

Original Article

Clinical value of homocysteine combined with blood lipid indexes in identifying vascular lesion subtypes of cerebral infarction in young and middle-aged and pre-elderly adults

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Received July 7, 2026; Accepted August 27, 2026; Epub October 15, 2026; Published October 30, 2026

Abstract: Objective: To investigate the diagnostic value of homocysteine (Hcy) combined with lipid indicators for TOAST subtypes in young, middle-aged, and pre-elderly cerebral infarction, and to establish and validate a predictive model for large artery atherosclerosis (LAA). Methods: A total of 163 patients were retrospectively enrolled. Hcy, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were compared among subtypes. A Logistic model was constructed using Hcy, LDL-C, and HDL-C, and validated by internal validation, 5-fold cross-validation, and external validation ($n = 80$). Results: Hcy, LDL-C, and HDL-C differed significantly among subtypes ($P < 0.05$). The combined index showed the best performance for LAA (AUC = 0.876, sensitivity = 84.6%, specificity = 78.8%). All three indicators were independent predictors. The model performed well in internal validation (mean AUC = 0.956) and external validation (AUC = 0.929, accuracy = 86.3%). Conclusions: Hcy combined with LDL-C and HDL-C is effective in identifying LAA. The model shows good stability and generalization ability, which can support clinical screening and individualized management.

Keywords: Homocysteine, serum lipid markers, cerebral infarction in young and middle-aged adults, vascular lesion subtypes, diagnostic value

Introduction

Ischemic stroke remains a leading cause of mortality and long-term disability worldwide. Along with social and economic development, disease burden has continued to increase. In the United States, nearly 700,000 adults experience a stroke each year [1, 2]. Symptoms often begin during rest or sleep, and neurological deficits frequently deteriorate within 48 hours [3, 4]. Common manifestations include dysphasia, headache, limb paralysis, and in severe cases, death. Stroke survivors often face persistent complications and functional dependence, imposing substantial pressure on families and healthcare systems.

Various pathogenic subtypes of ischemic stroke differ distinctly in etiology, therapeutic strategy, and long-term prognosis [5]. In recent years, the age of stroke onset has decreased

significantly, and the proportion of patients aged 18-45 years has increased annually, making stroke a major health threat to young and middle-aged adults [6-8]. Compared with elderly patients, younger individuals show more complex causes and more diverse vascular subtypes. Accurate subtype classification is critical for understanding pathogenesis, selecting targeted interventions, and improving long-term recovery [9, 10].

Homocysteine (Hcy) is a sulfur-containing amino acid metabolite [11, 12]. Elevated Hcy levels are widely accepted as an independent risk factor for cerebrovascular disease. It promotes the occurrence and progression of infarction by injuring endothelial cells and accelerating atherosclerotic plaque development [13]. Lipid metabolism disorder is another key risk factor; increased LDL-C and decreased HDL-C are closely associated with large artery

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Table 1. Baseline characteristics of each group

Vascular lesion subtype	N (%)	Age	Male/Female
LAA	78 (47.8)	56.10 ± 4.62	44/34
CE	29 (17.8)	54.48 ± 5.45	17/12
SAO	36 (22.1)	55.08 ± 4.87	18/18
OE	8 (4.9)	52.63 ± 4.14	5/3
UE	12 (7.4)	55.83 ± 5.13	7/5
F/χ^2	-	1.381	6.791
P	-	0.241	0.147

Note: LAA, Large Artery Atherosclerosis; CE, Cardioembolism; SAO, Small Artery Occlusion; OE, Other determined Etiology; UE, Undetermined Etiology.

admitted from July 2024 to October 2025, with no overlapping data with the modeling group, including 45 males and 35 females, with a mean age of 55.42 ± 5.38 years.

This study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University.

Research methods

atherosclerosis, the most common subtype in young and middle-aged patients [14-16].

Although many studies have investigated the diagnostic value of Hcy or lipid indicators alone in young and middle-aged cerebral infarction, research on their combined application in vascular subtyping remains insufficient [17, 18]. This study retrospectively analyzed clinical data from 163 patients to explore the combined diagnostic value of Hcy and lipid indicators, established a classification prediction model, and completed systematic internal and external validation, aiming to provide a practical quantitative tool for clinical diagnosis and treatment.

Materials and methods

General information

A total of 163 young and middle-aged and pre-elderly patients with cerebral infarction admitted to Xuanwu Hospital, Capital Medical University from January 2022 to June 2024 were retrospectively enrolled. Inclusion criteria: 1) Met the clinical diagnostic criteria of cerebral infarction and confirmed by cranial CT or MRI. 2) Aged 18-65 years. 3) Complete clinical, laboratory, and imaging data available. 4) Completed TOAST vascular subtype classification. Exclusion criteria: 1) Severe hepatic or renal dysfunction, malignant tumor, hematological disease, or autoimmune disease. 2) Severe infection, trauma, or surgical operation within one month. 3) Administration of drugs affecting Hcy or lipid metabolism in the past four weeks. 4) Previous history of cerebral infarction or cerebral hemorrhage. 5) Pregnancy or lactation period.

Another 80 consecutive eligible patients were enrolled as the external validation cohort

(1) Vascular lesion subtyping method: Two senior neurologists independently classified all patients into five subtypes based on the TOAST criteria [19], combined with clinical manifestations, imaging findings (CT/MRI, DSA), electrocardiography, and echocardiography. LAA: definite atherosclerosis in intracranial or extracranial large arteries, infarct lesions matching the vascular supply area, and no other identifiable causes. presence of cardiogenic embolism sources such as atrial fibrillation, myocardial infarction, or valvular heart disease, with multiple infarcts involving multiple vascular territories. CE: presence of cardiogenic embolism sources such as atrial fibrillation, myocardial infarction, or valvular heart disease, with multiple infarcts involving multiple vascular territories. SAO: infarct diameter < 15 mm located in the deep small cerebral vessel supply area, with no evidence of large artery atherosclerosis or cardiogenic embolism. OE: cerebral infarction caused by definite etiologies including vasculitis, coagulation disorders, or vascular malformations. UE: no clear etiology identified after comprehensive examination.

(2) Detection of laboratory indexes: Fasting venous blood (5 mL) was collected within 24 hours after admission and placed in non-anticoagulant tubes. After standing for 30 minutes, serum was separated by centrifugation at 3000 r/min for 10 minutes. Serum levels of Hcy, TC, TG, HDL-C, and LDL-C were measured using an automatic biochemical analyzer in accordance with standard protocols.

Observation indicators

(1) Statistics of the distribution of vascular lesion subtypes in 163 young and middle-aged and pre-elderly patients with cerebral infarction. (2) Comparison of serum Hcy, TC, TG,

Table 2. Comparison of laboratory index levels in patients with different vascular lesion types

Vascular lesion subtype	Hcy (μ M)	TC (mM)	TG (mM)	HDL-C (mM)	LDL-C (mM)
LAA	16.13 $\pm$ 2.90	4.89 $\pm$ 0.74	1.67 $\pm$ 0.52	0.85 $\pm$ 0.18	3.99 $\pm$ 0.62
CE	12.35 $\pm$ 3.23*	4.76 $\pm$ 0.84	1.59 $\pm$ 0.49	1.15 $\pm$ 0.21*	3.21 $\pm$ 0.59*
SAO	11.89 $\pm$ 2.99*	4.68 $\pm$ 0.80	1.62 $\pm$ 0.51	1.18 $\pm$ 0.23*	3.15 $\pm$ 0.62*
OE	12.17 $\pm$ 3.23*	4.72 $\pm$ 0.91	1.57 $\pm$ 0.49	1.12 $\pm$ 0.21*	3.27 $\pm$ 0.59*
UE	12.54 $\pm$ 3.21*	4.91 $\pm$ 0.78	1.65 $\pm$ 0.51	1.18 $\pm$ 0.22*	3.30 $\pm$ 0.48*
F	17.761	0.544	0.197	24.060	17.543
P	< 0.001	0.704	0.940	< 0.001	< 0.001

*Compared with LAA subtype, *P < 0.05. Note: Hcy, homocysteine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LAA, Large Artery Atherosclerosis; CE, Cardioembolism; SAO, Small Artery Occlusion; OE, Other determined Etiology; UE, Undetermined Etiology.

Table 3. Analysis on the efficacy of single index in differentiating LAA

Detection index	AUC	Sensitivity (%)	Specificity (%)	Cut-off	P
Hcy	0.822	78.2	88.2	13.695	< 0.001
TC	0.547	97.4	22.4	4.005	0.307
TG	0.528	66.7	45.9	1.535	0.544
HDL-C	0.128	0	100	2.760	< 0.001
LDL-C	0.818	64.1	83.5	3.450	< 0.001

Note: LAA, Large Artery Atherosclerosis; Hcy, homocysteine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

HDL-C and LDL-C levels among patients with different vascular lesion subtypes. (3) Analysis of the diagnostic efficacy of single indexes (Hcy, TC, TG, HDL-C, LDL-C) and combined indexes (LH1 (Hcy+TC+TG+HDL-C+LDL-C), LH2 (Hcy+HDL-C+LDL-C), LH3 (Hcy+LDL-C), and LH4 (Hcy+LDL-C+HDL-C)) for different vascular lesion subtypes. (4) Construction of Logistic prediction model. (5) Internal validation (7:3 division, 5-fold cross-validation). (6) External validation (independent cohort).

Statistical methods

Statistical analysis was performed using SPSS 26.0 software. Measurement data were expressed as mean $\pm$ standard deviation and group comparisons were performed using one-way ANOVA with LSD post-hoc test. Enumeration data were expressed as cases (percentages) and compared using the chi-square test. ROC curves were constructed to calculate AUC, sensitivity, and specificity. Logistic regression analysis was used for model building. Multicollinearity among the variables included in the Logistic regression model was tested

using the variance inflation factor (VIF). A VIF < 5 was regarded as indicating no significant multicollinearity. P < 0.05 was considered statistically significant.

Results

Baseline characteristics and subtype distribution

Among the 163 young and middle-aged and pre-elderly patients with cerebral infarction, 78 cases were LAA, 29 cases were CE, 36 cases were SAO, 8 cases were OE, and 12 cases were UE. LAA was the most common vascular lesion subtype. As shown in **Table 1**, there were no statistically significant differences in age and gender distribution among the five groups.

Comparison of laboratory indicators

Significant differences were found in Hcy, LDL-C, and HDL-C levels among different vascular subtypes (P < 0.05), while TC and TG levels showed no significant intergroup differences (P > 0.05). Patients with LAA had significantly higher Hcy and LDL-C and lower HDL-C than those with other subtypes (P < 0.05). No significant differences were detected among CE, SAO, OE, and UE groups (**Table 2**).

Diagnostic efficiency of single and combined indicators for LAA

Taking LAA subtype as the positive group and the other four subtypes as the negative group, results showed that among the single indexes,

Table 4. Analysis of the efficacy of combined indicators in differentiating LAA

Combination index	AUC	Sensitivity (%)	Specificity (%)	Cut-off	P
LH1 (Hcy+TC+TG+HDL-C+LDL-C)	0.850	87.2	68.2	24.355	< 0.001
LH2 (Hcy+HDL-C+LDL-C)	0.846	75.6	82.4	19.210	< 0.001
LH3 (Hcy+LDL-C)	0.862	80.8	78.8	17.715	< 0.001
LH4 (Hcy+LDL-C-HDL-C)	0.876	84.6	78.8	16.560	< 0.001

Note: LAA, Large Artery Atherosclerosis; Hcy, homocysteine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

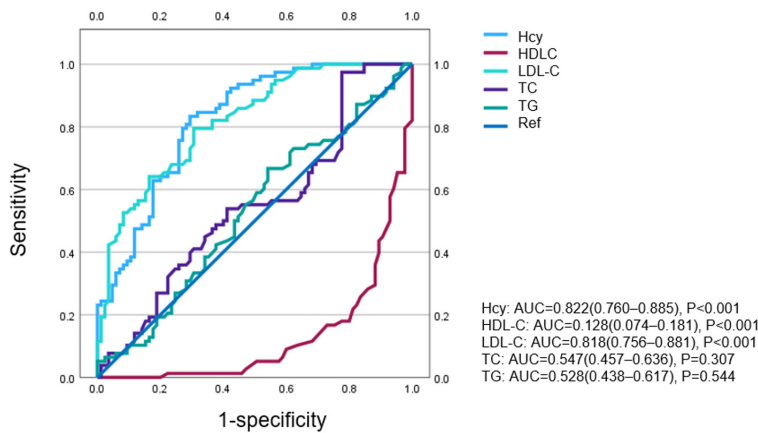


Figure 1. ROC curves of single index for distinguishing LAA subtype from other subtypes. Note: The ordinate represents sensitivity, and the abscissa represents 1-specificity; the reference line is the diagonal line of the coordinate system; the curves include Hcy, HDL-C, LDL-C, TC, and TG. LAA, Large Artery Atherosclerosis; Hcy, homocysteine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

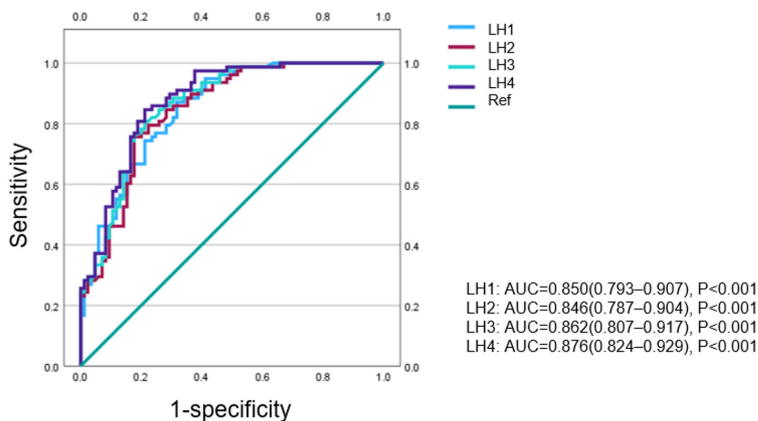


Figure 2. ROC curves of combination index for distinguishing LAA subtype from other subtypes. Note: The ordinate represents sensitivity, and the abscissa represents 1-specificity; the reference line is the diagonal line of the coordinate system; the curves include (LH1 (Hcy+TC+TG+HDL-C+LDL-C), LH2 (Hcy+HDL-C+LDL-C), LH3 (Hcy+LDL-C), and LH4 (Hcy+LDL-C-HDL-C). LAA, Large Artery Atherosclerosis; Hcy, homocysteine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Hcy had the highest diagnostic efficacy (AUC = 0.822), followed by LDL-C (AUC = 0.818), while HDL-C, TC and TG had no obvious diagnostic efficacy (AUC < 0.7). Among the combined index, LH4 (Hcy+LDL-C-HDL-C) achieved the best diagnostic performance (AUC = 0.876, with a sensitivity of 84.6% and a specificity of 78.8%), which was superior to other combination schemes ($P < 0.05$). The diagnostic efficacy of Hcy combined with all blood lipid indexes (AUC = 0.850) was slightly lower than that of Hcy+LDL-C-HDL-C. See **Tables 3, 4** and **Figures 1, 2** for details.

Diagnostic efficiency for other subtypes

Taking CE subtype and SAO subtype as the positive group and the other four subtypes as the negative group, results showed that among the single indexes, HDL-C had the highest diagnostic efficacy (AUC = 0.706) for CE and SAO (AUC = 0.744), while Hcy, LDL-C, TC and TG had no obvious diagnostic efficacy (AUC < 0.7). See **Figure 3** for details.

Construction and validation of prediction model

(1) Model construction: Hcy, LDL-C and HDL-C were included in Logistic regression to construct a prediction model

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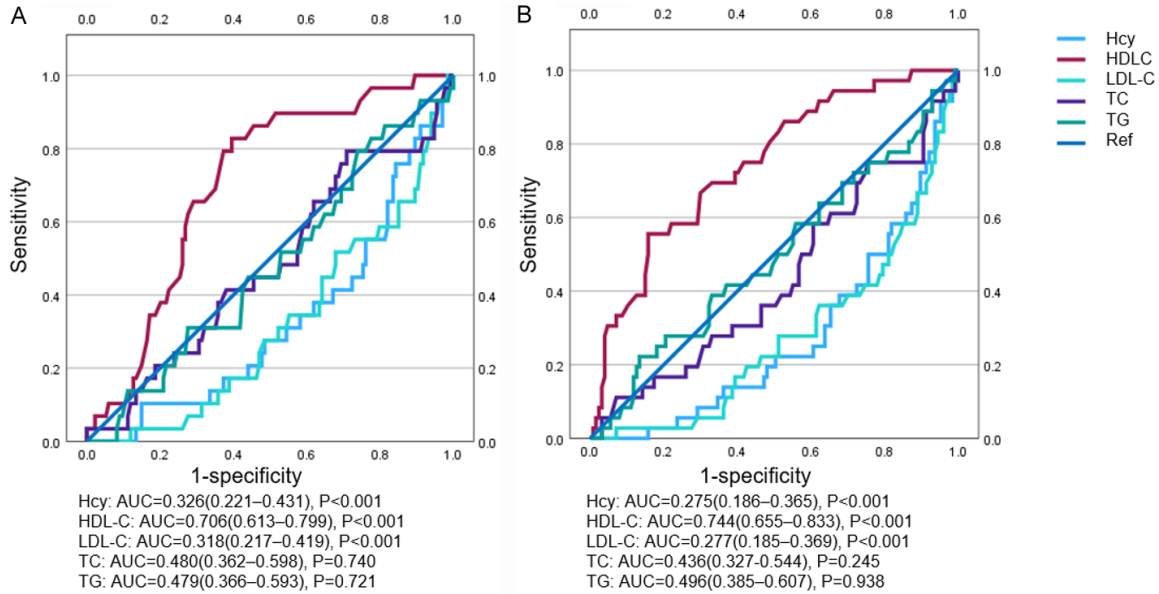


Figure 3. ROC curves of single index for distinguishing CE subtype (A) and SAO subtype (B) from other subtypes. Note: The ordinate represents sensitivity, and the abscissa represents 1-specificity; the reference line is the diagonal line of the coordinate system; the curves include Hcy, HDL-C, LDL-C, TC, and TG. CE, Cardioembolism; SAO, Small Artery Occlusion; Hcy, homocysteine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

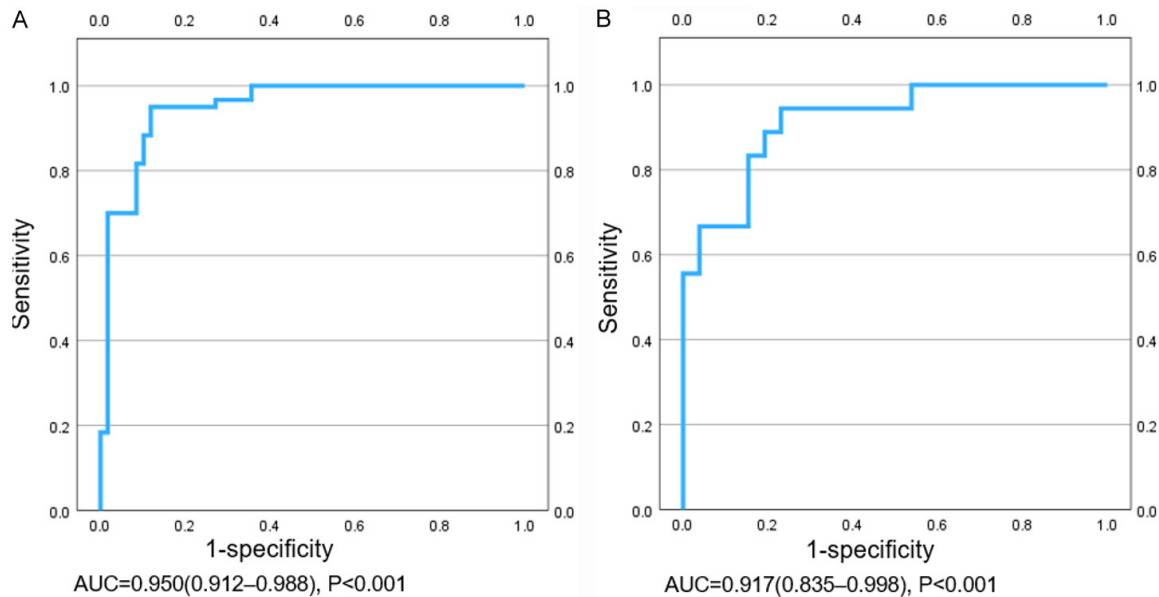


Figure 4. ROC curves of combination index for distinguishing LAA subtype from other subtypes. Training set (A), Validation set (B). Note: The ordinate represents sensitivity, and the abscissa represents 1-specificity. LAA, Large Artery Atherosclerosis.

for LAA classification, $P = 1/[1 + \exp(-(-3.192 + 0.398 \times \text{Hcy} + 1.336 \times \text{LDL-C} - 7.392 \times \text{HDL-C}))]$. All three indicators were independent predictors of LAA. Collinearity diagnostics confirmed no multicollinearity among Hcy, LDL-C, and HDL-C (VIF < 5 for all variables).

(2) Internal validation: The cohort was divided into training set (119 cases) and validation set (44 cases) at a ratio of 7:3, with training set AUC = 0.950, and validation set AUC = 0.917. The mean AUC of 5-fold cross-validation was 0.956 (95% CI: 0.934–0.977), indicating good

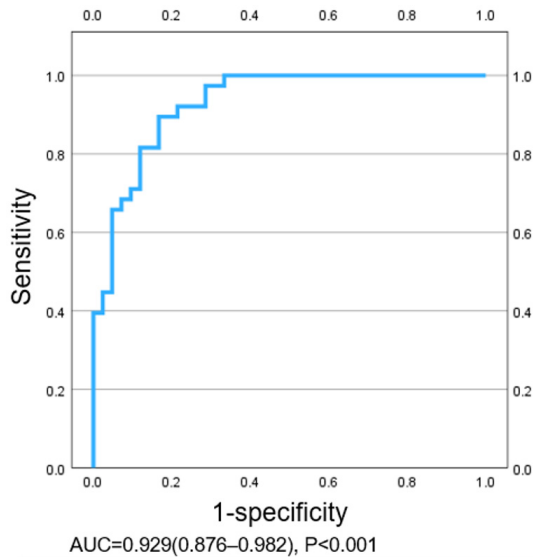


Figure 5. External validation set ROC curve of combination index for distinguishing LAA subtype from other subtypes. Note: The ordinate represents sensitivity, and the abscissa represents 1-specificity. LAA, Large Artery Atherosclerosis.

model fitting without obvious overfitting. See **Figure 4** for details.

(3) External validation: There were 80 cases in the external validation cohort, including 38 cases of LAA and 42 cases of non-LAA. AUC = 0.929 (95% CI: 0.876, 0.982). Sensitivity = 89.5%, specificity = 83.3%, accuracy = 86.3%, Youden index = 0.728. The model maintained high differentiation efficiency in the independent external cohort with good generalization ability. See **Figure 5** for details.

Discussion

Cerebral infarction in young and middle-aged individuals is characterized by complex etiology and diverse vascular subtypes, among which LAA is the most common one and is closely associated with atherosclerotic progression [20]. Accurate subtype identification helps clinicians clarify pathogenesis, select appropriate treatments, and reduce recurrence and disability rates. At present, imaging examination is the main method for vascular subtyping, but it is limited by high cost, invasiveness, and limited availability in primary hospitals. Therefore, developing a simple, rapid, and low-cost laboratory detection panel has important clinical value.

Elevated Hcy promotes cerebrovascular injury through multiple mechanisms, including endothelial damage [21, 22], enhanced lipid peroxidation [23-25], and accelerated vascular smooth muscle cell proliferation [26-28], all of which aggravate atherosclerosis. Our results demonstrate that Hcy level is significantly higher in LAA patients, which is consistent with previous research findings [29].

For lipid profiles, LDL-C exerts pro-atherogenic effects, while HDL-C has anti-atherogenic properties [30]. In this study, LAA patients showed significantly increased LDL-C and decreased HDL-C, whereas TC and TG showed no significant differential value among subtypes. This may be related to the characteristic lipid metabolism disorders caused by lifestyle factors in young and middle-aged populations.

ROC analysis indicated that combined detection of Hcy, LDL-C, and HDL-C significantly improved diagnostic accuracy compared with single indicators. Including TC and TG in the diagnostic panel did not yield additional improvements in diagnostic accuracy. This finding demonstrates that the streamlined three-indicator combination is sufficient for clinical screening purposes, while also reducing laboratory costs and alleviating patient burden. Notably, HDL-C functioned more effectively as a negative predictor in the combined model, which reinforces its role in protecting against atherosclerosis.

To our knowledge, this is the first study to develop and validate a Logistic prediction model for identifying the LAA subtype in young, middle-aged, and pre-elderly cerebral infarction patients, using Hcy, LDL-C, and HDL-C as core indicators. The model relies solely on routine biochemical markers, featuring low cost and simple operation; it provides quantitative results to facilitate rapid clinical decision-making, and has been proven to possess excellent stability and generalization ability through rigorous validation procedures.

Limitations of this study include its retrospective design, relatively small single-center sample size, and potential selection bias. The age range (18-65 years) is relatively broad, which differs from the standard definition of young and middle-aged cerebral infarction (18-45 years). The sample size of the OE subtype is

small, which may affect the reliability of related results. In addition, the model calibration curve and decision curve analysis (DCA) were not drawn in this study. Furthermore, lifestyle, family history, and other potential confounders were not adjusted. Future large-scale, multi-center, and prospective studies are needed to supplement calibration curve analysis and DCA, and to further verify and optimize the model.

Conclusion

The combined use of homocysteine, LDL-C, and HDL-C exhibits high diagnostic value for distinguishing the LAA vascular subtype in young, middle-aged, and pre-elderly cerebral infarction patients. The established Logistic prediction model is stable, reliable, and feasible for clinical application. It can serve as a rapid screening tool for vascular subtype classification, and provide support for etiological diagnosis, risk assessment, and the personalized treatment strategies.

Acknowledgements

This work was supported by National Science and Technology Major Project for Key Research on Prevention and Treatment of Cancer, Cardiovascular and Cerebrovascular Diseases, Respiratory Diseases, and Metabolic Diseases (Grant No. 2024ZD0532601), National Key R&D Program of China, Special Project for Diagnosis and Treatment Equipment and Biomedical Materials (Grant No. 2025YFC2422604), Beijing Municipal Science and Technology Commission, Special Project for Cultivation of Innovative Pharmaceutical Varieties and Platforms (Grant No. Z241100009024028) and Beijing Medical and Health Technology Promotion Center, Youpu Plan Empowerment Special Project (Grant No. YC202401QX0426).

Disclosure of conflict of interest

None.

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