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ORIGINAL RESEARCH

Correlation Between Liver Function and Risk of Post-Stroke Epilepsy

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Background: Abnormal liver function has often been associated with epilepsy, but there is a lack of large-scale clinical evidence to support the potential correlation between liver function and post-stroke epilepsy.

Objective: We aimed to explore a real correlation between liver function and secondary epilepsy after stroke.

Methods: From the Dryad database, we retrospectively identified 21,459 patients who had experienced acute ischemic stroke. Multivariate regression was used to clarify the correlation between liver function and secondary epilepsy post-stroke via cross-sectional analysis.

Results: Our multivariate nonlinear analysis, adjusted for age and gender, suggested that a significant correlation exists between liver function (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and the risk of secondary epilepsy post-stroke. Saturation effect analysis showed that a fold point (K) of blood AST level of 39.3 U/L was related to an epilepsy event. An increased AST level was related to a higher rate of epilepsy (1.2 [1.2–1.3], <0.001) among patients with AST levels of less than 39.3 U/L. Significance was weaker among patients with AST levels of more than 39.3 U/L. As for ALT, the fold point of blood ALT level revealed an association with epilepsy at 23.3 U/L. Similarly, elevated AST levels were related to a significantly higher risk of secondary epilepsy post-stroke (1.2 [1.1–1.2], <0.001) when they were less than 23.3 U/L. The significant correlation was weaker when blood AST levels were higher than 23.3 U/L. Importantly, ROC curve analysis displayed a high AUC value (0.8101) of blood AST in terms of detecting epilepsy risk, with a sensitivity of 0.7254 and specificity of 0.7997, respectively.

Conclusion: Our study provided potential evidence for the correlation between liver function and secondary epilepsy after acute stroke, indicating that early protection and management of liver dysfunction among post-stroke patients might be beneficial for reducing epileptic seizures. More studies with a high level of evidence are needed to confirm this finding, however.

Keywords: secondary epilepsy, hepatic insufficiency, ischemic stroke, diagnostic value, prognosis

Introduction

Secondary epilepsy post-stroke refers to a common complication of cerebral vascular diseases, including cerebral aneurysm, cerebral hemorrhage, cerebral infarction and cerebral vascular malformation,[1,2] which is characterized by an abnormal excessive discharge of brain neurons, resulting in short-term central nervous system dysfunction.[3,4] Evidence suggested that epileptic seizures post-stroke might significantly worsen the primary disease, prolong hospitalization time, and even increase the risk of mortality among stroke patients.[5,6] Further exploration of the risk factors for secondary epilepsy post-stroke is greatly needed.

In fact, the liver is one of the organs most closely related to epilepsy,[7] which is the center for the synthesis, transformation, and excretion of metabolic substances in the human body.[8] Abnormal liver function can lead to the accumulation of metabolites such as blood ammonia and result in neurological abnormalities.[9,10] Furthermore, the liver is still the main organ for detoxification in the human body, and excessively high levels of toxic substances in the body can cause hepatic injury, disrupting the activity of the brain's nervous system to generate epileptic waves.[11,12] For example, excessive use of anti-epileptic drugs can easily lead to the accumulation of drug toxicity, thereby increasing the burden on the liver and resulting in an increased frequency of epileptic seizures.[9–12] Previous studies have also confirmed that,

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for epilepsy patients with liver diseases, more attention should be paid to drug selection and dosage adjustment during the treatment process to reduce damage to the liver.[13] Alcoholic liver disease might increase the risk of epileptic seizures, as alcohol poisoning can cause an imbalance of neurotransmitters in the brain.[13] Serious liver injuries such as hepatic encephalopathy can lead to the accumulation of metabolic products in the body and affect brain function and stability, ultimately triggering epilepsy.[14] However, it is still unclear whether circulating blood transaminase levels, as the most important liver function indicators in clinical practice, can be used as a risk factor for post-stroke epileptic seizures.

In view of this, we conducted a retrospective analysis of a previous observational study involving 21,459 patients who had suffered an acute ischemic stroke in Chongqing Emergency Center between June 2017 and June 2022. We aimed to explore the potential correlation between liver function (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and the risk of secondary epilepsy post-stroke within one year.

Methods and Materials

Study Samples

The Dryad database is open to the world and can be downloaded free for secondary analysis. From this database we identified 21,459 patients who had experienced an acute ischemic stroke and were admitted to the Chongqing Emergency Center between June 2017 and June 2022.[15] This database was designed to explore predictive models of secondary epilepsy within one year (datadryad.org/stash/dataset/doi:10.5061/dryad.w0vt4b92c). We have already described the design of the previousstudy.[15,16] Patients diagnosed with acute ischemic stroke requesting admission were included in our analysis. Our inclusion and exclusion criteria have been described previously.[15,16] In this study, we mainly focused on the following clinical characteristics: age, sex, National Institutes of Health Stroke Scale (NIHSS) score, secondary epilepsy, complications, and comorbidities.[15,16] Comorbidities mainly included coronary heart disease, hypertension, diabetes and atrial fibrillation. Complications mainly included cerebral hernia and hydrocephalus. Laboratory indicators included routine blood tests, AST, ALT, creatinine and urea nitrogen, international normalized ratio (INR), activated partial throm-boplastin time (APTT), and prothrombin time (PT). All laboratory tests have been described previously.[16,17]

Patients' confidential information was hidden. No additional ethical approval was required, according to the Helsinki Declaration and Ethical Review of Life Science and Medical Research Involving Human Subjects, dated February 18, 2023, China.

Secondary Epilepsy Post-Stroke

In order to focus on the research purpose of this study, the occurrence of post-apoplectic epilepsy was defined as secondary epilepsy after an acute ischemic stroke. The diagnosis of secondary epilepsy post-stroke has already been described in the Dryad database.[15,16]

Statistical Analysis

All continuous data were described as mean values (standard deviations), and categorical data were described as N (%). A multivariate logistic regression model was utilized to investigate the association between liver function (AST and ALT) and risk of secondary epilepsy post-stroke. Odds ratios (ORs) and confidence intervals (CIs) were used in the regression analysis. For epilepsy risk, the model was adjusted for the following confounding factors: age, gender, NIHSS score, diabetes, hypertension, atrial fibrillation, coronary heart disease, cerebral hernia, hydrocephalus, hyperuricemia, hyperlipidaemia, hypoproteinemia, serum creatinine, and urea nitrogen. For sensitivity analysis, the logistic regression was further adjusted for fatty liver on the basis of the above model. Moreover, adjusted analysis of the smooth curve was performed to assess the nonlinear relationship between liver function (AST and ALT) and risk of secondary epilepsy post-stroke by adjusting these same confounding factors. Additionally, a saturation-effect analysis was used to investigate whether the association between liver function (AST and ALT) and epilepsy risk differed in the real world. Empower (version 4.1) was used for all analyses, and a P-value of <0.05 defined statistical significance.

Table 1 Clinical Characteristics (N=21,459)

Clinical Variables	Mean Value (Standard Deviation) (N, %)
Age (years)	66.4 (12.4)
Gender (male)	10843 (50.5)
Postapoplectic epilepsy	936 (4.4%)
National Institutes of Health Stroke Scale (NIHSS) score	8.0 (2.9)
Complications	
Cerebral hernia	181 (0.8%)
Hydrocephalus	281 (1.3%)
Comorbidities	
Diabetes	7322 (34.1%)
Hypertension	14751 (68.7%)
Atrial fibrillation	2043 (9.5%)
Coronary heart disease	9672 (45.1%)
Laboratory indicators	
C-reactive protein (mg/L)	17.0 (22.7)
Creatinine (μmol/L)	84.9 (51.2)
Urea nitrogen (mmol/L)	6.4 (1.4)
Aspartate aminotransferase (U/L)	26.6 (13.4)
Alanine aminotransferase (U/L)	24.4 (10.2)
Prothrombin time (PT, seconds)	13.8 (1.1)
Activated partial thromboplastin time (APTT, seconds)	35.7 (2.3)
International normalized ratio (INR, ratio)	1.1 (0.1)

Abbreviation: PSE, post-stroke epilepsy.

Results

Characteristics of Acute Ischemic Stroke Patients

The characteristics of 21,459 patients who had experienced an acute ischemic stroke are summarized in Table 1. Among these patients, 936 (4.4%) individuals had experienced epilepsy post-stroke within one year, and the mean value of NIHSS score was 8.0. Other characteristics, such as complications, comorbidities and laboratory indicators, were also statistically analyzed (see Table 1). Importantly, multivariate nonlinear (smooth curve) analysis with adjusted age and gender revealed a significant association between blood AST (Figure 1A) and ALT (Figure 1B) levels and risk of secondary epilepsy post-stroke, respectively.

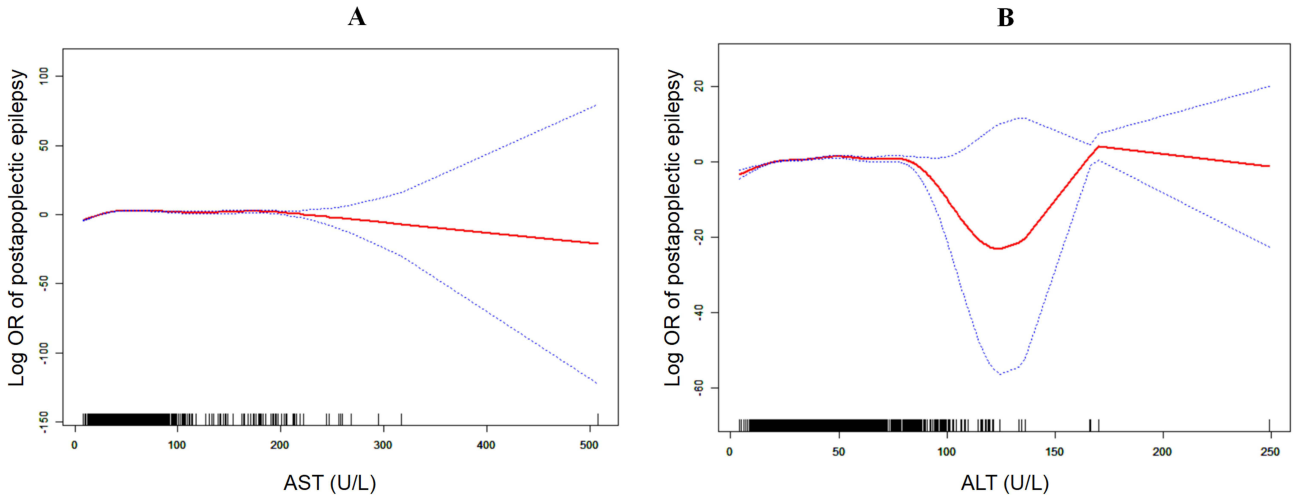

Figure 1 (**A** and **B**) Nonlinear relationship, adjusted for age and gender, between liver function and secondary epilepsy post-stroke.

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Table 2 Association Between Liver Function and Postapoplectic Epilepsy

Exposure Variables	Epilepsy Risk	
	Adjusted Model 1	Adjusted Model 2
AST (U/L)		
Q1	1.0 (reference)	1.0 (reference)
Q2	1.6 (1.1–2.3), 0.018	3.9 (2.4–6.1), <0.001
Q3	2.8 (2.0–3.9), <0.001	7.2 (4.6–11.2), <0.001
Q4	18.5 (13.7–25.0), <0.001	58.2 (38.5–87.9), <0.001
AST for 1 U/L	1.0 (1.0–1.0), <0.001	1.0 (1.0–1.0), <0.001
ALT (U/L)		
Q1	1.0 (reference)	1.0 (reference)
Q2	2.1 (1.6–2.7), <0.001	4.4 (3.2–6.0), <0.001
Q3	2.9 (2.3–3.6), <0.001	6.4 (4.7–8.7), <0.001
Q4	3.3 (2.6–4.2), <0.001	7.9 (5.8–10.7), <0.001
AST for 1 U/L	1.0 (1.0–1.0), <0.001	1.0 (1.0–1.0), <0.001

Notes: Model 1: Adjusted for age and gender. Model 2: Adjusted for age, gender, NIHSS score, diabetes, hypertension, atrial fibrillation, coronary heart disease, cerebral hernia, hydrocephalus, hyperuricemia, hyperlipidaemia, hypoproteinemia, serum creatinine, and urea nitrogen.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIHSS, National Institutes of Health Stroke Scale.

Multivariate Analysis of Secondary Epilepsy Post-Stroke

To further confirm the influence of liver function (AST and ALT) on secondary epilepsy after acute stroke, correlation analysis using multivariate logistic regression models was performed. Our multivariate logistic models, adjusted for age and gender, showed that elevated AST (1.6 [1.1–2.3], 0.018) and ALT (2.1 [1.6–2.7]), <0.001] levels at Q2 had a significant association with a higher epilepsy risk using Q1 as the reference, respectively (adjusted model 1). After NIHSS score, diabetes, hypertension, atrial fibrillation, coronary heart disease, cerebral hernia, hydrocephalus, hyperuricemia, hyperlipidaemia, hypoproteinemia, serum creatinine, and urea nitrogen were further controlled for, the associations between elevated AST (3.9 [2.4–6.1], <0.001) and ALT (4.4 [3.2–6.0], <0.001) levels at Q2 and epilepsy risk were relatively stronger (adjusted model 2). As expected, elevated AST levels at Q3 (7.2 [4.6–11.2], <0.001) and Q4 (58.2 [38.5–87.9], <0.001) were separately associated with a higher epilepsy risk, as well as elevated AST levels at Q3 and Q4 (Table 2).

Sensitivity Analysis

To further clarify the impact of fatty liver on this independent association, a sensitivity analysis was conducted by adding "fatty liver" as the covariate into multivariate logistic regression models, as shown in Table 3. Our results suggested that elevated AST and ALT levels at Q2, Q3, and Q4 still demonstrated a significant association withhigher epilepsy risk respectively, and the relationship strength of these adjusted models remained largely unchanged.

Saturation-Effect Analysis

The results of saturation-effect analysis of the association between liver function and risk of secondary epilepsy post-stroke are shown in Table 4. The fold point (K) of blood AST level for the relationship was 39.3 U/L. A high AST level was associated with a significantly increased rate of epilepsy (1.2 [1.2–1.3], <0.001) among patients with blood AST levels less than 39.3 U/L. However, the significant relationship become weak among those patients with blood AST levels more than 39.3 U/L. The statistical difference between the two subgroups was significant according to the log likelihood ratio test (P <0.001). As for ALT, the fold point of blood ALT level for the association was 23.3 U/L. The elevated AST levels were related to a significantly higher risk of secondary epilepsy post-stroke [(.2 [1.1–1.2], <0.001)

Table 3 Sensitivity Analysis

Exposure Variables	Epilepsy Risk	
	Adjusted Model 1	**Adjusted Model 2**
AST (U/L)		
Q1	1.0 (reference)	1.0 (reference)
Q2	1.6 (1.1–2.3), 0.018	3.8 (2.4–6.1), <0.001
Q3	2.8 (2.0–3.9), <0.001	7.2 (4.6–11.2), <0.001
Q4	18.5 (13.7–24.9), <0.001	58.3 (38.6–88.0), <0.001
AST for 1 U/L	1.0 (1.0–1.0), <0.001	1.0 (1.0–1.0), <0.001
ALT (U/L)		
Q1	1.0 (reference)	1.0 (reference)
Q2	2.1 (1.7–2.7), <0.001	4.4 (3.2–6.0), <0.001
Q3	3.0 (2.4–3.8), <0.001	6.4 (4.7–8.7), <0.001
Q4	3.4 (2.7–4.3), <0.001	7.9 (5.8–10.7), <0.001
AST for 1 U/L	1.0 (1.0–1.0), <0.001	1.0 (1.0–1.0), <0.001

Notes: Model 1: Adjusted for age, gender and fatty liver. Model 2: Adjusted for age, gender, NIHSS score, diabetes, hypertension, atrial fibrillation, coronary heart disease, cerebral hernia, hydrocephalus, hyperuricemia, hyperlipidaemia, hypoproteinemia, serum creatinine, urea nitrogen, and fatty liver.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIHSS, National Institutes of Health Stroke Scale.

Table 4 Saturation-Effect Analysis of the Association Between Liver Function and Postapoplectic Epilepsy

Exposure Variables	Epilepsy Risk	
	Adjusted Model	**Log Likelihood Ratio Test**
Fold point (K) for AST		
<K (39.3 U/L)	1.2 (1.2–1.3), <0.001	<0.001
>K (39.3 U/L)	1.0 (1.0–1.0), <0.001	
Fold point (K) for ALT		
<K (23.3 U/L)	1.2 (1.1–1.2), <0.001	<0.001
>K (23.3 U/L)	1.0 (1.0–1.0), 0.442	

Notes: Adjusted Model: Adjusted for age, gender, NIHSS score, diabetes, hypertension, atrial fibrillation, coronary heart disease, cerebral hernia, hydrocephalus, hyperuricemia, hyperlipidaemia, hypoproteinemia, serum creatinine and urea nitrogen.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIHSS, National Institutes of Health Stroke Scale.

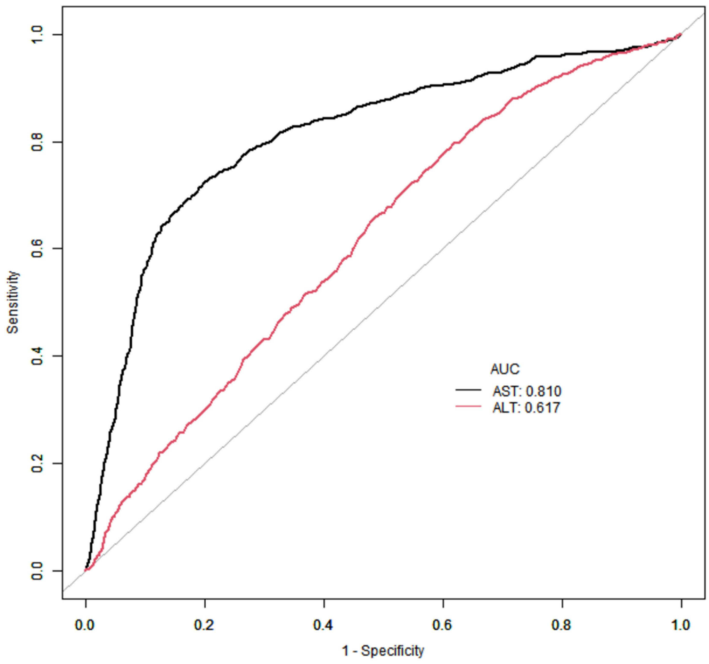
when blood AST levels were less than 23.3 U/L. Similarly, the significant association was weaker after blood AST levels were more than 23.3 U/L. The log likelihood ratio test for the two subgroups was significant (P <0.001).

Diagnostic Value of Detecting Secondary Epilepsy Post-Stroke

As shown in Figure 2, ROC curve analysis showed a high AUC value (0.8101) of blood AST on detecting epilepsy risk, with a sensitivity of 0.7254 and specificity of 0.7997, respectively. As for blood ALT, the indicator had a relatively lower AUC value (0.6165), with a sensitivity of 0.7981 and specificity of 0.3823, respectively. These results indicated the significant value of liver function on predicting post-stroke epilepsy.

Discussion

The present study was the first to provide evidence demonstrating a strong correlation between liver function and secondary epilepsy risk after acute ischemic stroke from a large-sample cohort. Our results suggested that abnormal liver function was positively associated with a higher risk of experiencing an epilepsy event. Furthermore, we observed that



ROC analysis for continuous predictor

Test	1	0	ROC area(AUC)	95%CI low	95%CI upp	Best threshold	Specificity	Sensitivity
AST	936	20523	0.8101	0.7947	0.8255	28.4500	0.7997	0.7254
ALT	936	20523	0.6165	0.5993	0.6337	20.6500	0.3823	0.7981

Figure 2 ROC analysis of the diagnostic value of liver function to detect secondary epilepsy post-stroke.

blood AST demonstrated valuable ability (AUC value = 0.8101) to predict epilepsy risk, with high sensitivity and specificity.

Previous studies have shown that an epilepsy event is the second most common neurological disorder, placing a heavy medical burden on approximately 50 million people worldwide.[17–19] Secondary epilepsy can be caused by ischemic or hemorrhagic stroke, intracranial tumor, acute vascular diseases, and other intracranial disorders.[20] As a main type of epilepsy, evidence has suggested that post-stroke epilepsy can further lead to a decline in cognitive function and deteriorating life skills, and present a high mortality risk.[21,22] Epidemiological investigation showed that patients with epilepsy might have an eight times higher risk of experiencing, other brain disorders including dementia and mental disorders, compared with the general population.[23,24] Identifying the independent risk factors linked to epilepsy could be helpful for establishing valuable clinical interventions to alleviate the burden of craniocerebral diseases, thereby improving the prognosis of patients experiencing an acute stroke.

In fact, the mechanism behind hepatic dysfunction following an epilepsy event has been explored. For instance, growing evidence has confirmed that metabolic abnormalities and inflammation caused by abnormal liver function could change neural circuits, ultimately resulting in recurrent or prolonged epilepsy.[25,26] A recent study was based on the clinical diagnostic data of 426,527 participants in the UK Biobank, of whom 3251 were diagnosed with epilepsy at baseline.[27] Here, mediation analysis was performed to investigate potential mechanisms among molecular markers, epilepsy and brain diseases, and results demonstrated that a significant effect of gamma-glutamyltransferase and high-density lipoprotein on liver dysfunction and abnormal lipid metabolism was linked to epileptic seizures.[27] Therefore, bearing in mind that epilepsy patients often take long-term anti-epileptic drugs, our findings suggested that preventing anti-epileptic drug-related liver injury and dyslipidemia was necessary to reduce the occurrence of epilepsy events.

There were several strong points to this study. This analysis was a pioneering exploration of the association between liver function (ALT and AST) and secondary epilepsy within one year after an acute ischemic stroke. It was also an observational study based on a large-scale population (N=21,459) to create a model for predicting epilepsy risk. We

also need to acknowledge several shortcomings. First, the data in the Dryad database was obtained primarily from a Chinese population, making it possible that the results can not be widely extrapolated to other populations. Second, we only studied the existence of secondary epilepsy and did not further explore different subtypes of stroke complication. Analyzing different subtypes of epilepsy might provide a more detailed understanding. Third, this was a retrospective study, and we cannot use Cox regression to clarify the causal relationship between liver function (ALT and AST) and secondary epilepsy due to the lack of follow-up of these patients. Finally, because of the difficulty in obtaining complete data on accompanying brain diseases, brain imaging examinations, epilepsy events, and other important information in other cohorts, our findings lack the solid support provided by the validation of other stroke-related populations. Stronger evidence is necessary to validate our conclusions in future cohorts, further confirming the association between liver function and epilepsy events among patients who have experienced acute ischemic stroke.

Conclusion

In conclusion, our study identifed an obvious correlation between liver function and risk of secondary epilepsy after acute stroke. Underlying mechanisms for the association might be related to abnormal metabolism and immune inflammation. This study emphasized the necessity of early diagnosis and treatment of hepatic dysfunction for reducing epilepsy risk, providing new insights to improve prognosis for patients post-acute ischemic stroke.

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Disclosure

The authors report no conflicts of interest in this work.

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