International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Association of Butyryl Cholinesterase and Recurrent Ischemic Stroke: A Cross-Sectional Study

Ruomeng Chen[1,2], Kun Zhang[1,2], Hui Liu[1,2], Lijuan Liu[1,2], Hui Li[3], Yan Yan[1,2], Zhou Zhou[1,2], Chaoyue Meng[1,2], Xuelin Wang[4], Haoran Wu[4], Ruihan Miao[4], Rui Wang[1,2], Xiaoyun Liu[1,2,4,5]

[1]Department of Neurology, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei, People's Republic of China; [2]Department of Neurology, Hebei Hospital of Xuanwu Hospital Capital Medical University, Shijiazhuang, Hebei, People's Republic of China; [3]Department of Neurology, Hengshui People's Hospital, Hengshui, Hebei, People's Republic of China; [4]Department of Neurology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, People's Republic of China; [5]Neuroscience Research Center, Medicine and Health Institute, Hebei Medical University, Shijiazhuang, Hebei, People's Republic of China

Correspondence: Xiaoyun Liu, Department of Neurology, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei, People's Republic of China, Email 57404217@hebmu.edu.cn

Objective: Exploring novel relevant factors associated with recurrent ischemic stroke.

Methods: This is a retrospective study, patients were divided into first-ever ischemic stroke group and recurrent ischemic stroke groups. We conducted a comparative analysis of baseline data between the two groups. Multifactorial logistic regression analysis was performed to identify factors associated with recurrent ischemic stroke. Grouped according to butyryl cholinesterase levels, to elucidate the relationship between butyryl cholinesterase levels and stroke recurrence.

Results: A total of 2029 patients were included, with 1174 in the first-ever ischemic stroke group and 855 in the recurrent ischemic stroke group. Age, hypertension, diabetes, alanine aminotransferase, and lipoprotein(a) were identified as risk factors for recurrent ischemic stroke (ALL $p<0.05$). Erythrocyte count, butyryl cholinesterase, low-density lipoprotein, and non-atherosclerotic type of large arteries were found to be negative associated with recurrent ischemic stroke (ALL $p<0.05$). Subgroup analyses indicated that butyryl cholinesterase levels were significantly negatively associated with recurrent ischemic stroke in males (OR=0.814, $p<0.001$, 95% CI: 0.761 ~ 0.871), especially under 60 years (OR=0.781, $p<0.001$, 95% CI: 0.708 ~ 0.862). After adjusting for multifactorial regression analyses, the recurrent rate in the lowest quartile of butyryl cholinesterase levels was 2.281 times that of the highest quartile (OR=2.281, $p<0.05$, 95% CI: 1.318 ~ 3.948).

Conclusion: Age, hypertension, diabetes, alanine aminotransferase, and lipoprotein(a) are independent risk factors for the recurrence of ischemic stroke. The inverse association between butyryl cholinesterase levels and stroke recurrence suggests butyryl cholinesterase may serve as a potential target for therapeutic intervention to improve the prognosis of ischemic stroke.

Keywords: recurrent ischemic stroke, butyryl cholinesterase, cross-sectional study, Lipoprotein a, cerebral infarction

Introduction

Ischemic stroke is characterized by ischemic necrosis or softening of localized brain tissue caused by ischemia and hypoxia as a result of impaired blood circulation in the brain. It is notable for its high rate of disability, recurrence, and mortality.[1] Globally, stroke ranks as the fourth most common cause of disability and the second leading cause of death.[2] Recurrent ischemic stroke is defined as any infarctive event occurring 21 days after the initial ischemic stroke, lasting for more than 24 hours.[3,4] Recurrent ischemic strokes tend to be more severe and have a more detrimental impact on patients and their families, often resulting in a poorer prognosis compared to the initial stroke. In China, the recurrence rate within one year following an ischemic stroke is 17.7%.[5] Risk factors for ischemic stroke are classified into irreversible and reversible categories. Reversible risk factors include hypertension, diabetes (DM), smoking, and hyperlipidemia, etc.[6] Despite active management of these reversible risk factors, the recurrence rate of ischemic stroke remains high. This

Received: 3 December 2024
Accepted: 19 March 2025
Published: 26 March 2025

impels us to continuously explore new factors associated with the recurrence of ischemic stroke. After preliminary analysis, we have discovered a noteworthy new clue-butyrylcholinesterase (BChE) is associated with recurrent ischemic stroke. Cholinesterases include acetylcholinesterase (AChE) and BChE. Among them, BChE is mainly present in serum.[7] Previous studies have shown that it is related to a variety of neurological disease states.[8–10] However, the relationship between it and cerebral infarction, especially recurrent cerebral infarction, has not been fully and thoroughly studied. This study will focus on analyzing the connection between BChE and recurrent ischemic stroke, with the hope of providing new ideas and evidence for the prevention and management of ischemic stroke. Therefore, the present study aims to analyze these risk factors to identify novel factors that may be associated with the recurrence of ischemic stroke, with a particular focus on the relationship between BChE and recurrent ischemic stroke. This will provide a foundation for improved prevention and management strategies.

Materials and Methods

Study Population

This is a cross-sectional study. Patients treated in the Department of Neurology of the Second Hospital of Hebei Medical University in northern China from January 2019 to June 2023. Inclusion criteria: Patients who met the diagnostic criteria for acute ischemic stroke according to the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2018.[11] Presence of acute focal neurological deficit symptoms, imaging evidence of cerebral infarction shown on diffusion weighted imaging (DWI) of cranial magnetic resonance imaging (MRI) or computed tomography (CT). These patients were categorized into two groups: the first-ever cerebral infarction group and the recurrent ischemic stroke group, based on the presence or absence of a prior history of cerebral infarction. Recurrent ischemic stroke was defined as new neurological deficits lasting more than 24 hours, occurring at least 21 days after the onset of the initial ischemic stroke.[3,4] Patients with insufficient information were excluded. For patients with multiple test data results, the first test result after hospitalization was selected.

The authors declare that all the data that support the findings of this study are available from the corresponding author upon reasonable request. The demographic data of the patients were collected, including age, gender, duration of hospitalization, whether they were admitted to the intensive care unit (ICU) or not, and history of hypertension, DM, atrial fibrillation (AF), and other relevant medical conditions. Laboratory tests conducted within 24 hours of admission were collected, including blood counts, lipid profiles, liver and renal functions, blood glucose levels, electrolyte levels, and homocysteine levels. The National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS) were used to assess stroke severity and outcomes. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification was used to categorize the etiology of cerebral infarction. During data analysis, exclude patients with the missing data.

The study was approved by the Ethics Committee (2023-R082). Informed consent was waived due to the retrospective nature of the study.

Statistical Analysis

Demographic characteristics and laboratory results were compared between the first-ever cerebral infarction group and the recurrent ischemic stroke group using Pearson's chi-square test or Fisher's exact test for categorical variables and the *t*-test or nonparametric test for continuous variables. Multifactorial logistic regression analysis was performed to identify independent factors associated with recurrent ischemic stroke. Only variables with $p<0.05$ in the univariate analysis were included in the multifactorial regression analysis and their *p* value are as presented in the Table 1. To prevent bias, we did not include the medication background in the multivariate analysis, even though there were statistically significant differences in their univariate analyses. A *p* value of <0.05 was considered statistically significant. BChE levels were normalized by dividing the raw values by 1000 for statistical analysis. To explore the relationship between BChE and recurrent ischemic stroke, subgroup analysis was conducted according to age and gender to explore the relationship between BChE and recurrent ischemic stroke in different populations. All statistical analyses were performed using SPSS version 26.0.

Table 1 Univariate Analysis of Laboratory Test Related to Recurrent Ischemic Stroke

	First-ever Ischemic Stroke (n=1174)	Recurrent Ischemic Stroke (n=855)	*p* value
White blood cell count (10^9/L)	6.39 (5.40–7.69)	6.32 (5.24–7.48)	0.22
Neutrophil count (10^9/L)	3.99 (3.13–5.13)	3.97 (3.08–5.09)	0.358
Lymphocyte count (10^9/L)	1.65 (1.30–2.03)	1.6 (1.26–2.00)	0.131
Monocyte count (10^9/L)	0.44 (0.35–0.57)	0.44 (0.36–0.56)	0.855
Eosinophil (10^9/L)	0.10 (0.06–0.17)	0.10 (0.06–0.18)	0.423
Basophil (10^9/L)	0.03 (0–0.04)	0.03 (0.01–0.04)	0.328
Erythrocyte count (10^{12}/L)	4.54 (4.22–4.86)	4.42 (4.06–4.74)	<0.001
Hemoglobin (g/L)	140 (130–150)	136 (127–146)	<0.001
Hematocrit (%)	41.6 (39.0–44.4)	40.7 (37.5–43.4)	<0.001
Mean erythrocyte volume (fl)	91.6 (88.8–94.7)	92.0 (89.1–95.0)	0.099
Platelet count (10^9/L)	219 (183–262)	214 (179–256)	0.076
Mean platelet volume (fl)	8.65 (8.00–9.61)	8.70 (7.99–9.58)	0.841
CRP (mg/L)	2.1 (1.1–5)	2.3 (1.1–6.6)	0.397
Myoglobin (ng/mL)	54 (43–68)	57 (45–75)	<0.001
Creatine kinase (U/L)	71.00 (51.00–102.25)	70.00 (49.00–102.00)	0.391
Creatine kinase isoenzyme (U/L)	15 (12–19)	15 (12–19)	0.195
Lactate dehydrogenase (U/L)	176 (154–199)	176 (154–199)	0.817
Alpha hydroxybutyric acid (U/L)	133 (117–152.25)	133 (116–153)	0.7
Total bilirubin (umol/L)	11.1 (8.0–14.8)	10.3 (7.6–14.2)	0.007
Direct bilirubin (umol/L)	4.2 (3.12–5.5)	4.02 (0.41–49.5)	0.199
Indirect bilirubin (umol/L)	6.79 (4.80–9.50)	6.29 (4.40–9.00)	<0.001
Total protein (g/L)	66.2 (62.9–70.0)	65.5 (62.0–69.6)	0.01
Albumin (g/L)	41.6 (39.1–44.0)	40.8 (38.2–43.3)	<0.001
Globulin (g/L)	24.6 (22.2–27.5)	24.9 (22.5–27.6)	0.241
Albumin/globulin	1.68 (1.48–1.90)	1.63 (1.43–1.84)	<0.001
ALT (U/L)	17.00 (12.48–23.90)	18.00 (12.80–26.80)	0.034
AST (U/L)	17.4 (14.7–21.7)	18.0 (14.5–22.9)	0.146
ALP (U/L)	77 (64–92)	76 (63–92)	0.466
GGT (U/L)	23 (16–33)	22 (16–35)	0.947
BChE (U/L)	8.19 (7.16–9.27)	7.68 (6.73–8.82)	<0.001
ADA (U/L)	10.0 (8.7–13.0)	11.0 (9.0–13.0)	0.172
Total bile acids (umol/L)	3.0 (1.7–5.0)	3.0 (1.8–4.9)	0.847
Urea (mmol/L)	4.84 (4.06–6.00)	4.94 (4.10–6.20)	0.215
Creatinine (umol/L)	68 (59–79)	68 (57–80)	0.35
Uric acid (umol/L)	291 (237–353)	287 (229–347)	0.127
Sodium (mmol/L)	141.5 (139.8–142.93)	141.7 (140.0–143.2)	0.147
Potassium (mmol/L)	3.96 (3.69–4.18)	3.97 (3.72–4.21)	0.127
Chlorine (mmol/L)	104.4 (102.2–106.3)	104.6 (102.4–106.4)	0.302
Carbon dioxide (mmol/L)	23.8 (22.4–25.3)	24.1 (22.5–25.5)	0.02
Calcium (mmol/L)	2.26 (2.19–2.34)	2.25 (2.18–2.33)	0.065
Phosphorus (mmol/L)	1.12 (0.98–1.24)	1.1 (0.97–1.24)	0.09
Magnesium (mmol/L)	0.86 (0.81–0.91)	0.86 (0.81–0.91)	0.563
TC (mmol/L)	4.20 (3.56–4.87)	3.85 (3.21–4.61)	<0.001
TG (mmol/L)	1.36 (1.04–1.84)	1.27 (0.96–1.71)	<0.001
HDL (mmol/L)	1.05 (0.88–1.22)	1.04 (0.88–1.22)	0.692
LDL (mmol/L)	2.65 (2.09–3.26)	2.27 (1.8–2.95)	<0.001
Apo A (g/L)	1.17 (1.02–1.34)	1.16 (0.97–1.33)	0.052
Apo B (g/L)	0.92 (0.76–1.11)	0.81 (0.67–1.02)	<0.001
Lp(a) (mg/dl)	13.416 (6.54–31.07)	15.38 (7.18–33.26)	0.039
Glu (mmol/L)	5.59 (4.98–7.46)	5.65 (4.96–7.05)	0.532
HCY (umol/L)	13.0 (10.5–17.5)	12.4 (10.2–16.0)	0.001

(*Continued*)

Table 1 (Continued).

	First-ever Ischemic Stroke (n=1174)	Recurrent Ischemic Stroke (n=855)	*p* value
Glycosylated hemoglobin (%)	6.0 (5.7–7.5)	6.2 (5.7–7.2)	0.248
NIHSS	2 (1–4)	2 (1–5)	0.002
mRS	1 (1–3)	1 (1–3)	<0.001

Note: Continuous variables are expressed as means ± (SD) or medians IQRs) as appropriate.
Abbreviations: CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, γ-glumatyltranspeptidase; BChE, butyryl cholinesterase; ADA, adenosine Deaminase; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo A, apolipoprotein(A); Apo B, apolipoprotein(B); LP(a), lipoprotein a; Glu, glucose; HCY, homocysteine.

Results

Baseline Characteristics

From January 2019 to March 2023, a total of 3010 patients diagnosed with ischemic stroke were enrolled in this study. After excluding 981 patients due to lack of information, 2029 patients were finally evaluated. Among these, 1174 patients were in the first-ever ischemic stroke group, and 855 patients were in the recurrent ischemic stroke group. Flow diagram of recurrent ischemic stroke patients (Figure 1).

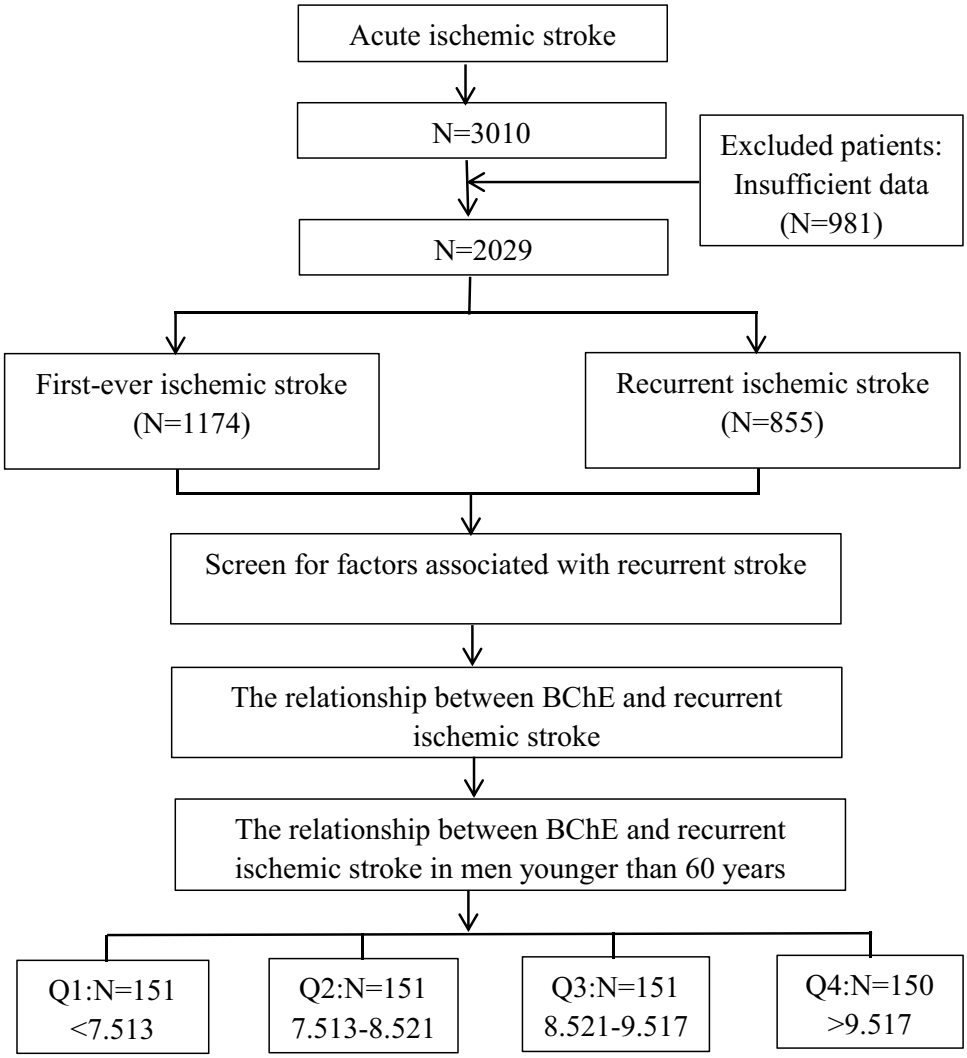

Figure 1 Flow diagram of recurrent ischemic stroke patients.

Table 2 Comparison of Baseline Characteristics Between First-Ever Ischemic Stroke and Recurrent Ischemic Stroke Patients

	First-ever Ischemic Stroke (n=1174)	Recurrent Ischemic Stroke (n=855)	*p* value
Demographic characteristics (n,%)			
Age (years)	62 (15–90)	65 (26–97)	<0.001
Gender-Male	813 (69.25%)	582 (68.07%)	0.571
Gender-Female	361 (30.75%)	273 (31.93%)	
Admitted to ICU	23 (1.96%)	18 (2.11%)	0.817
Length of stay in hospital (days)	10 (3–34)	9 (2–42)	0.651
Medical history (n,%)			
Hypertension	752 (64.05%)	659 (77.08%)	<0.001
DM	338 (28.79%)	307 (35.91%)	<0.001
Hyperlipidemia	55 (4.68%)	44 (5.15%)	0.349
AF	25 (2.13%)	32 (3.74%)	0.03
TOAST classification (n,%)			
LAA	779 (66.35%)	683 (79.88%)	<0.001
Non-LAA	395 (33.65%)	172 (20.12%)	
Pharmacological Background (n,%)			
Antiplatelet Drugs	39 (3.32%)	205 (23.98%)	<0.001
Antihypertensive Drugs	481 (49.49%)	523 (61.70%)	<0.001
Antidiabetic Drugs	278 (23.68%)	261 (30.53%)	0.001
Lipid-lowering Drugs	45 (3.83%)	189 (22.11%)	<0.001
Anticoagulant Drugs	3 (0.26%)	7 (0.82%)	0.074

Abbreviations: DM, diabetes; AF, atrial fibrillation; LAA, large artery atherosclerosis.

The median age of patients in the recurrent ischemic stroke group was 65 years old, which was higher than that of the first-ever ischemic stroke group (62 years old, $p<0.001$). The prevalence of hypertension in the recurrent ischemic stroke group was 77.08%, significantly higher than that in the first-ever ischemic stroke group (64.05%, $p<0.001$). Similarly, the prevalence of DM was significantly higher in the recurrent ischemic stroke group compared to the first-ever ischemic stroke group (35.91% vs 28.79%, $p<0.001$). The incidence of AF was also higher in the recurrent ischemic stroke group (3.74% vs 2.13%, $p=0.03$). According to the TOAST classification, the percentage of large artery atherosclerosis (LAA) in the recurrent ischemic stroke group was 79.88%, significantly higher than that in the first-ever ischemic stroke group (66.35%, $p<0.001$). Regarding the pharmacological background of the patients, the patients in the recurrent ischemic stroke group had a much higher rate of taking antiplatelet, antihypertensive, antidiabetic, and lipid-lowering medications than the patients with first-ever ischemic stroke (Table 2). This is because the recurrent ischemic stroke patients have had at least one cerebral infarction previously.

Differences in Risk Factors and Laboratory Findings Between First-Ever Ischemic Stroke and Recurrent Ischemic Stroke (Table 1)

Significant differences were observed in several risk factors and laboratory findings between patients with first-ever ischemic stroke and those with recurrent ischemic stroke (Table 1). Key differences included erythrocyte count, hemoglobin, hematocrit, myoglobin, total bilirubin, indirect bilirubin, total protein, albumin, albumin/globulin ratio, alanine aminotransferase (ALT), BChE, carbon dioxide, cholesterol, triglyceride (TG), low-density lipoprotein (LDL), apolipoprotein(B) (ApoB), Lipoprotein a (LP(a)), homocysteine, mRS score, and NIHSS score. Total cholesterol (TC), TG, and LDL levels were significantly lower in the recurrent ischemic stroke group compared to the first-ever ischemic stroke group, which may be attributed to the use of lipid-lowering medications by patients with recurrent ischemic stroke.

Conversely, LP(a) levels were significantly higher in the recurrent ischemic stroke group than in the first-ever ischemic stroke group. Other laboratory results did not show significant differences between the two groups.

Risk Factors for Recurrence Ischemic Stroke

Variables showing significant differences ($p<0.05$) in univariate analysis were selected for multivariate analysis. Considering the relationship between the pharmacological background and comorbidities, we did not include the pharmacological background in the multivariate analysis. The multivariate analysis indicated that age, hypertension, DM, ALT, and LP(a) were independent risk factors for recurrent ischemic stroke. In contrast, erythrocyte count, BChE, LDL, and NIHSS scores were negatively correlated with ischemic stroke recurrence, and patients with ischemic stroke in the Non-LAA category had a lower rate of recurrence compared with the LAA category (Figure 2).

Baseline Characteristics Based on Quartiles of BChE

Based on these findings, we focused on the role of BChE in cerebral infarction recurrence. After grouping patients according to BChE quartiles (≤6.941, 6.941–7.991, 7.992–9.094, >9.094) and analyzing the baseline data, we observed a higher percentage of patients <60 years of age in the group with higher BChE levels. Additionally, patients with higher BChE levels exhibited higher levels of lymphocytes, erythrocytes, hematocrit, platelets, total protein, albumin, albumin/globulin ratio, ALT, ALP, GGT, uric acid, magnesium, TC, TG, HDL (high-density lipoprotein), LDL, apolipoprotein(A) (Apo A), Apo B and glucose (Table S1).

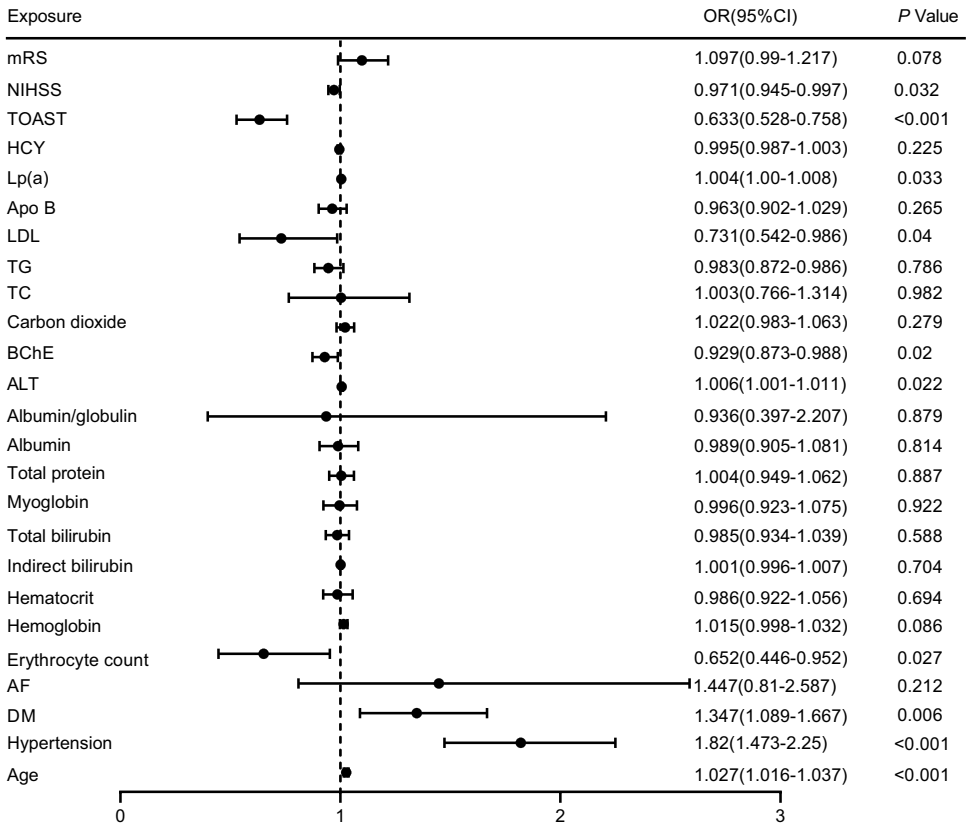

Figure 2 Multivariate regression analysis of recurrent ischemic stroke.

Abbreviations: DM, diabetes; AF, atrial fibrillation; ALT, alanine aminotransferase; BChE, butyryl cholinesterase; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; Apo B, apolipoprotein (B), LP(a), lipoprotein a; HCY, homocysteine.

Table 3 Subgroup Analyses

BChE	First-ever Ischemic Stroke (n=1174)	Recurrent ischemic stroke (n=855)	*p* value	*p* value, OR 95CI%
Gender				
Male	8.17 (7.11–9.24)	7.53 (6.60–8.64)	<0.001	<0.001 0.814 (0.761–0.871)
Female	8.26 (7.24–9.40)	8.04 (7.01–9.30)	0.098	
Age				
<60	8.71 (7.73–9.70)	8.25 (7.22–9.15)	<0.001	<0.001 0.781 (0.708–0.862)
≥60	7.68 (6.61–8.68)	7.28 (6.43–9.29)	0.009	0.056 0.917 (0.839–1.002)
Gender and Age				
<60 Male	8.73 (7.75–9.70)	8.10 (7.12–8.95)	<0.001	<0.001 0.753 (0.672–0.843)
≥60 Male	7.68 (6.61–8.68)	7.28 (6.43–8.29)	0.09	
<60 Female	8.62 (7.73–9.77)	8.87 (7.37–9.56)	0.638	
≥60 Female	8.08 (7.07–9.31)	7.89 (6.94–9.07)	0.436	

BChE Levels are Negatively Associated with Recurrence Ischemic Stroke in Men Younger Than 60 years

Nonparametric test were used to analyze the differences of BChE levels between the groups. In males, BChE levels were significantly higher in the first-ever ischemic stroke group than in the recurrent ischemic stroke group (8.17 vs 7.53, $p<0.001$). Among female patients, there was no significant difference between the first-ever ischemic stroke and recurrent ischemic stroke groups (8.26 vs 8.04, $p=0.098$). In men <60 years of age, the first-ever ischemic stroke group also had significantly higher BChE levels than the recurrent ischemic stroke group (8.73 vs 8.10, $p<0.001$). In men ≥60 years of age, the first-ever ischemic stroke group higher BChE levels than the recurrent ischemic stroke group (7.68 vs 7.28, $p=0.09$). Binary logistic regression analysis revealed that BChE levels was negative related with recurrent ischemic stroke in men aged <60 years (OR=0.753, 95% CI: 0.672–0.843, $p<0.001$) (Table 3).

Correlations Between BChE Levels and Clinical Outcomes in Men Younger Than 60 years of Age

603 patients were categorized into four groups based on BChE quartiles, Q1, Q2, Q3, and Q4. The rates of recurrent ischemic stroke in the four groups were 44.37%, 37.75%,29.8%, and 22%, respectively, showing a decreasing trend across groups. Erythrocyte count, hemoglobin, hematocrit, total protein, albumin, GGT, uric acid, TG, and LDL showed an increasing trend across groups, while total bilirubin and indirect bilirubin showed a decreasing trend (Table S2).

Regression analysis was performed using group Q4 as the reference group, after multivariate adjustment, the odds ratios for recurrent ischemic stroke in the highest versus the lowest quartile were 2.281 (95% confidence interval: 1.318–3.948; $p<0.05$) for BChE, suggesting that lower BChE levels are associated with a higher risk of stroke recurrence (Table 4). To further explore the linear or nonlinear relationship between BChE and the risk of recurrent ischemic stroke, multivariable-adjusted (Model4) RCS model based on logistic regression was performed (Figure 3). RCS analysis showed a negative linear association between BChE and the risk of recurrent ischemic stroke (nonlinear $p = 0.803$).

Table 4 Multivariate-Adjusted OR and 95% CI for Recurrent Ischemic Stroke According to Quartiles of BChE Levels

	Q1 (<7.513)	Q2 (≤8.521)	Q3 (≤9.517)	Q4 (>9.517)	*p* value
Model0	2.828 (1.711–4.673)	2.15 (1.294–3.571)	1.505 (0.894–2.533)	1	<0.001
Model1	2.457 (1.469–4.109)	2.007 (1.194–3.373)	1.453 (0.855–2.469)	1	<0.004
Model2	2.617 (1.542–4.441)	2.051 (1.205–3.493)	1.491 (0.868–2.561)	1	<0.003
Model3	2.315 (1.339–4.004)	1.95 (1.134–3.352)	1.443 (0.837–2.488)	1	0.017
Model4	2.281 (1.318–3.948)	1.909 (1.108–3.289)	1.446 (0.839–2.493)	1	0.021

Notes: Multivariate-adjusted OR and 95% CI for recurrent ischemic stroke according to quartiles of BChE levels. The HR of quartile 4 was set as the reference. Model 1 was adjusted for age. Model 2 was adjusted for the factors in model 1 plus hypertension, DM, hyperlipidemia, atrial fibrillation. Model 3 was adjusted for the factors in model 2 plus erythrocyte count, total protein, ALT. Model 4 was adjusted for the factors in model 3 plus NIHSS, mRS.

Discussion

In this study, age, hypertension, DM, ALT, and LP(a) were identified as independent risk factors for the recurrence of ischemic stroke. Erythrocyte count, butyryl cholinesterase, low-density lipoprotein, and non-atherosclerotic type of large arteries were found to be negative associated with recurrent ischemic stroke. Wang Yongjun's team found that patients with minor stroke or transient ischemic attack and elevated ALT and AST levels had a higher rate of stroke recurrence or TIA recurrence within 90 days compared to those with normal ALT and AST levels (14.5% vs 11.2%, p=0.029),[12] which is consistent with our findings. Elevated serum LP(a) level is a known risk factor for ischemic stroke and can predict the risk of early stroke recurrence in patients with a first-ever ischemic stroke.[13] Previous studies have shown that erythrocyte distribution width is risk factor for stroke in patients with TIA (transient ischemic attack) and a predictor of high mortality following ischemic stroke with hemorrhagic conversion and after intravenous thrombolysis.[14,15] Elevated hemoglobin has been associated with an increased risk of stroke recurrence and composite vascular events.[16]

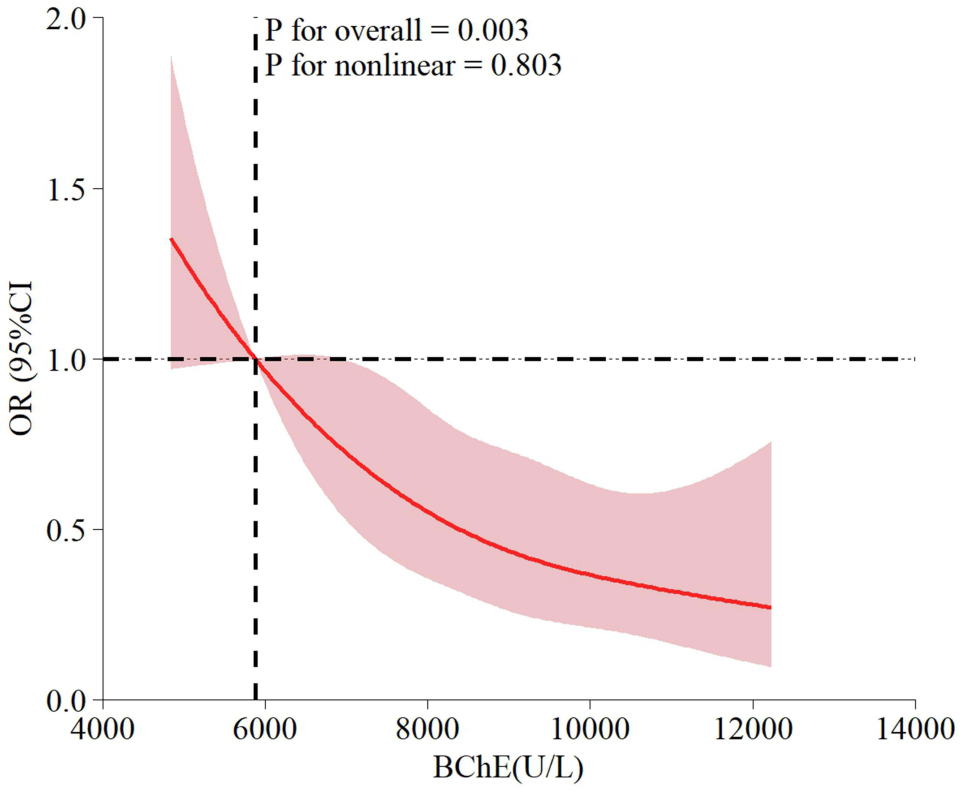

Figure 3 Association between the cumulative average BChE and recurrent ischemic stroke. The model was adjusted for age, hypertension, DM, hyperlipidemia, atrial fibrillation, erythrocyte count, total protein, ALT, NIHSS, mRS.

Additionally, erythrocyte count has been identified as an independent predictor of adverse cardiovascular events during hospitalization in patients with ST-segment elevation myocardial infarction.[17] However, no studies have specifically explored the relationship between erythrocyte count and ischemic stroke. The mechanism underlying this association remains unclear. In this study, LDL appeared to be a protective factor against the recurrence of ischemic stroke, which contradicts the results of previous studies. This discrepancy may be because most patients with a previous history of ischemic stroke were taking oral lipid-lowering drugs at the time of admission. The relationships between the other factors in this study and cerebral infarction have been extensively studied. Although BChE is closely related to diseases of the nervous system,[18,19] its relationship with cerebral infarction remains unclear. Therefore, in the subgroup analysis of this study, we focused on the research of the relationship between BChE and recurrent cerebral infarction.

In the present study, BChE levels were found to be positively correlated with TC, triglyceride, LDL, ApoA, and ApoB levels, which is consistent with previous studies. [20] Cholinesterase include acetylcholinesterase (AChE) and BChE. BChE is predominantly found in serum and hydrolyzes acetylcholine and various ester-bond-containing substances, including succinylcholine, procaine, and gastric starvation. Recent research has shown that BChE is similar to lipase in its ability to hydrolyze carboxylated ester bonds, with the catalytic activity sites of the two enzymes differing by only one amino acid. [21,22] Previous clinical studies have found that BChE is associated with metabolic syndrome, with its activity positively correlated with body mass index (BMI), LDL, TC, and TG. [23–25] In occupationally exposed pesticide workers, BChE activity is positively correlated with lipid parameters (LDL, VLDL, TG, and total lipids. [26] BChE levels are significantly elevated in obese children compared to normal children, [27] and dietary control over 8 weeks significantly reduces BChE activity to near-normal levels in obese individuals. [28] In addition, high levels of BChE are positively correlated with blood glucose levels and diabetic retinopathy, with the correlation being more pronounced in men. [29] However, obese patients have a higher frequency of the BCHH gene 1914G (SNP:A/G; rs3495) allele than non-obese individuals, which is associated with low BChE activity, lipid metabolism disorders, and an increased risk of obesity and DM. [30,31] In animal experiments, mice injected with a BChE inhibitor gained weight significantly. [32] BChE knockout mice exhibited 50% higher levels of gastric starvation hormone than normal mice and developed obesity and fatty liver when fed a high-fat diet, with TC levels 88% higher than those of control mice. The increase in intake and decreased energy expenditure might be the cause of obesity in these mice. The transfer of lipids from other parts of the body to the liver leads to fatty liver, promoting the synthesis of TG and the production of very low-density lipoproteins, thereby playing a key role in lipid metabolism.[30–34] Injection of adenovirus-associated vectors to increase BChE expression resulted in a significant decrease in gastric starvation hormone levels, leading to a return to normal dietary intake and body weight. [35] These findings indicate that BChE levels are closely related to blood lipid levels.

The present study found a low rate of recurrent ischemic stroke in individuals with elevated BChE levels, particularly significant in men <60 years of age. This suggests that BChE may play a role in improving the prognosis of ischemic cerebrovascular disease. Previous studies have indicated that during the acute phase of stroke, serum AChE activity decreases while BChE activity increases, suggesting that circulating BChE levels are vital for early stroke diagnosis.[36] Moreover, patients with low BChE activity levels at the time of coronary angiography have an increased risk of death over a 10-year follow-up.[37] Low BChE levels are also associated with a higher risk of myocardial infarction and adverse cardiovascular events.[38] Additionally, in patients undergoing angioplasty and stenting for lower extremity peripheral arterial disease, Low BChE levels are linked to an increased risk of long-term adverse ischemic events.[39] Among the elderly, low BChE levels at admission are an independent risk factor for all-cause mortality in patients with acute ischemic stroke.[40] In conclusion, high levels of BChE appear to be associated with a more favorable prognosis of vascular disease.

The results of the aforementioned studies seem contradictory; however, they all indicate that BChE is closely related to lipid metabolism, although the specific mechanisms remain unclear and require further investigation. It has been suggested that lipids may act as endogenous regulators of the cholinergic system. For instance, Gok et al found that purified human serum BChE can hydrolyze 4-methylumbelliferyl (4-mu) palmitate at both pH 7.4 and pH 8, suggesting that BChE possesses lipolytic activity,[41] Additionally, they discovered that applyingα-linolenic acid (ALA) and linoleic acid (LA) to liver HepG2 cells induced an increase in BChE expression.[42] This implies that elevated blood lipid levels can induce high BChE expression, establishing a positive correlation between BChE levels and blood lipid levels. In basic experiments,

BChE knockout mice developed obesity and abnormal lipid metabolism due to the loss of BChE's lipid-hydrolyzing effect. Another study suggested that BChE deficiency might regulate low-density lipoprotein receptor (LDLR) transcription via the BChE-PRMT5-ERK-LDLR pathway, which in turn regulates hepatocyte cholesterol metabolism. In vivo restrictive silencing of BChE in hepatocytes significantly reduced plasma cholesterol levels, and BChE knockout mice were prone to hypercholesterolemia. Therefore, targeting hepatic BChE could be an effective therapeutic strategy for treating hypercholesterolemia.[43] Additionally, the cholinergic anti-inflammatory pathways may also be involved. The association of BChE with lipid metabolism through multiple pathways- whether through lipid hydrolysis or regulating LDLR transcription- helps explain the positive correlation between BChE and lipid levels. However, the initiating factor in patients remains unknown. The more pronounced correlation between BChE levels and recurrence of cerebral infarction in men under 60 years of age might be due to the interaction of BChE with gender and age. The Shanghai Nisei cohort study found that among participants aged 55 years and older, BChE levels were higher in women than in men, and among participants aged 60 years and older, there was an interaction between BChE levels and age.[29]

The present study is a retrospective analysis conducted with a standardized protocol and strict quality control procedures for data collection and outcome statistics, involving a large sample size. These factors provide a solid basis for the prevention of recurrent ischemic stroke. However, the study has some limitations. Patients with recurrent ischemic stroke underwent periods of oral lipid-lowering and plaque repair medication. Due to the retrospective nature of this study, it is impossible to accurately count the patients, pharmacological background, and the medication history of some patients might have been overlooked, which could have influenced the results. Additionally, the comprehensive analysis of risk factors for recurrent ischemic stroke was constrained due to a significant lack of data on weight and height. This study only established a correlation between BChE levels, lipids, and cerebral infarction, without exploring the underlying causality and mechanism. In this study, we found that ALT and BChE were closely associated with recurrent ischemic stroke, whether this means that there is a close relationship between liver enzymes and recurrent ischemic stroke, we will pay close attention to the relationship between liver function and ischemic stroke in future studies.

Conclusion

Age, hypertension, DM, ALT, and LP(a) as independent risk factors for recurrent ischemic stroke. The association of BChE with recurrence after ischemic stroke in men younger than 60 years suggests that BChE could be a potential target for intervention to improve the prognosis. Thus, addressing these risk factors and considering BChE as a therapeutic target could enhance strategies for preventing recurrent ischemic stroke.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Ethics Approval and Consent to Participate

The study was approved by the Research Ethics Committee of the second hospital of Hebei Medical University (Approval letter No: 2023-R082). Informed consent was waived due to the retrospective nature of the study. The waiver was due to the retrospective nature of the research, as the analysis was based on anonymized data with minimal potential risks to patient privacy. Conducted in accordance with the principles of the Declaration of Helsinki, all patient related data were de-identified and handled confidentially. Only aggregated and anonymized data were used for analysis, ensuring patient identities remained unidentifiable.

Acknowledgments

We thank all the authors and team members who have helped us. Thanks to the corresponding author who guided us.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, giving insight/feedback and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The project was supported by the S&T Program of Hebei No.22377712D, The Hebei Provincial Department of Finance and the Health Commission, ZF2024142; Hebei Provincial Health Commission Medical Science Research Project, 20252051.

Disclosure

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Tu WJ, Wang LD. China stroke surveillance report 2021. *Military Med Res*. 2023;10(1):33. doi:10.1186/s40779-023-00463-x
2. Padwale V, Chivate C, Kirnake V, Patil H, Kumar S, Pantbalekundri N. Comparative prognostic value of the National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS) in supratentorial and infratentorial stroke patients in Western India. *Cureus*. 2024;16(7):e65778. doi:10.7759/cureus.65778
3. Chen Y, Wright N, Guo Y, et al. Mortality and recurrent vascular events after first incident stroke: a 9-year community-based study of 0·5 million Chinese adults. *Lancet Glob Health*. 2020;8(4):e580–e590. doi:10.1016/S2214-109X(20)30069-3
4. Hankey GJ, Jamrozik K, Broadhurst RJ, et al. Long-term risk of first recurrent stroke in the Perth Community Stroke Study. *Stroke*. 1998;29(12):2491–2500. doi:10.1161/01.str.29.12.2491
5. Wang Y, Xu J, Zhao X, et al. Association of hypertension with stroke recurrence depends on ischemic stroke subtype. *Stroke*. 2013;44(5):1232–1237. doi:10.1161/STROKEAHA.111.000302
6. Chung JY, Lee BN, Kim YS, Shin BS, Kang HG. Sex differences and risk factors in recurrent ischemic stroke. *Front Neurol*. 2023;14:1028431. doi:10.3389/fneur.2023.1028431
7. Xu L, Zhu B, Huang Y, et al. Butyrylcholinesterase levels on admission predict severity and 12-month mortality in hospitalized AIDS patients. *Mediators Inflamm*. 2018;2018:5201652. doi:10.1155/2018/5201652
8. Schlake K, Teller J, Hinken L, et al. Butyrylcholinesterase activity in patients with postoperative delirium after cardiothoracic surgery or percutaneous valve replacement- an observational interdisciplinary cohort study. *BMC Neurol*. 2024;24(1):80. doi:10.1186/s12883-024-03580-9
9. Atay MS, Sari S, Bodur E. Molecular and computational analysis identify statins as selective inhibitors of human butyrylcholinesterase. *Protein J*. 2023;42(2):104–111. doi:10.1007/s10930-023-10090-z
10. Chen YC, Chou WH, Fang CP, et al. Serum level and activity of butylcholinesterase: a biomarker for post-stroke dementia. *J Clin Med*. 2019;8(11):1778. doi:10.3390/jcm8111778
11. Chinese Society of Neurology CSS. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. *Chin J Neurol*. 2018;51(9):666–682.
12. Suo Y, Pan Y, Chen W, et al. Aminotransferase level and the effects of dual antiplatelet in minor stroke or transient ischemic attack: a post hoc analysis of a randomized control trial. *Cerebrovascular Dis*. 2023;52(4):442–450. doi:10.1159/000527611
13. Hong XW, Wu DM, Lu J, Zheng YL, Tu WJ, Yan J. Lipoprotein (a) as a predictor of early stroke recurrence in acute ischemic stroke. *Mol Neurobiol*. 2018;55(1):718–726. doi:10.1007/s12035-016-0346-9
14. Xie KH, Liu LL, Liang YR, et al. Red cell distribution width: a novel predictive biomarker for stroke risk after transient ischaemic attack. *Ann Med*. 2022;54(1):1167–1177. doi:10.1080/07853890.2022.2059558
15. Fan H, Liu X, Li S, et al. High red blood cell distribution width levels could increase the risk of hemorrhagic transformation after intravenous thrombolysis in acute ischemic stroke patients. *Aging*. 2021;13(16):20762–20773. doi:10.18632/aging.203465
16. Zhang R, Xu Q, Wang A, et al. Hemoglobin concentration and clinical outcomes after acute ischemic stroke or transient ischemic attack. *J Am Heart Assoc*. 2021;10(23):e022547. doi:10.1161/JAHA.121.022547
17. Xiao LJ, Liu JL, Pan NN, et al. The predictive value of red cell distribution width and red cell distribution width to erythrocyte count ratio for adverse cardiovascular events during the hospitalization of patients of ST-segment elevation myocardial infarction. *Clin Lab*. 2020;66(7).
18. Zhang J, Tang X, Qi H, Li Z, He X. A new near-infrared fluorescence probe for highly selective and sensitive detection and imaging of Butyrylcholinesterase in Alzheimer's disease mice. *Talanta*. 2025;285:127377. doi:10.1016/j.talanta.2024.127377
19. Ravichandar R, Gadelkarim F, Muthaiah R, et al. Dysregulated cholinergic signaling inhibits oligodendrocyte maturation following demyelination. *J Neurosci*. 2024;44(28):e0051242024. doi:10.1523/JNEUROSCI.0051-24.2024
20. Iwasaki T, Yoneda M, Nakajima A, Terauchi Y. Serum butyrylcholinesterase is strongly associated with adiposity, the serum lipid profile and insulin resistance. *Intern Med*. 2007;46(19):1633–1639. doi:10.2169/internalmedicine.46.0049
21. Leung MR, van Bezouwen LS, Schopfer LM, et al. Cryo-EM structure of the native butyrylcholinesterase tetramer reveals a dimer of dimers stabilized by a superhelical assembly. *Proc Natl Acad Sci USA*. 2018;115(52):13270–13275. doi:10.1073/pnas.1817009115
22. Nguyen PTV, Huynh HA, Truong DV, Tran TD, Vo CT. Exploring aurone derivatives as potential human pancreatic lipase inhibitors through molecular docking and molecular dynamics simulations. *Molecules*. 2020;25(20). doi:10.3390/molecules25204657

23. Valle A, O'Connor DT, Taylor P, et al. Butyrylcholinesterase: association with the metabolic syndrome and identification of 2 gene loci affecting activity. *Clin Chem*. 2006;52(6):1014–1020. doi:10.1373/clinchem.2005.065052
24. Vallianou NG, Evangelopoulos AA, Bountziouka V, et al. Association of butyrylcholinesterase with cardiometabolic risk factors among apparently healthy adults. *J Cardiovasc Med*. 2014;15(5):377–383. doi:10.2459/JCM.0b013e3283627700
25. Villeda-González JD, Gómez-Olivares JL, Baiza-Gutman LA, et al. Nicotinamide reduces inflammation and oxidative stress via the cholinergic system in fructose-induced metabolic syndrome in rats. *Life Sci*. 2020;250:117585. doi:10.1016/j.lfs.2020.117585
26. Molina-Pintor IB, Rojas-García AE, Bernal-Hernández YY, Medina-Díaz IM, González-Arias CA, Barrón-Vivanco BS. Relationship between butyrylcholinesterase activity and lipid parameters in workers occupationally exposed to pesticides. *Environ Sci Pollut Res Int*. 2020;27(31):39365–39374. doi:10.1007/s11356-020-08197-2
27. Valle-Martos R, Valle M, Martos R, Cañete R, Jiménez-Reina L, Cañete MD. Liver enzymes correlate with metabolic syndrome, inflammation, and endothelial dysfunction in prepubertal children with obesity. *Front Pediatr*. 2021;9:629346. doi:10.3389/fped.2021.629346
28. Santos WD, Tureck LV, Saliba LF, et al. Effects of energetic restriction diet on butyrylcholinesterase in obese women from southern Brazil—a longitudinal study. *Arch Endocrin Metab*. 2017;61(5):484–489. doi:10.1590/2359-3997000000268
29. Yu R, Ye X, Wang X, et al. Serum cholinesterase is associated with incident diabetic retinopathy: the Shanghai Nicheng cohort study. *Nutr Metab*. 2023;20(1):26.
30. Hashim Y, Shepherd D, Wiltshire S, et al. Butyrylcholinesterase K variant on chromosome 3 q is associated with Type II diabetes in white Caucasian subjects. *Diabetologia*. 2001;44(12):2227–2230. doi:10.1007/s001250100033
31. Lima JK, Leite N, Turek LV, et al. 1914G variant of BCHE gene associated with enzyme activity, obesity and triglyceride levels. *Gene*. 2013;532(1):24–26. doi:10.1016/j.gene.2013.08.068
32. Brimijoin S, Chen VP, Pang YP, Geng L, Gao Y. Physiological roles for butyrylcholinesterase: a BChE-ghrelin axis. *Chem Biol Interact*. 2016;259(Pt B):271–275. doi:10.1016/j.cbi.2016.02.013
33. Chen VP, Gao Y, Geng L, Parks RJ, Pang YP, Brimijoin S. Plasma butyrylcholinesterase regulates ghrelin to control aggression. *Proc Natl Acad Sci USA*. 2015;112(7):2251–2256. doi:10.1073/pnas.1421536112
34. Chen VP, Gao Y, Geng L, Stout MB, Jensen MD, Brimijoin S. Butyrylcholinesterase deficiency promotes adipose tissue growth and hepatic lipid accumulation in male mice on high-fat diet. *Endocrinology*. 2016;157(8):3086–3095. doi:10.1210/en.2016-1166
35. Chen VP, Gao Y, Geng L, Brimijoin S. Butyrylcholinesterase regulates central ghrelin signaling and has an impact on food intake and glucose homeostasis. *Int J Obesity*. 2017;41(9):1413–1419. doi:10.1038/ijo.2017.123
36. Ben Assayag E, Shenhar-Tsarfaty S, Ofek K, et al. Serum cholinesterase activities distinguish between stroke patients and controls and predict 12-month mortality. *Mol Med*. 2010;16(7–8):278–286. doi:10.2119/molmed.2010.00015
37. Shenhar-Tsarfaty S, Brzezinski RY, Waiskopf N, et al. Blood acetylcholinesterase activity is associated with increased 10 year all-cause mortality following coronary angiography. *Atherosclerosis*. 2020;313:144–149. doi:10.1016/j.atherosclerosis.2020.10.004
38. Lu J, Song J, Liu F, Chen B, Dong Y, Yang Y. Study on the expression significance of Mb, BChE and cTnI in myocardial infarction and their relationship with prognosis. *Alt Ther Health Med*. 2023;29(8):798–802.
39. Gremmel T, Wadowski PP, Mueller M, Kopp CW, Koppensteiner R, Panzer S. Serum cholinesterase levels are associated with 2-year ischemic outcomes after angioplasty and stenting for peripheral artery disease. *J Endovascular Ther*. 2016;23(5):738–743. doi:10.1177/1526602816655521
40. Li M, Chen Y, Zhang Y, et al. Admission serum cholinesterase concentration for prediction of in-hospital mortality in very elderly patients with acute ischemic stroke: a retrospective study. *Aging Clin Exp Res*. 2020;32(12):2667–2675. doi:10.1007/s40520-020-01498-z
41. Gok M, Cicek C, Sari S, Bodur E. Novel activity of human BChE: lipid hydrolysis. *Biochimie*. 2023;204:127–135. doi:10.1016/j.biochi.2022.09.008
42. Gok M, Zeybek ND, Bodur E. Butyrylcholinesterase expression is regulated by fatty acids in HepG2 cells. *Chem Biol Interact*. 2016;259(Pt B):276–281. doi:10.1016/j.cbi.2016.04.029
43. Wang D, Tan KS, Zeng W, et al. Hepatocellular BChE as a therapeutic target to ameliorate hypercholesterolemia through PRMT5 selective degradation to restore LDL receptor transcription. *Life Sci*. 2022;293:120336.