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Research Article

Liver Injure is Associated with Increased Mortality of Young Patients with Ischemic Stroke in China

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Abstract

Background and Purpose: Morbidity and mortality in young ischemic stroke are increasing. Therefore, it is necessary to study the risk and consequences of ischemic stroke in young people. The objective of this study was to investigate the recurrence and survival rate of five-year ischemic stroke in young patients in the rural of China.

Methods: This retrospective cohort study included patients with the first ischemic stroke from the Anhui health system between June 2010 to February 2017. The outcomes included all-cause mortality and relapse at five years of ischemic stroke. Cumulative incidence function, kaplan-Meier estimator and Cause-specific hazard model were used to evaluate the relationship of independent variables with the outcomes. Ischemic stroke model was generated to text the casual effect of liver injury upon ischemic stroke.

Results: A total of 916 first-time ischemic stroke patients were included in the study, with 152 (16.6%) patients in the 30–55 age group and 764 (83.4%) patients in the >55 age group. In the 30–55 age group, the five-year survival probability was 85.5%, and the cumulative incidence of recurrence was 18.5%. Patients in the 30–55 age group had significantly lower hazard or all-cause mortality (HR=0.37, 95% CI 0.29–0.46, p<0.001), and non-significant hazard for five-year recurrence (HR=0.81, 95% CI 0.58–1.12, p=0.193) compared to the >55 age group. Liver Injure diseases were found to be associated with increased mortality in the 30–55 age group. In addition, Carbon Tetrachloride (CCL4)-induced liver injury could further aggravate stroke in mouse ischemic stroke model.

Conclusion: In the rural population of China, younger ischemic stroke patients were low-risk of the older ischemic stroke patients. Identifying the factors which is liver injury disease may aggravate the risk of younger ischemic stroke patients.

Keywords: Ischemic stroke; Liver disease; Young stroke; Recurrence; Risk

Abbreviations: CCL4: Carbon Tetrachloride; HR: Hazard Ratio; CI: Confidence Interval; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Nonalcoholic Steatohepatitis; HCC: Hepatocellular Carcinoma; MRI: Magnetic Resonance Imaging; tMCAO: Transient Middle Cerebral Artery Occlusion; IACUC: Institutional Animal Care and Use Committee; ALT: Alanine Aminotransferase; AST: Aspartate Amino Transferase; OCT: Optical Coherence Tomography; SEM: Standard Error of Mean

Introduction

Stroke is a devastating disorder which affects more than 15 million population worldwide. 80% of strokes are ischemic strokes [1,2]. Despite reduction of overall occurrence rate, hospitalization rate of young adults with ischemic stroke increased in past decades [2,3]. It was reported more than 10% ischemic strokes occur in young populations [2,4,5]. Different from old population mainly effected by cardiovascular factors, the ischemic strokes in young adults resulted by heterogenous factors.

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Hypertension, heart failure, smoking, diabetes and large artery atherosclerosis were found to be independent predictors of long-term mortality in young ischemic stroke patients [6].

Risk factors and management strategies for young stroke differ across the world, depending on factors such as genetic differences, environmental influences, and accessibility of health services [7,8]. From the prospective of young patients who usually have life of decades, understanding the prognosis after stroke is of vital importance. The additional knowledge regarding the long-term outcomes and associated factors among the young stroke population could help with targeted treatment and measurable interventions and reduction of socioeconomic burden [8].

Liver disease, is a major cause of illness in worldwide, including hepatitis virus infections, nonalcoholic fatty liver disease, alcoholic liver disease and drug induced liver injury [9]. In China, liver diseases affect about 400 million people. In fact, 28% of the world's population is thought to have Nonalcoholic Fatty Liver Disease (NAFLD). Nonalcoholic steatohepatitis (NASH) is the subtype of NAFLD that can progress to cirrhosis and Hepatocellular Carcinoma (HCC) [10,11]. Liver injury increases blood density and blood coagulating, which associated with stroke [12,13]. Increased blood lipid concentration and viscosity in NAFLD patients is the main factor of cardiovascular and cerebrovascular diseases [14]. Unfortunately, whether liver injury affect the mortality and prognosis of ischemic stroke remains unclear.

To date, however, Long-term outcome and risk factors among young stroke patients in Chinese populations rarely studied in previous studies. Thus, this study aimed to investigate the long-term ischemic stroke recurrence and survival probability among young patients compared to elder population and to examine the involvement of liver disorder in the occurrence of ischemic stroke. Further explore the risk factors for stroke recurrence in middle-aged people in the rural of China.

Materials and Methods

Data Source

Patients with ischemic stroke in our institution from 13 June 2010 to 16 February 2017 were retrospectively enrolled for this study. Patients were included according to following criteria: 1) patients who diagnosed ischemic stroke based on International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification (ICD-9/10-CM) codes; 2) patients who had brain Magnetic Resonance Imaging (MRI) in the same encounter; 3) patients aged more than 30 years; 4) minim of 5 years follow-up; 5) accessible of hospital chart that records detailed demographics of patients. Patients were excluded if they: 1) had a prior history of ischemic or hemorrhagic stroke; 2) lack of MRI materials; 3) without a primary diagnosis of ischemic stroke. The patient inclusion/exclusion flow chart is shown in Figure 1. The institutional review board following the Declaration of Helsinki principles has approved this study.

Patients' Classifications and Outcome Measures

Patients were divided into two subgroups based on their age at index stroke "30–55" and "above 55" age group. Patients with index stroke date after 16 February 2017 were excluded as a five-year follow-up would not be complete for these patients on 16 February 2022, and their inclusion could result in biased estimates in the survival analysis. The outcomes were ischemic stroke recurrence and all-cause mortality within five years of the stroke date (index stroke). All-cause mortality was assessed from the clinical chart data and cross-referenced with phone-call follow-up on 16 February 2022. Thus, the follow-up time was defined as the time between the index stroke date and the last encounter in the clinical chart for recurrence and between the index stroke date and the end of the study period (16 February 2022) for the all-cause mortality.

Animal Experiments

C57BL/6J mice (male; 6-8 weeks of age) were purchased from Charles River Laboratory Animal Facility (Beijing, China). CCl4 and olive oil mixture (1:1 dosage of 1 mL/kg b.w.) induced hepatic injury in mice. Then, Transient Middle Cerebral Artery Occlusion (tMCAO) was performed in mice as reported previously (Sun et al., 2008). All experiments were approved and conducted by an Institutional Animal Care and Use Committee (IACUC) at Nanjing Medical University (AP#2019-17-149) and the Laboratory Animal Management Committee of Jiangsu Province.

The Alanine Aminotransferase (ALT) and aspartate Amino Transferase (AST) levels were determined using an HITACHI7080 Automatic Clinical Analyzer (Tokyo, Japan). Livers were embedded in Leica Optical Coherence Tomography (OCT) and immediately frozen at -80°C. 8 μm thick sections of livers were generated. Sections were stained in hematoxylin & eosin and 0.5% Oil red O (Sigma-Aldrich) according to the standard protocol.

Euthanasia: Put the animal in a clean container and slowly introduce carbon dioxide. As the concentration of carbon dioxide increases (7.5%-10%), the animal will slowly die without pain. Generally 10 minutes is enough to sacrifice the animal, but the animals euthanized by carbon dioxide asphyxiation method must be checked one by one for complete death. If undead animals are found, they will be given cervical dislocation.

Behavioral Assessment

The adhesive removal test was performed to assess sensorimotor function. Stick the tape (4 mm^2) on the palm surface of the two forepaws, then put the mice into a transparent glass beaker. Mice were allowed to remove the tape on their teeth for a maximum of two minutes. The latencies of remove each tape were recorded. The asymmetry score was calculated (latencies of the left forepaw/ total latencies of both forepaws). The rotarod test was used to test the animals' balance and neuromuscular coordination. Briefly, the mice were trained on the rotarod at 15 rpm for 15 min/day three days before stroke. After stroke, mice were performed on the rotarod with a speed from 4 rpm to 40 rpm within 5min, and recorded the time when the mice fell.

Statistical Analysis

As previously reported [15], the categorical variables were summarized as count and percentage, and continuous variables as mean ± Standard Error of Mean (SEM). Differences between subgroups were examined using Fisher's exact test or Pearson's chi-square test for categorical variables.

The Kaplan–Meier estimator was used to analysis of survival probability at various time points, and the log-rank test was used to examine the difference in survival curves of different groups. All data shows mean ± SEM. with a statistically significant difference defined as a value of $P<0.05$.

Results

Patient Demographics and Stroke Risk Factors

There were 1336 first-time ischemic stroke patients included in this study, with 916 patients were included in the final analysis. In addition, 152 patients were 30-55 years and 764 patients were 55 years or older as shown in Figure 1. Moreover, Table 1 includes the clinical characteristics of patients in this study. Among the young patient group, 152 patients (62 female and 90 male) had an average age of 45.3±4.2 compared to 764 older patients (412 female and 352 male) with an average age of 71.9±5.5. Young patients demonstrated lower rate comorbidities including hypertension (48.6% vs 70.9%, p<0.001, diabetes (17.1% vs 32.1%, p<0.001), chronic kidney diseases (3.9% vs 10.7%, p=0.044), congestive heart failure (3.9% vs 16%, p = 0.011), hypercoagulable state (1.3% vs 7.1%, p=0.003) and peripheral vascular disease (6.8% vs 15.4%, p=0.016). There was no statistically significant difference in terms of rheumatic diseases (3.9% vs 2.1%, p=0.190) Table 1.

Table 1: Demographics and clinical characteristics of patients in this study.

	Overall	30-55 age group	>55 age group	*p*
Number of patients (n)	916	152	764	
Sex(F/M)	474/442	62/90	412/352	0.003
BMI (Kg/m^2)	25.1±1.3	24.5±1.4	26.9±1.1	<0.001
Age at index in years	69.1±2.1	45.3±4.2	71.9±5.5	<0.001
Hypertension	608(66.4)	74(48.6)	542(70.9)	<0.001
Diabetes	272(29.7)	26(17.1)	246(32.1)	<0.001
Rheumatic diseases,	22(2.4)	6(3.9)	16(2.1)	0.190
Myocardial infarction,	114(12.4)	8(5.3)	106(13.7)	0.003
Chronic kidney disease	88(9.6)	6(3.9)	82(10.7)3	0.011
Congestive heart failure	128(13.9)	6(3.9)	121(16.0)	<0.001
Hypercoagulable state	56(6.1)	2(1.3)	54(7.1)	0.003
Peripheral vascular disease	128(13.9)	10(6.8)	118(15.4)	0.016
Chronic liver diseases	306(33.4)	48(31.6)	258(33.7)	0.476
Smoking status				
Never smoker	280(30.6)	42(27.6)	238(31.1)	<0.001
Former smoker	296(38.7)	11(14.)	274(35.9)	
Current smoker	166(18.1)	50(32.9)	116(15.1)	
Unknown	174(18.9)	39(25.0)	136(17.80)	

Mortality Occurrence within 5 Years in Stroke Patients

22 patients in young stroke patient group deceased during 5 years follow-up. The deceased patients complicated higher rate of chronic kidney diseases (36.4% vs 15%, *p*<0.001) and chronic liver injury (72.3% vs 24.6%, *p*<0.001) compared to others. Although the deceased patients showed higher rate of peripheral vascular disease, the difference was not statistically significant (18.8% vs 6.2%, *p*=0.053) Table 2. The Kaplan–Meier estimator analysis demonstrated the survival probability was significantly higher for the young patient group compared to old patients (log-rank test p<0.0001, Figure 2). the survival probability was found to be 98.7% (95% confidence interval CI 96.0–99.4), 93.4% (95% CI 90.8–96.2), and 85.5% (95% CI 85.7–89.8) at 1 year, 3 years and 5 years for young stroke patient group. the old stroke group had a lower survival probability of 93.7% (95% CI 92.1–94.5), 67.0% (95% CI 70.8–74.7), and 54.7% (95% CI 60.5–63.6) at 1 year, 3 years and 5 years, respectively (Figure 2). The cox hazard regression analysis performed to examine the factors associated with five-year mortality in young age group. Chronic liver disorders were found to be significantly associated with increased hazard of mortality in 30–55-year-old group (HR=3.32, 95% CI 2.12-5.63, p<0.001).

Ischemic Stroke Recurrence within Five Years of Index Stroke in Young Stroke Patients

In young stroke group, 130 patients had minimum of 5 years follow-up. Of these 130 patients, 24 had ischemic stroke recurrence during follow-up period. There was no statistically significant difference in terms of age, BMI, and gender. Moreover, the complicated factors including hypertension, Congestive heart failure, and chronic kidney disorder were not statistically significant in the young stroke patients with or without ischemic recurrence. Patients with ischemic stroke recurrence had higher proportion of complication with chronic liver disorder (33.3% vs 22.7%, p=0.272). In addition, patients with recurrence showed higher rate of current or former smoking status (p=0.012). Stroke recurrence rate among young stroke patient group was not statistically different from that of old stroke patients (p=0.632). The recurrence rate in young stroke patients were 2.1% (95% CI 1.5–3.8), 6.5% (95% CI 5.7–8.4), and 15% (95% CI 11.2–17.2) at 1 year, 3 years and 5 years, respectively. In comparison, the cumulative incidence of ischemic stroke recurrence in old group was 5.4% (95% CI 3.8–7.0), 8.9% (95% CI .4–9.3), and 8.0% (95% CI 24.8-28.2) at 1 year, 3 years and 5 years, respectively Figure 3.

Table 2: Patient characteristics in the 30–55 age groups stratified by five-year outcomes.

	All-Cause Mortality at 5 Years in the 30-55 Age Group			Ischemic Stroke Recurrence at 5 Years in the 30-55 Age Group		
	Alive	Deceased	*p*	Recurrence	No Recurrence	*p*
Number of patients (n)	130	22		24	106	
Sex(F/M)	54/76	13/9	0.125	14-Oct	44/62	0.989
BMI (Kg/m^2)	25.1±1.2	24.9±1.3	0.673	24.8±1.2	24.9±13.5	0.659
Age at index stroke in years	47.3±4.2	48.1±3.1	0.567	47.9±3.3	48.3±4.5	0.762
Hypertension	46(35.4)	10(45.5)	0.365	10(41.6)	48(45.2)	0.988
Diabetes	26(20.0)	8(36.4)	0.148	6(25)	34(32.1)	0.498
Patent foramen ovale	24(18.4)	2(9.1)	0.28	4(16.7)	22(23)	0.651
Rheumatic diseases	2(1.5)	0(0)	1	2(8.3)	2(1.8)	0.136
Myocardial infarction	11(8.4)	4(18.2)	0.157	2(8.3)	6(5.7)	0.623
Hypercoagulable state	4(3.1)2	2(9.1)	0.18	2(8.3)	8(7.5)	0.896
Peripheral vascular disease	8(6.2)	4(18.8)	0.053	2(8.3)	10(9.4)	0.866
Dyslipidemia	54(41.5)	10(45.5)	0.731	8(33.3)	38(35.8)	0.816
Chronic kidney disease	10(15)	8(36.4)	0	2(8.3)	6(6.5)	0.623
Chronic liver diseases	32(24.6)	16(72.3)	0.001	8(33.3)	24(22.7)	0.272
Congestive heart failure	11(8.5)	4(18.2)	0.157	8(33.3)	38(35.8)	0.816
Smoking status			0.062			0.053
Never smoker	26(20.0)	4(18.2)		2(8.3)	22(20.8)	
Former smoker	12(9.2)	2(9.1)		2(8.3)	16(12.3)	
Current smoker	62(47.6)	12(54.5)		12(50.0)	44(41.5)	
Unknown	30(23.1)	4(18.2)		8(33.3)	28(26.4)	

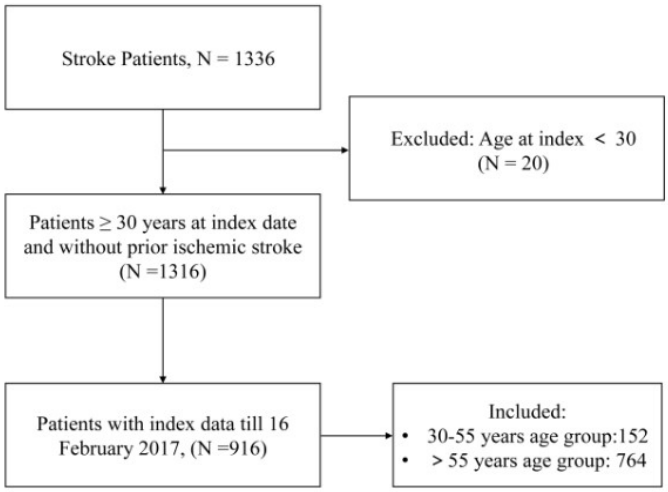
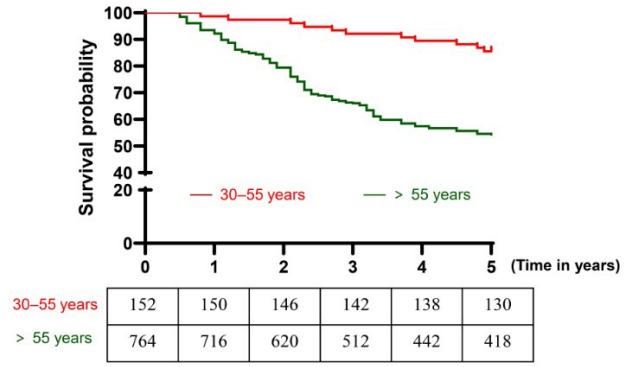


Figure 1: Inclusion and exclusion flowchart of patients in this study.



30–55 years	152	150	146	142	138	130
> 55 years	764	716	620	512	442	418

Figure 2: Comparison of survival probabilities between 30–55 age group and >55 age group using Kaplan-Meier estimator.

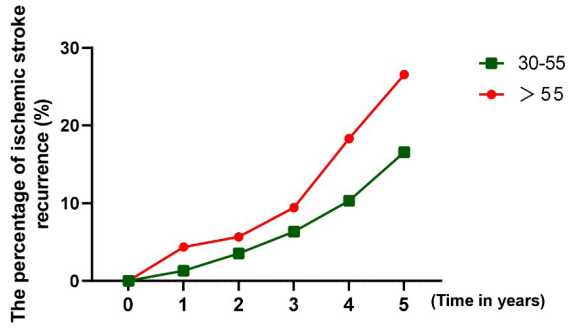


Figure 3: Comparison of the percentage of ischemic stroke recurrence between 30–55 age group and >55 age group using Kaplan-Meier estimator.

Liver Injure Aggravates Stroke in Mice

To further exam liver injure is associated with increased the risk of death in patients with ischemic stroke, we built a stroke mouse model and explored the effects of CCL4-induced liver injury on ischemic stroke. Oil red O and H&E staining of histological sections provided evidence of liver fat deposition in CCL4 treated mice (Figure 4A). Figure 4B and 4C shows that concentration levels of serum AST and ALT were increased after CCL4 treatment (Figure 4B and C). We further examined the effect of CCL4-induced liver injury on stroke. We observed a bigger the area of cerebral infarction in CCL4 treated mice (Figure 4D). In addition, we found CCL4 induced liver injury worsen sensorimotor deficits 14 days after stroke onset in the tape removal test (Figure 4F) and rotarod test (Figure 4G), the ladder walking test (Figure 4E) exhibited no statistical difference. These data indicate that liver injury could further aggravate stroke injury in mouse model although the ladder walking test with no statistical difference.

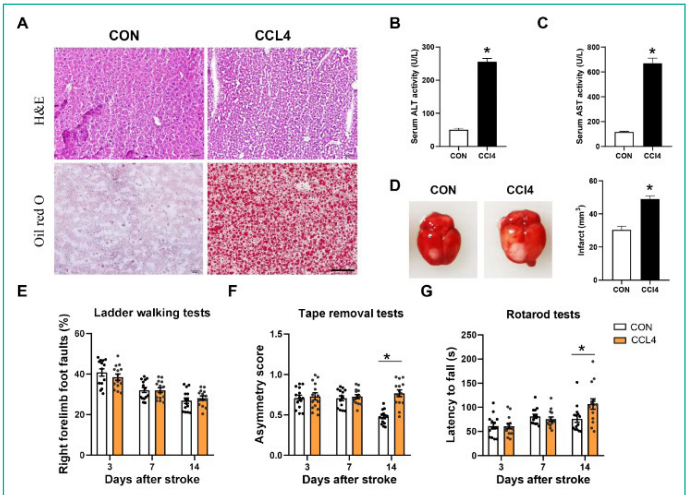


Figure 4: CCL4 induced liver injure did aggravated stroke in mice. (A) H&E (top) and oil O red (bottom) stain of mouse. Scale bar: 20 μm. n=6 mice per group. (B) Serum ALT and (C) AST level. (D) Representative images of cerebral infarction in CCL4 treated mice. (E-F) Sensorimotor functions were detected by (D) ladder walking tests, (E) tape removal tests, (F) rotarod tests. n=6 per group. Values represent mean ± SEM. **P*<0.05, significantly different from CON or CCL4 treated mice. P value was determined using two-tailed unpaired Student's t-test.

Discussion

In present study, for the first time, we evaluated long-term outcome and risk factors of ischemic stroke in young patients in rural Chinese populations. In our rural population, the five-year risk of mortality and recurrence in young ischemic stroke patients was 14.5% and 18.5%, respectively. Younger ischemic stroke patients were at the same risk of long-term ischemic stroke recurrence as the older ischemic stroke patients. Interestingly, we firstly reported that liver injury is an indispensable risk factor for the occurrence and prognosis of young ischemic stroke in China. Chronic liver disorders were found to be significantly associated with increased hazard of mortality in 30–55-year-old group. In addition, CCl4-induced liver injury could further aggravate stroke in mouse model. As previously reported that increased blood lipid concentration and viscosity in NAFLD patients is the main factor of cardiovascular and cerebrovascular diseases [14]. Therefore, chronic liver injury is an indispensable risk factor for the occurrence and prognosis of young ischemic stroke in China.

The mortality rates after ischemic stroke in young populations varies among studies. A review by Varona et al, reported the mortality rate increased cumulatively as years progressed from initial stoke in young patients [15,16]. The mortality rate was increased 4.9% in first year after stroke and reached up to 10-13% at 5 years. Chaudhary et al., [6] reported culminative modality rate of young rural Caucasian populations. This result was similar with our findings that culminative increasing of mortality rate which is reached 1.2% at first year and reached to 14.47% at 5 years. Consistent with previous studies, we also found higher mortality rate in elderly patients in present study. In addition, the recurrence rate of ischemic stroke was similar between two groups and is consistent with the results by Smajlovic et al., [17].

Identifying the factors and optimizing adequate long-term secondary prevention may reduce the risk of poor outcomes among younger ischemic stroke patients [7,18]. Studies have shown several risk factors related to ischemic stroke in young patients, including dyslipidemia, diabetes mellitus etc. unlike el-

der populations, rare etiologies were involved in young patients [5,19-21]. Anyaehie et al., reported chronic kidney disease were associated with increase mortality and reoccurrence in patients aged 18-55 [6,22]. In present study, we also found chronic kidney diseases were correlated to the mortality of young ischemic patients. in addition, liver injury also was found to be correlated with mortality rate of ischemic patients while there no significant difference in elder patients. What's more, mice with CCl4-induced liver also demonstrated higher rate of mortality compared to their littermates. This result demonstrated that clinician may raise attention optimize therapeutic strategy to prevent poor outcomes young patients with liver injury.

Several reasons support a tight link of liver injury with stroke. First, our study suggest that liver dysfunction may promote the progress of stroke [2,23]. Second, previous study has reported liver cirrhosis increased the risk of stroke in China [23, 24]. Liver diseases often cause abnormal hemostasis and coagulation, thus elevating the risk of stroke. In addition, recent reports suggested that liver injury patients may have a higher risk of atrial fibrillation and venous thromboembolism, especially liver cirrhosis [25-27]. Considering that hemorrhagic stroke is often lethal, the prophylactic strategy should be adopted in selective patients with liver cirrhosis [18,28]. The potential risk of stroke should be fully recognized in cirrhotic patients. However, which cirrhotic patients are at a risk of hemorrhagic stroke should be further identified. Although, we still don't know why liver injury patients have a higher risk of stroke. Next, we will further explore it in animal model.

There are several limitations in this study. Firstly, the sample size was relatively small, especially the proportion of young ischemic stroke patients were limited compared to entire cohort. Secondly, the health care management and changes of risk factors were not included in present study, a further longitudinal is warranted. Finally, we evaluated the effect of liver injury in young mice, but further studies are needed to investigate the impact of liver injury on ischemic stroke in generic mice.

Conclusion

In the rural population of China, younger ischemic stroke patients were low-risk of the older ischemic stroke patients. The five-year risk of mortality and recurrence in young ischemic stroke patients was 14.5% and 18.5%. Identifying the factors which is liver injury disease may aggravate the risk of younger ischemic stroke patients.

Author Statements

Author Contributions

Cunsheng Wei and Zhiqing Yang researched the data and wrote the manuscript. Xiaorong Yu, Yuan Chen and Tingting Yang analyzed the data. All authors reviewed the manuscript. Cunsheng Wei and Zhiqing Yang conceived the experiments and edited/reviewed the manuscript. Xuemei Chen is the guarantor of this work, had full access to all data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Informed Consent

Written informed consents were obtained from all the subjects recruited into our study.

Study Statement

The study is reported in accordance with ARRIVE guidelines (www.https://arriveguidelines.org).

Availability of Data and Materials

The datasets generated during and/or analysed during the current study are not publicly available due to confidentiality agreements but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was performed in accordance with the ethical standards laid down in the 2010 Declaration of Fujian. The study was approved by the National Ethical Committee of Nanjing medical University and Anhui Chest Hospital (NCT number: ACH20100130). All animal experiments were approved and conducted by an Institutional Animal Care and Use Committee (IACUC) at Nanjing Medical University (AP#2019-17-149) and the Laboratory Animal Management Committee of Jiangsu Province. In addition, all methods were carried out in accordance with relevant guidelines and regulations.

Consent for Publication

All the authors give their consent for the publication of this study.

Competing Interests

The authors declare that there are no conflicts of interest.

References

1. Boot E, Ekker MS, Putaala J, Kittner S, De Leeuw FE, Tuladhar AM. Ischaemic stroke in young adults: a global perspective. J Neurol Neurosurg Psychiatry. 2020; 91: 411-7.

2. Maaijwee NAMM, Rutten-Jacobs LCA, Schaapsmeerders P, van Dijk EJ, de Leeuw FE. Ischaemic stroke in young adults: risk factors and long-term consequences. Nat Rev Neurol. 2014; 10: 315-25.

3. Perera KS, de Sa Boasquevisque D, Rao-Melacini P, Taylor A, Cheng A, Hankey GJ, et al. Evaluating rates of recurrent ischemic stroke among young adults with embolic stroke of undetermined source: the young ESUS longitudinal cohort study. JAMA Neurol. 2022; 79: 450-8.

4. Adamson J, Beswick A, Ebrahim S. Is stroke the most common cause of disability? J Stroke Cerebrovasc Dis. 2004; 13: 171-7.

5. Putaala J, Curtze S, Hiltunen S, Tolppanen H, Kaste M, Tatlisumak T. Causes of death and predictors of 5-year mortality in young adults after first-ever ischemic stroke: the Helsinki Young Stroke Registry. Stroke. 2009; 40: 2698-703.

6. Chaudhary D, Anyaehie M, Demiraj F, Bavishi S, Shahjouei S, Li J, et al. Comparison of long-term outcomes and associated factors between younger and older rural ischemic stroke patients. J Clin Med. 2022; 11: 5.

7. Ferro JM, Massaro AR, Mas JL. Aetiological diagnosis of ischaemic stroke in young adults. Lancet Neurol. 2010; 9: 1085-96.

8. Waje-Andreassen U, Naess H, Thomassen L, Eide GE, Vedeler CA. Long-term mortality among young ischemic stroke patients in western Norway. Acta Neurol Scand. 2007; 116: 150-6.

9. Duan Y, Pan X, Luo J, Xiao X, Li J, Bestman PL, et al. Association of inflammatory cytokines with non-alcoholic fatty liver disease. Front Immunol. 2022; 13: 880298.

10. Xia SW, Wang ZM, Sun SM, Su Y, Li ZH, Shao JJ, et al. Endoplasmic reticulum stress and protein degradation in chronic liver disease. Pharmacol Res. 2020; 161: 105218.

11. Ullah R, Rauf N, Nabi G, Ullah H, Shen Y, Zhou YD, et al. Role of nutrition in the pathogenesis and prevention of non-alcoholic fatty liver disease: recent updates. Int J Biol Sci. 2019; 15: 265-76.

12. Xu W, Cui C, Cui C, Chen Z, Zhang H, Cui Q, et al. Hepatocellular Cystathionine γ lyase/hydrogen sulfide Attenuates NonAlcoholic Fatty Liver Disease by Activating farnesoid X receptor. Hepatology. 2022; 76: 1794-810.

13. He L, Guo ZN, Qu Y, Jin H. Hyponatremia is associated with post-thrombolysis hemorrhagic transformation and poor clinical outcome in ischemic stroke patients. Front Mol Neurosci. 2022; 15: 879863.

14. Kasper P, Martin A, Lang S, Kütting F, Goeser T, Demir M, et al. NAFLD and cardiovascular diseases: a clinical review. Clin Res Cardiol. 2021; 110: 921-37.

15. Varona JF. Long-term prognosis of ischemic stroke in young adults. Stroke Res Treat. 2010; 2011: 879817.

16. Kappelle LJ, Adams HP, Heffner ML, Torner JC, Gomez F, Biller J. Prognosis of young adults with ischemic stroke. A long-term follow-up study assessing recurrent vascular events and functional outcome in the Iowa Registry of Stroke in Young Adults. Stroke. 1994; 25: 1360-5.

17. Smajlović D. Strokes in young adults: epidemiology and prevention. Vasc Health Risk Manag. 2015; 11: 157-64.

18. Edwards JD, Kapral MK, Lindsay MP, Fang J, Swartz RH. Young stroke survivors with no early recurrence at high long-term risk of adverse outcomes. J Am Heart Assoc. 2019; 8 :e010370.

19. Waje-Andreassen U, Thomassen L, Jusufovic M, Power KN, Eide GE, Vedeler CA, et al. Ischaemic stroke at a young age is a serious event--final results of a population-based long-term follow-up in Western Norway. Eur J Neurol. 2013; 20: 818-23.

20. Putaala J, Yesilot N, Waje-Andreassen U, Pitkäniemi J, Vassilopoulou S, Nardi K, et al. Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke: the 15 cities young stroke study. Stroke. 2012; 43: 2624-30.

21. Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2019; 69: 2672-82.

22. Zhou J, Zhou F, Wang W, Zhang XJ, Ji YX, Zhang P, et al. Epidemiological features of NAFLD from 1999 to 2018 in China. Hepatology. 2020; 71: 1851-64.

23. Zheng K, Yoshida EM, Tacke F, Li Y, Guo X, Qi X. Risk of stroke in liver cirrhosis: A systematic review and meta-analysis. J Clin Gastroenterol. 2020; 54: 96-105.

24. Ruban A, Daya N, Schneider ALC, Gottesman R, Selvin E, Coresh J, et al. Liver enzymes and risk of stroke: the atherosclerosis risk in communities (ARIC) study. J Stroke. 2020; 22: 357-68.

25. Yoon JH, Jun CH, Kim JH, Yoon EL, Kim BS, Song JE, et al. Changing trends in liver cirrhosis etiology and severity in Korea: the increasing impact of alcohol. J Korean Med Sci. 2021; 36: e145.

26. Idilman R, Aydogan M, Oruncu MB, Kartal A, Elhan AH, Ellik Z, et al. Natural history of cirrhosis: changing trends in etiology over the years. Dig Dis. 2021; 39: 358-65.

27. Zhang X, Qi X, Yoshida EM, Méndez-Sánchez N, Hou F, Deng H, et al. Ischemic stroke in liver cirrhosis: epidemiology, risk factors, and in-hospital outcomes. Eur J Gastroenterol Hepatol. 2018; 30: 233-40.

28. Choi SJ, Kim NY, Kim JY, An YS, Kim YW. Changes in the brain metabolism associated with central post-stroke pain in hemorrhagic pontine stroke: an (18)F-FDG-PET study of the brain. Brain Sci. 2022; 12: 7.