fibrosis. The incidence rate of SAH was 2.9 (95% CI, 1.8–4.0) per 10 000 person-years in participants with high probability of liver fibrosis versus 1.6 (95% CI, 1.5–1.7) per 10 000 person-years in those without.

Kaplan–Meier curves indicated greater risk of stroke, stroke-related death, and all-cause death in participants with high risk of advanced fibrosis using the Fibrosis-4 index (Figure 2). In multivariable Cox proportional hazard analyses, the Fibrosis-4 >2.67 index was associated with all stroke incidence (HR, 1.86 [95% CI, 1.66–2.09]), IS (HR 1.94, 95% CI 1.70–2.22)., ICH (HR, 2.14 [95% CI, 1.63–2.81]), SAH (HR, 1.90 [95% CI, 1.27–2.84]), stroke-related death (HR, 2.20 [95% CI, 1.73–2.80]), and all-cause death (HR, 2.59 [95% CI, 2.46–2.73]) in the fully adjusted models (Table 2).

Of the 379 953 participants, 1509 (0.4%) were identified as having a high risk of advanced liver fibrosis using a cutoff point of APRI ≥1.0. Baseline characteristics of participants with and without a high probability of advanced fibrosis using APRI are shown in Table S5. When determined by APRI, liver fibrosis remained related to elevated risk of stroke incidence and death in Kaplan–Meier analyses (Figure S1). High probability of fibrosis as determined by APRI independently correlated with higher HRs for ICH (adjusted HR, 3.76 [95% CI, 2.38–5.93]), SAH (adjusted HR, 3.05 [95% CI, 1.51–6.13]), stroke-related death (adjusted HR, 2.02 [95% CI, 1.21–3.37]), and all-cause death (adjusted HR, 3.33 [95% CI, 3.03–3.67]) compared with IS (adjusted HR, 1.58 [95% CI, 1.17–2.14]; Table S6).

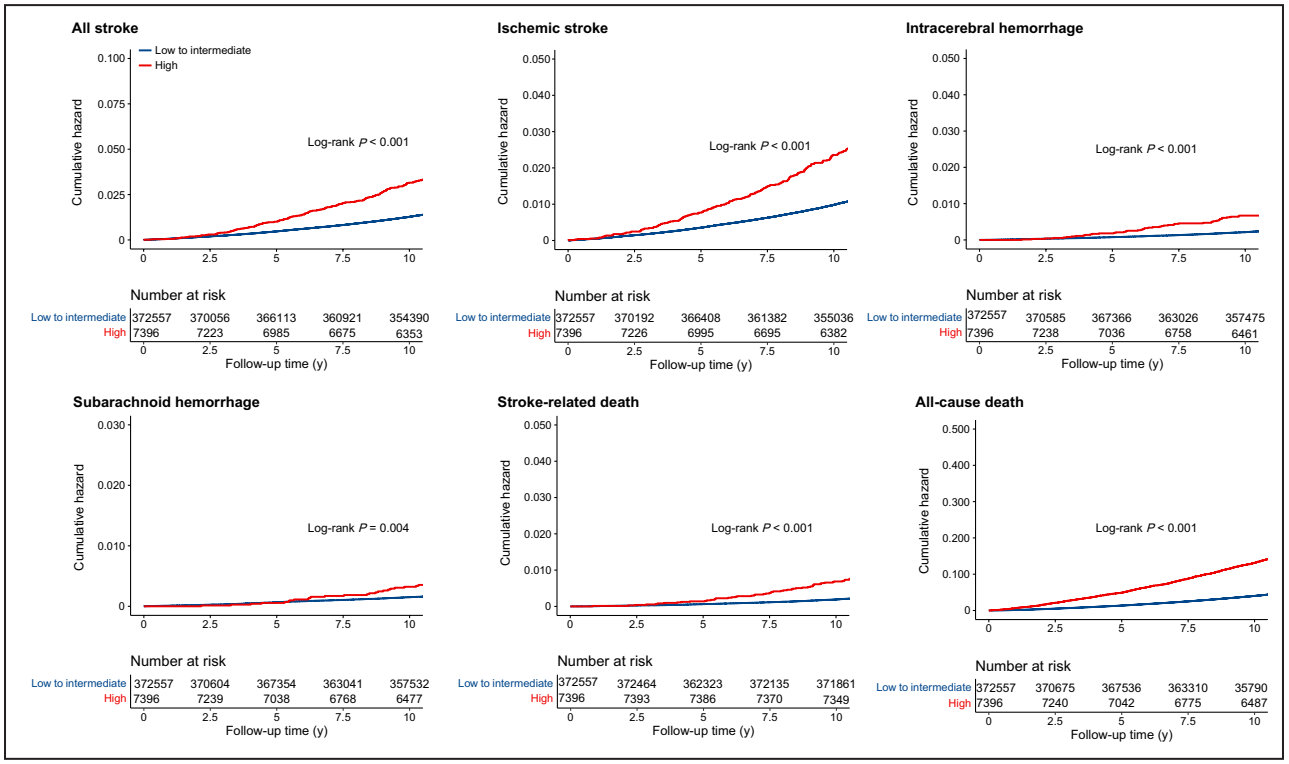

Figure 2. Kaplan–Meier analysis to estimate cumulative hazard for stroke outcomes stratified by the Fibrosis-4 index.
High risk of advanced liver fibrosis was defined as Fibrosis-4 index >2.67.

Table 2. Univariable and Multivariable Cox Hazard Proportional Analyses of the Association Between High Probability of Liver Fibrosis Identified by the Fibrosis-4 Index and Risk of Outcomes

Outcomes	Low/intermediate risk (N=372 557)	High risk (N=7396)	Univariable	Multivariable
			HR (95% CI)	HR (95% CI)
All stroke	6845 (1.8)	298 (4.0)	2.42 (2.16–2.72)	1.86 (1.66–2.09)
Ischemic stroke	5357 (1.4)	236 (3.2)	2.45 (2.15–2.79)	1.94 (1.70–2.22)
ICH	1182 (0.3)	55 (0.7)	2.57 (1.96–3.37)	2.14 (1.63–2.81)
SAH	759 (0.2)	25 (0.3)	1.80 (1.21–2.67)	1.90 (1.27–2.84)
Stroke-related death	1350 (0.4)	71 (1.0)	2.80 (2.20–3.55)	2.20 (1.73–2.80)
All-cause death	27 119 (7.3)	1499 (20.3)	3.20 (3.03–3.37)	2.59 (2.46–2.73)

Adjusted for sex, race, Townsend deprivation index, smoking status, alcohol intake frequency, physical activity, diet status, hypertension, diabetes, chronic kidney disease, use of antihypertensive and lipid-lowering medications, body mass index, waist–hip ratio, total cholesterol, and C-reactive protein.

HR indicates hazard ratio; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

Sensitivity Analysis

The restricted cubic spline analysis revealed nonlinear relationships between the Fibrosis-4 index and incidence of any stroke, IS, and all-cause death ($P_{nonlinear}$<0.001). Stronger associations were observed between the Fibrosis-4 index and ICH, SAH, and stroke-related death ($P_{nonlinear}$>0.05), with a significantly increased gradient of risk above a Fibrosis-4 index of 2.67. Results remain consistent in restricted cubic spline visualization investigating nonlinear associations between APRI and clinical outcomes (Figure 3). Similar results were observed in sensitivity analyses excluding those with previous chronic liver conditions or hepatocellular carcinoma (Table S7) and replacing hypertension, diabetes, and chronic kidney disease with continuous systolic blood pressure, glycated hemoglobin, and estimated glomerular filtration rate in the fully adjusted models (Table S8). Participants with previously diagnosed liver cirrhosis exhibited higher incidences of stroke and death. The associations between liver cirrhosis and stroke and death remained consistent irrespective of wider CIs resulting from limited cases of prevalent cirrhosis (Table S9). Using a combination of Fibrosis-4 index and APRI, we identified 1177 participants with both Fibrosis-4 index >2.67 and APRI ≥1.0, 6219 with Fibrosis-4 index >2.67 and APRI <1.0, 333 with Fibrosis-4 index ≤2.67 and APRI ≥1.0, and 372 224 with both Fibrosis-4 index ≤2.67 and APRI <1.0. Individuals with a high risk of hepatic fibrosis identified by a combination of Fibrosis-4 index >2.67 and APRI ≥1.0 (n=1177) exhibited the greatest risk of stroke incidence, stroke-related death, and all-cause death (Figure S2).

DISCUSSION

Our study demonstrated a nonlinear association between liver fibrosis and overall stroke incidence at the population level after adjusting for multiple demographic, clinical, lifestyle, and laboratory characteristics. Furthermore, there were magnified associations between liver fibrosis and incidence of ICH and SAH compared with IS. Additionally, advanced liver fibrosis was associated with stroke-related and all-cause death.

Depending solely on abnormal liver function tests will significantly underestimate the prevalence of underlying liver injury.[28] Our analysis using easily accessible noninvasive tests found positive correlations between subclinical advanced fibrosis and stroke incidence among individuals without prevalent stroke or cardiovascular diseases. In our analysis of the UK population, high risk of advanced liver fibrosis determined by the Fibrosis-4 index was associated with ≈1.86-fold increase in the risk of overall stroke compared with low to intermediate risk of advanced fibrosis. Among those with a high probability of advanced fibrosis, the incidence rate of ICH was 3-fold higher than the low-risk participants, and the incidence of SAH doubled among those with high risk of liver fibrosis. These findings corroborate and expand the findings from large-scale studies of multiple populations.[11,29–33] In contrast, recent population-based studies and meta-analyses from multiple ethical groups showed conflicting findings, which may be attributed to study design and ethical disparities.[34–36] It is crucial to understand the regional variations of liver cirrhosis for tailoring public health interventions, improving risk stratification, and optimizing stroke prevention strategies in populations with liver diseases.

There may be multiple mechanistic links between liver fibrosis and stroke incidence. Advanced liver fibrosis increases the bleeding risk due to coagulative disorders and platelet defects, which are secondary to thromboprotein underproduction and splenic sequestration.[2,3,37] Previous studies have found positive correlations between liver stiffness and microvascular injuries including white matter hyperintensity[38] and cerebral microbleed,[39] both of which are well-established

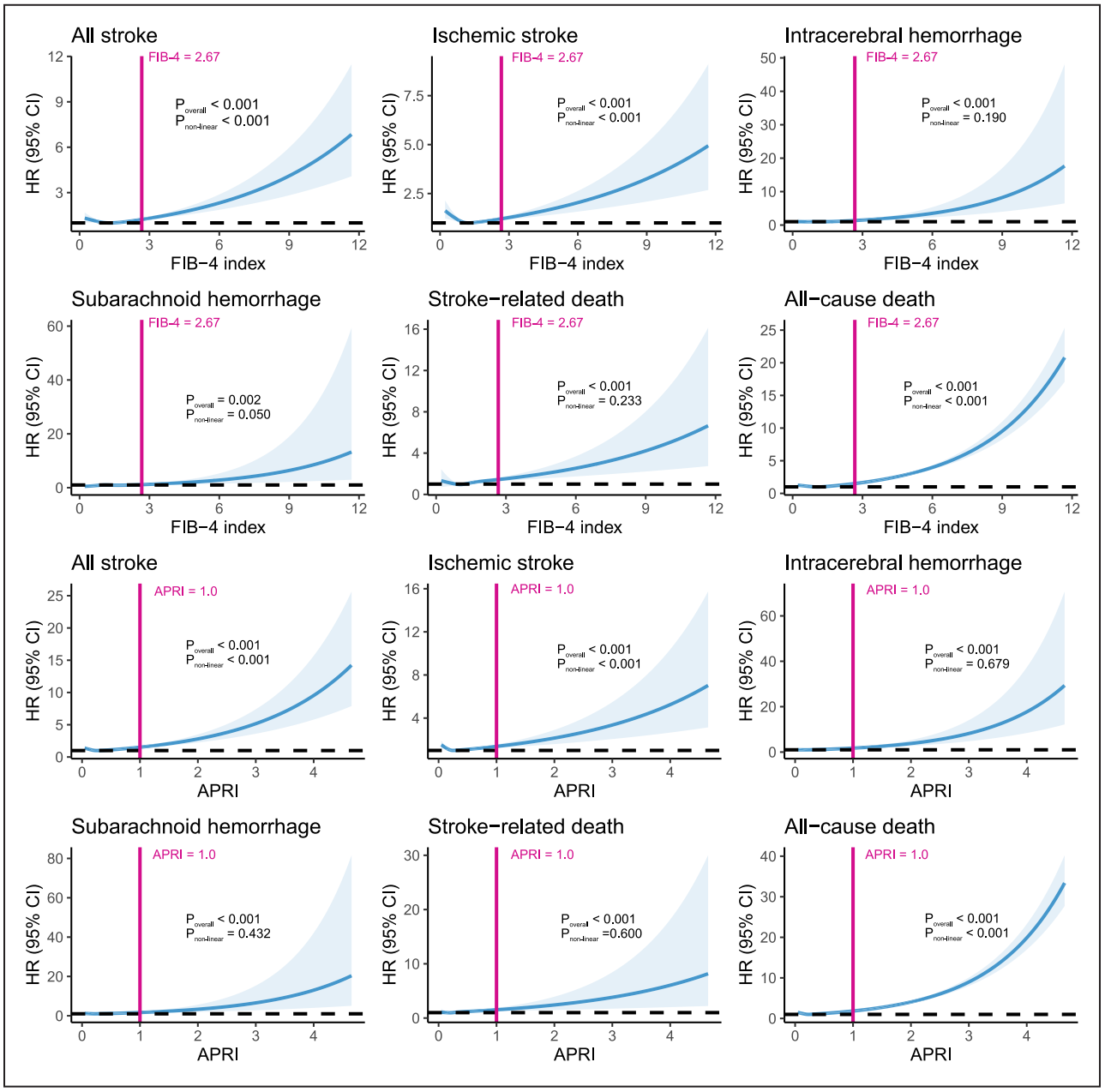

Figure 3. Restricted cubic spline plots for the association between noninvasive fibrosis scores and risk of incident stroke and death.

Restricted cubic spline visualization of associations of Fibrosis-4 index and APRI with all stroke, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, stroke-related death, and all-cause death. The Fibrosis-4 index of 2.67 and the APRI of 1.0 were set as the threshold to determine high risk of advanced fibrosis. All models were adjusted for age at recruitment, sex, race, Townsend deprivation index, smoking status, alcohol intake frequency, physical activity, diet status, hypertension, diabetes, chronic kidney disease, antihypertensive and lipid-lowering medication use, body mass index, waist–hip ratio, cholesterol, and C-reactive protein. APRI indicates aspartate aminotransferase to platelet ratio index; and FIB-4, Fibrosis-4.

magnetic resonance imaging markers predisposed to small-vessel disease–related ICH. However, progressive fibrosis may also lead to thrombosis events due to multiple pathways such as imbalanced coagulopathy, platelet defects, and subclinical inflammation.[40] Numerous studies have indicated that liver cirrhosis is associated with an increasing burden of atherosclerosis evidenced by elevated risk of carotid atherosclerosis and coronary heart disease.[10,11,33,41–43] Beyond dyslipidemia, liver fibrosis is also accompanied by chronic systemic inflammation, another major contributor to atherogenesis. We found that participants with advanced liver fibrosis had lower cholesterol but a higher C-reactive protein level, aligning

with another UK Biobank study that found liver inflammatory changes, manifested as liver disease activity (corrected T1) on magnetic resonance imaging rather than hepatic steatosis heralded a higher risk of cardiovascular and stroke events.[33] In addition, impaired secretion of hepatokines following liver fibrosis was correlated with greater risk of insulin resistance, atrial fibrillation, and heart failure, which may lead to cardioembolic stroke.[44,45]

A greater mortality rate after stroke in participants with high risk of advanced liver fibrosis, as shown in our work, suggests that stroke management in the context of advanced liver conditions represents a challenging scenario, yet there is limited clinical evidence to guide interventions.[40] Due to reduced levels of platelet or coagulation disorders, patients with IS may be less likely to be treated with thrombolysis and have poor functional outcomes.[46] Liver disease may increase the risk of hemorrhagic transformation after thrombolysis and restrict the prescription of antithrombotic agents for IS.[40] The clinical management of hemorrhagic stroke with concurrent liver cirrhosis represent a more complex dilemma. A recent study found that both the APRI and Fibrosis-4 index were correlated with larger hematoma volume and an elevated risk of hematoma expansion and death after ICH onset.[47] In a study involving >6000 patients with aneurysmal SAH, liver cirrhosis was related to in-hospital death and poststroke complications including rebleeding, pneumonia, and acute kidney injury.[48] Another study of 1419 patients with SAH also demonstrated that liver cirrhosis was robustly correlated with in-hospital death with an odds ratio of 12.7.[49] Further studies are needed to explore potential therapeutic strategies to reverse hepatic function in this patient group.

It is noteworthy that the prevalence of compensated cirrhosis was 10 times higher than that of decompensated cirrhosis as shown in a recent study by the Global Burden of Disease Group.[5] In addition, standard liver chemistries could be normal in ≈75% of patients with imaging-detected fibrosis.[6] Therefore, the presence of significant fibrosis may be greatly overlooked in the clinical setting. Our study underscores the importance of early screening of liver fibrosis on the basis of a combination of clinical routine blood panels, which may facilitate the development of potential preventive strategies to prevent further hepatic fibrotic replacement and reduce the stroke burden. Future studies are warranted to further explore the mechanisms of liver diseases leading to increased stroke risk to discover potential therapeutic targets and intervention therapies.

The strengths of this study included large sample size, standardized sample collection and analysis methods, and extended follow-up duration of >10 years to investigate the influence of liver fibrosis on stroke incidence. However, several limitations must be considered when interpreting our results. First, the Fibrosis-4 index and APRI are indirect surrogate markers for estimating the probability of liver fibrosis. Compared with direct measures of hepatic injury such as transient elastography or magnetic resonance elastography, noninvasive indices have limitations including a tendency to false-positive results and inability to accurately reflect the severity of liver fibrosis in the general population. In addition, the predictive value of the Fibrosis-4 index for advanced liver fibrosis is good in middle-aged people but significantly reduced in the older populations aged >70 years.[13] Therefore, our results may not be generalizable to other age groups. Potential misclassification of advanced fibrosis could lead to inaccurate estimations of stroke risk. By analyzing serologic indices using both dichotomized cutoff points and as continuous variables, we found consistent associations of liver fibrosis with the risk of 3 major stroke types and death, which may decrease the influence of misclassification. Future studies using direct serum or imaging-based methods to further explore the associations between liver fibrosis severity and long-term stroke risk may be of potential interest.[37] Second, the prevalence of advanced fibrosis in our analysis was similar to that reported in a previous UK Biobank publication[9] but was lower than that in other reports of the general population.[5] The lower prevalence of liver fibrosis may be explained by a "healthy volunteer" selection bias of the UK Biobank with lower prevalence of vascular risk factors. Third, the data for precise categorization of the causes of liver fibrosis and stroke pathogenetic subtypes are not available in the UK Biobank. Future studies are warranted to investigate differential risk of IS subtypes in the context of liver fibrosis due to various pathogeneses.

CONCLUSIONS

Advanced liver fibrosis is associated with an increased risk of stroke and death among the general population with no history of cardiovascular events or stroke. There are stronger associations between liver fibrosis and ICH and SAH. Future studies may use noninvasive scores assessing liver health to ameliorate the stratification of stroke risk within community settings.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S9
Figures S1–S2

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