Lack of Association between Nonalcoholic Fatty Liver Disease and Intracerebral Hemorrhage: A Community-based Cohort Study

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Research Article

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Abstract

Background: This study aimed to investigate whether Nonalcoholic Fatty Liver Disease (NAFLD) and its severity predict future intracerebral hemorrhage (ICH) events.

Methods: We used data from the Kailuan study. Participants free of history of stroke, myocardial infarction, cancer, other liver diseases or alcohol abuse were enrolled in this study. Abdominal ultrasonography was used to diagnose NAFLD and access its severity. We stratified the participants into different groups including nonfatty liver, mild, moderate and severe NAFLD. Multivariable Cox proportional hazards regression models, adjusted for potential covariates, were applied to estimate the Hazard ratios (HRs) and 95% CI of ICH events in the 11-year follow-up.

Results: A total of 77,461 participants enrolled in our study. Among them, NAFLD was diagnosed in 23,890 (30.83%) participants, including 15,581 (20.11%) mild NAFLD, 6,839 (8.83%) moderate NAFLD and 1,470 (1.90%) severe NAFLD. We documented 692 ICH events during 848,579 person years of follow-up. Patients with more severe NAFLD tended to be older, had higher levels of BMI, higher proportions of hypertension, diabetes and other known risk factors of cerebrovascular disease. However, we did not find significant associations between NAFLD, its severity and incident ICH events. Relative to nonfatty liver participants, HRs for participants with mild NAFLD, moderate and severe NAFLD were 0.98 (95% CI, 0.80 to 1.20), 1.19 (95% CI, 0.92 to 1.54) and 1.29 (95% CI, 0.81 to 2.06), respectively.

Conclusions: NAFLD and its severity appear not to be significantly associated with ICH after adjustment for potential risk factors.

Trial registration: The Kailuan study was registered at International Clinical Trials Registry Platform (Unique identifier: ChiCTR-TNRC-11001489, date of registration: 24/08/2011).

Background

Intracerebral hemorrhage (ICH) is a life-threatening and disabling cerebrovascular disease. Globally, ICH affected more than 3 million people each year, approximately accounts for 28% of stroke[1]. Unlike other stroke subtypes, ICH still lacks effective therapies, the best treatment is effective detection and control of potential risk factors[2]. Age, hypertension, smoking, alcohol intake and use of anticoagulant medications are known risk factors of ICH[3, 4].

Nonalcoholic Fatty Liver Disease (NAFLD) is becoming the leading cause of chronic liver disease and an important public health issue globally[5]. NAFLD is the hepatic manifestation of metabolic syndrome and has been found to be associated with metabolic risk factors including hypertension, diabetes and obesity[6]. Over the past decade, there were sufficient evidence showed NAFLD is not only associated with higher liver-related morbidity or mortality, but also affects cardiovascular and cerebrovascular system. A meta-analysis with 34,043 individuals demonstrated patients with NAFLD, especially more severe NAFLD, had a higher risk of cardiovascular events[7]. A recent meta-analysis with 135,602

individuals further showed NAFLD increases the risk of carotid atherosclerosis and ischemic stroke[8]. Endothelial dysfunction, elevated homocysteine and oxidative stress, deranged adipokine profile, activation of hepatic and systemic and inflammatory cascades might be the underlying mechanisms of vascular remodeling and result in higher risk of cardiovascular disease[9]. However, the association between NAFLD and another fatal subtype of cerebral vascular disease, ICH, has rarely been studied.

Noteworthy, the severity of NAFLD ranges from simple steatosis to progressive liver fibrosis and cirrhosis[10]. The progression of NAFLD might be mirrored by increasing oxidative stress, inflammatory cascades and other pathologies that are associated with cardiovascular disease. Different severity stages of NAFLD can lead to different clinical outcomes. However, the few published studies of NAFLD and ICH did not stratify their participants according to NAFLD severity. Besides, the sample size of these studies was relatively small, which became important limitations [8, 11, 12]. Therefore, we conducted a large community-based prospective study to further investigate the associations between NAFLD, its severity and future incident ICH.

Methods

Study Population

The Kailuan study is a community-based, prospective study aims at investigating the risk factors for common noncommunicable diseases in Chinese adults. The details of the Kailuan study have been reported previously [13]. Briefly, a total of 101,506 participants aged elder than 18 years underwent baseline examinations in 2006. Each participant underwent questionnaire assessments, laboratory tests and abdominal ultrasonography in 11 hospitals. The same examinations were repeatedly performed every two years from 2006 to 2016. At baseline, we excluded 3,660 participants with a history of stroke, myocardial infarction, cancer or other known liver diseases; 3,689 participants with missing data of alcohol intake or ultrasonography data of NAFLD; 16,696 Participants with excessive alcohol abuse (defined as men who drink 20 g per day and women with a drinking history for at least a year). Eventually, a total of 77,461 participants enrolled in this study. The study was performed according to the guidelines of Helsinki Declaration and was approved jointly by the Ethics Committee of the Kailuan General Hospital, Beijing Chaoyang Hospital, and TianTan Hospital. Written informed consent was obtained from all participants. The Kailuan study was registered at International Clinical Trials Registry Platform (Unique identifier: ChiCTR-TNRC-11001489, date of registration: 24/08/2011).

Nafld And Potential Covariates Assessment

Abdominal ultrasonography using a high-resolution B-mode topographical ultrasound system with a 3.5 MHz probe (ACUSON X300, Siemens, Germany) was used to diagnose NAFLD and access its severity. Experienced radiologists were blinded to the information of the participants. After excluding excessive alcohol intake and other liver diseases, NAFLD was diagnosed by the presence of at least two of three

abnormal findings: (1) diffusely increased echogenicity liver with echogenicity greater than spleen or kidney; (2) deep attenuation of ultrasound signal and (3) intrahepatic structures poor visualization [14]. We further classified the participants into 4 groups according to their severity stages of NAFLD including nonfatty liver, mild NAFLD when there is a diffuse increase of fine echoes in the liver parenchyma, moderate NAFLD when there was slightly impaired visualization of the intra-hepatic vessels and diaphragm and severe NAFLD when there was diffuse increase in fine echoes with no visualization of the intra-hepatic vessels and diaphragm [15].

Information including demographic variables, medical history, drinking condition, smoking status, education level, income level and physical activity were collected by trained investigators at baseline in 2006 with questionnaires. Body mass index (BMI) was calculated as weight (kg)/square of height (m2). An auto-analyser (Hitachi 747; Hitachi, Tokyo, Japan) was used to analysis the levels of fasting blood glucose (FBG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), high-sensitivity C-reactive protein (hsCRP) and liver function indexes. Blood samples were collected under fasting condition and within four hours of preparation.

Ich Identification And Follow-up Assessment

The outcome was the first occurrence of ICH, either nonfatal or fatal. ICH was diagnosed according to the World Health Organization criteria [16]. The details have been described in a previous study [17]. In brief, trained investigators took medical examinations for each participants every 2 years by face-to face interviews. ICH were confirmed by checking discharge lists from local hospitals and medical insurance records. For potential ICH patients, investigators reviewed their symptoms and neuroimages including computed tomography and magnetic resonance imaging. All of the neuroimages were further assessed by trained physicians. The follow-up of the participants was continued until the occurrence of first ICH or December 31, 2016, which ever came first.

Statistical Analysis

Baseline characteristics are presented as medians and interquartile range (IQR) for continuous variables because of skewed distributions. Categorical variables are described as frequencies and percentages. Comparisons between groups for continuous variables were tested by Kruskal-Wallis analysis, while categorical variables were tested by Chi-square test. Cox proportional hazards regression models were used to investigate the associations between NAFLD, its severity and incident ICH. Model one was adjusted for age, sex, BMI, smoking status and physical activity. Model two was adjusted for model one plus education levels, history of diabetes, hypertension, dyslipidemia, antidiabetic agents, antihypertensive agents, lipid lowering agents, antiplatelet and anticoagulants agents. Model three was further adjusted for TG, TC, LDL-C, HDL-C, FBG and hs-CRP. We used a trend test to assess dose-dependent relationship between different severities of NAFLD and incident ICH. All statistical analyses

were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Among the total of 77,461 participants enrolled in our study with a median age of 51.19 years, 53,571 (69.16%) participants were found to be free of fatty liver, 23,890 (30.83%) participants had NAFLD, including 15,581 (20.11%) mild NAFLD, 6,839 (8.83%) moderate NAFLD and 1,470 (1.90%) severe NAFLD. The distribution of baseline demographic and clinical characteristics according to the severity of NAFLD are showed in **Table 1**. Patients with more severe NAFLD at baseline were more likely to have elder age, higher levels of BMI, FBG, LDL-C, TG, ALT and hs-CRP, lower level of HDL-C, higher systolic blood pressure, more likely to suffer from diabetes, hypertension and dyslipidemia, and have higher proportions of current antihypertensive, antidiabetic and lipid-lowering agents use. A total of 692 ICH cases were identified during the 848,579 person-year of follow-up.

Table 1. Baseline Characteristics According to Severity of NAFLD

Variable	Nonfatty liver	Mild NAFLD	Moderate NAFLD	Severe NADLD	P value
N (%)	53571 (69.16)	15581 (20.11)	6839 (8.83)	1470 (1.90)	
Age, years	50.72 (42.08-58.36)	52.08 (44.36-58.82)	52.18 (44.09-58.60)	52.33 (44.11-58.63)	0.0001
Male, n (%)	39616 (73.95)	12148 (77.97)	5305 (77.57)	1106 (75.24)	0.0001
High school or above, n (%)	11357 (21.38)	3068 (20.00)	1270 (18.76)	278 (19.11)	0.0001
Income >1000 RMB/m, n (%)	3334 (6.28)	1046 (6.82)	493 (7.29)	112 (7.70)	0.0008
Body mass index, kg/m2	23.88 (21.83-25.91)	26.79 (24.91-28.73)	28.04 (26.12-30.18)	29.76 (27.36-32.32)	0.0001
Physical activity≥3 times/week, n (%)	7185 (13.53)	1921 (12.53)	941 (13.92)	255 (17.54)	0.0001
Current or previous smoking, n (%)	15739 (29.40)	4950 (31.79)	1987 (29.08)	443 (30.18)	0.0001
Fasting blood glucose, mmol/L	5.02 (4.60-5.53)	5.30 (4.80-6.01)	5.38 (4.83-6.30)	5.48 (4.88-6.69)	0.0001
LDL-C, mmol/L	2.30 (1.78-2.80)	2.35 (1.86-2.82)	2.40 (1.94-2.80)	2.45 (2.10-2.87)	0.0001
HDL-C, mmol/L	1.51 (1.28-1.76)	1.48 (1.27-1.74)	1.48 (1.25-1.74)	1.47 (1.23-1.73)	0.0001
TC, mmol/L	4.81 (4.20-5.44)	5.06 (4.42-5.74)	5.03 (4.35-5.78)	5.01 (4.31-5.78)	0.0001
TG, mmol/L	1.11 (0.80-1.57)	1.64 (1.17-2.44)	1.92 (1.35-2.98)	1.98 (1.41-3.12)	0.0001
PLT, 10^9/L	199.00 (168.00-235.00)	203.00 (171.00-240.00)	202.00 (169.00-237.00)	202.00 (169.00-244.00)	0.0001
ALT, U/L	16.20 (12.00-22.00)	20.50 (15.00-28.00)	23.00 (18.00-33.00)	25.00 (19.00-40.00)	0.0001
ALB, g/L	47.00 (44.80-48.70)	47.00 (46.00-49.00)	47.00 (45.00-48.00)	48.00 (48.00-49.00)	0.0297
TBIL, μmol/L	12.10 (9.70-15.00)	12.30 (10.00-15.00)	11.80 (9.60-14.80)	12.10 (10.20-15.20)	0.0001
DBIL, μmol/L	5.00 (4.00-7.35)	4.55 (3.20-8.00)	4.50 (3.30-8.00)	8.00 (3.40-8.00)	0.4604

Systolic blood pressure, mm Hg	121.70 (110.70-140.00)	130.00 (120.00-149.30)	140.00 (122.00-150.00)	140.00 (129.30-159.30)	0.0001
hs CRP, mg/L	0.65 (0.24-1.74)	1.08 (0.43-2.70)	1.30 (0.58-3.10)	1.67 (0.72-3.62)	0.0001
Diabetes Mellitus, n (%)	1190 (2.22)	682 (4.38)	337 (4.93)	102 (6.94)	0.0001
Hypertension, n (%)	4432 (8.27)	2457 (15.77)	1297 (18.96)	361 (24.56)	0.0001
Dyslipidemia, n (%)	1957 (3.65)	1256 (8.06)	658 (9.62)	196 (13.33)	0.0001
Antihypertensive agents, n (%)	3801 (7.10)	2154 (3.53)	1134 (15.28)	332 (22.59)	0.0001
Antidiabetic agents, n (%)	906 (1.69)	530 (3.40)	269 (3.93)	89 (6.05)	0.0001
Lipid-lowering agents, n (%)	267 (0.50)	194 (1.25)	116 (1.70)	22 (1.50)	0.0001
Antiplatelet agents, n (%)	46 (0.09)	14 (0.09)	11 (0.16)	4 (0.27)	0.0978

NAFLD, nonalcoholic fatty liver disease; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; PLT, platelet; ALT, aminoleucine transferase; ALB, Albumin; TBIL, total bilirubin; DBIL, direct bilirubin; hs CRP, high-sensitivity C-reactive protein.

NAFLD and ICH

During a median of 11-year follow-up, 0.82% (437 out of 53,571) participants without NAFLD, and 1.07% (255 out of 23,890) participants with NAFLD developed ICH. After adjusted for age, sex, BMI, smoking status, physical activity, education levels, history of diabetes, hypertension, dyslipidemia, antidiabetic agents, antihypertensive agents, lipid lowering agents, antiplatelet and anticoagulants agents, TG, TC, LDL-C, HDL-C, FBG and hs-CRP, NAFLD was not significantly associated with increased risk of ICH. Compared with participants without NAFLD, the HR values for those with NAFLD were 1.10 (95% CI, 0.93-1.31), 1.07 (95% CI, 0.90-1.27) and 1.05 (95% CI, 0.88 to 1.26) in three models **(Table 2)**.

Table 2. HRs (95% CI) for ICH in participants with/without NAFLD.

	Nonfatty liver	NAFLD
Cases, n (%)	437 (0.82)	255 (1.07)
Model 1	Reference	1.10 (0.93-1.31)
Model 2	Reference	1.07 (0.90-1.27)
Model 3	Reference	1.05 (0.88-1.26)

Model 1 was adjusted for age, sex, BMI, smoking status and physical activity. Model 2 was adjusted for model 1 plus education levels, history of diabetes, hypertension, dyslipidemia, antidiabetic agents, antihypertensive agents, lipid lowering agents, antiplatelet and anticoagulants agents. Model 3 was further adjusted for TG, TC, LDL-C, HDL-C, FBG and hs-CRP. BMI, body mass index; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; hs CRP, hypersensitive C-reactive protein.

NAFLD severity and ICH

During the follow-up period, 0.82% (437 out of 53,571) of nonfatty liver participants, 0.95% (148 out of 15,581) participants with mild NAFLD, 1.26% (86 out of 6,839) participants with moderate NAFLD and 1.43% (21 out of 1,470) participants with severe NAFLD developed ICH. Participants with more severe NAFLD tended to have a higher risk of ICH. But this trend was not statistic significant after adjusting potential covariates. In the fully adjusted model, compared with participants without NAFLD, the HR values for participants with mild NAFLD, moderate and severe NAFLD were 0.98 (95% CI, 0.80 to 1.20), 1.19 (95% CI, 0.92 to 1.54) and 1.29 (95% CI, 0.81 to 2.06), respectively. The P value was 0.1828 in the trend test **(Table 3)**.

Table 3. HRs (95% CI) for ICH according to different severities of NAFLD.

NAFLD severity	Cases, n (%)	Model 1	Model 2	Model 3
Nonfatty liver	437 (0.82)	Reference	Reference	Reference
Mild NAFLD	148 (0.95)	1.02 (0.84-1.25)	1.00 (0.81-1.21)	0.98 (0.80-1.20)
Moderate NAFLD	86 (1.26)	1.25 (0.97-1.61)	1.21 (0.94-1.56)	1.19 (0.92-1.54)
Severe NAFLD	21 (1.43)	1.42 (0.90-2.25)	1.31 (0.83-2.08)	1.29 (0.81-2.06)
P for trend		0.0557	0.1352	0.1828
Continuous Scale		1.11 (0.98-1.23)	1.08 (0.98-1.21)	1.08 (0.97-1.20)

Model 1 was adjusted for age, sex, BMI, smoking status and physical activity. Model 2 was adjusted for model 1 plus education levels, history of diabetes, hypertension, dyslipidemia, antidiabetic agents, antihypertensive agents, lipid lowering agents, antiplatelet and anticoagulants agents. Model 3 was further adjusted for TG, TC, LDL-C, HDL-C, FBG and hs-CRP. BMI, body mass index; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; hs-CRP, hypersensitive C-reactive protein.

Discussion

In this large, population-based follow-up study of 77,461 adults, we did not find any significant associations between NAFLD, its severity and ICH after adjustment for demographic characteristics, potential ICH risk factors and relevant comorbidities. These data suggest that neither a diagnosis of NAFLD nor a more severe stage of NAFLD necessarily indicate a need for ICH prevention treatments.

Currently, evidence of the association between NAFLD and ICH is very limited and controversial. In a prospective observational cohort with a total of 1150 participants, ICH events were found to be significantly higher in patients with NAFLD than those without [12]. This result, however, should be interpreted with caution as only univariate analysis was used to assess the relationship between NAFLD and ICH. In contrast, another small sample study with 128 participants demonstrated that NAFLD did not affect ICH development or severity [11]. Recently, a meta-analysis showed that there is no significant association between NAFLD and higher risk of ICH [8]. But the majority of studies included in this meta-analysis were about atherosclerosis and ischemic stroke, only a few studies had information of ICH. Of, NAFLD encompasses a wide spectrum range from steatosis to nonalcoholic steatohepatitis with varying amounts of fibrosis and cirrhosis [10]. At a pathophysiological level, the progression of NAFLD might be accompanied by increasing activation of inflammatory cascades and other potential pathologies that are associated with a heightened risk of cerebrovascular disease. However, none of the previous studies stratified patients according to NAFLD severity, which restricts the conclusions that can be made. In this large community-based prospective study conducted to assess the relationship between NAFLD and incident ICH, we add to previous reports that there is no significant associations between NAFLD, its severity and future incident ICH. One potential for the contradictory conclusions in previous studies and the current study is that the population of participants in different studies was probably heterogeneous. In addition, some studies only use univariate analysis or partially adjusted for known risk factors, the relatively small sample sizes in these studies might also contribute to insufficient statistical power and result in different conclusions.

Several previous studies have demonstrated that NAFLD was associated with increased risk of ischemic cardiovascular and cerebrovascular events[15, 18], the current study provide further evidence of the relationship between NAFLD and a hemorrhagic cerebrovascular disease, ICH. However, although we identified patients with NAFLD tended to have a higher rate of incident ICH, and the risk of incident ICH raised with increasing severity of NAFLD, but the trends did not meet statistical significance. One potential reason is that pathogenesis is different between ischemic stroke and ICH. It is known that the most common cause of ischemic vascular disease is atherosclerosis [19]. NAFLD has been found to be associated with an increase in atherogenic dyslipidemia [20], which might contribute to the development of atherosclerosis and ischemic stroke [8, 21]. ICH, on the other hand, is often caused by deep perforating vasculopathy related to high blood pressure [22]. Previous studies demonstrated that NAFLD is an important driving force in the development and progression of hypertension and shared several other risk factors with ICH like diabetes and obesity [23, 24]. Consistently, our study demonstrated a growth trend of hypertension, diabetes and several other risk factors of ICH in different NAFLD severity groups. But there

was no direct relation between NAFLD itself and ICH after adjusting the potential risk factors. Another potential reason for the non-significant results in this study is that NAFLD might be a reversible progress through weight losing and improvement of lifestyle [23]. But the impact of NAFLD is a long-term process, which indicates that assessment of NAFLD status at a single time point may not be enough to reflect the effect of NAFLD on ICH. Therefore, we plan to further investigating effects of evolution of NAFLD across a period of time on incident ICH in the next study.

Taken together, conclusions regarding the relationship between NAFLD and ICH remained controversial. It should not be assumed that patients with NAFLD are at increased risk of ICH based on existing evidence. But it is important to screen patients with a diagnosis of NAFLD for cardiovascular risk factors and take interventions for patients at a high risk. For NAFLD patients, maintaining a healthy lifestyle and taking vigorous control of blood pressure, body weight and other risk factors might be more important for preventing ICH.

A notable strength of this study is being a prospective community-based cohort study with a large sample size. Yet, this study also has several limitations. First, we use abdominal ultrasonography for NAFLD detection instead of liver biopsies, which is considered to be the criterion standard for NAFLD diagnosis. However, implementation of invasive liver biopsy in a healthy population would be neither feasible nor ethical. Abdominal ultrasonography, on the other hand, is a noninvasive and safe technique which could be used for NAFLD diagnosis and steatosis severity assessment [14]. The sensitivity and specificity of ultrasound for the detection of moderate-severe fatty liver were 84.8% and 93.6% compared with histology, respectively [25], indicating it was a reliable and accurate technique for NAFLD. Second, we measured alcohol consumption with a questionnaire, although conducted by trained investigators, the measurement error might still exist and be a cause of residual confounding.

Conclusions

In conclusion, our study did not establish any significant association between NAFLD, its severity and ICH. It should not be assumed that patients with NAFLD are at increased risk of ICH based on existing evidence. Even so, screening and controlling for risk factors of ICH are important for NAFLD patients. Further large-scale studies are needed to confirm these findings.

Abbreviations

NAFLD, nonalcoholic fatty liver disease; ICH, intracerebral hemorrhage; HR, hazard ratio; BMI, body mass index; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; hsCRP, high-sensitivity C-reactive protein; GGT, gamma-glutamyl transferase.

Declarations

Ethics approval and consent to participate: The study was performed according to the guidelines of Helsinki Declaration and was approved jointly by the Ethics Committee of the Kailuan General Hospital, Beijing Chaoyang Hospital, and TianTan Hospital. Written informed consent was obtained from all participants. The Kailuan study was registered at International Clinical Trials Registry Platform (Unique identifier: ChiCTR-TNRC-11001489, date of registration: 24/08/2011).

Consent for publication: Not applicable.

Availability of data and materials: The raw data of the current study are not publicly available due to the protection of participants' personal information but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: JW and JG contributed to the study concept, design, interpreted the data, and drafted the article. AW and YZ interpreted the data. XZ and SW supervised the analysis, commented on the drafts, had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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