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Association between the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and cognitive impairment in patients with acute mild ischemic stroke

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Abstract

Background The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) is a recently developed lipid parameter, but there are insufficient studies exploring its relationship with early cognitive impairment in patients with acute mild stroke. This study aims to determine the potential association between NHHR and early cognitive impairment in patients with acute mild stroke. By collecting data from patients with acute minor ischemic stroke in hospital, we will analyze the relationship between NHHR and cognitive function in these patients.

Methods This study enrolled 817 acute ischemic stroke (AIS) patients (NIHSS ≤ 5), Cognitive function was assessed using Mini-Mental State Examination (MMSE) within 2 weeks, with cognitive impairment defined by education-stratified thresholds. Statistical analysis of the baseline was performed. Multivariate logistic regression was performed to analyze the association between NHHR and cognitive impairment, and Receiver Operating Characteristic Curve (ROC) analysis were performed to evaluate the predictive value.

Results Patients were classified into cognitive impairment group ($n = 473$) and normal cognition group ($n = 344$). NHHR in the cognitive impairment group was significantly higher than that in the normal group (3.24 ± 1.63 vs. 3.02 ± 1.43, $P = 0.046$). There were significant differences in age and education level. There was a dose–response relationship between NHHR quartiles and the incidence of cognitive impairment (trend test $P = 0.021$). Multivariate regression analysis showed that for each unit increase in NHHR, the risk of cognitive impairment increases by 13.2% (OR = 1.13, 95% confidence interval 1.02–1.25, $P = 0.018$). The predictive model constructed by combining age and education level has an area under the ROC curve(AUC) of 0.71 (95% confidence interval 0.67–0.74).

Conclusions NHHR is an independent risk factor for early cognitive impairment in mild AIS patients. The NHHR-based model demonstrates moderate predictive accuracy, supporting its potential clinical utility.

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Keywords Non-high-density lipoprotein cholesterol to HDL-C ratio (NHHR), Cognitive impairment, Acute mild ischemic stroke, Dose–response relationship, Predictive modeling

Introduction

Ischemic stroke is a multifactorial disease characterized by high morbidity and disability rates, placing a significant burden on both patients and society [1]. Early cognitive impairment is commonly observed in patients with AIS and severely affects their quality of life and functional recovery [2, 3]. Multiple factors are associated with the occurrence of early cognitive impairment following AIS [4–7]. Research indicates that dyslipidemia is not only an independent risk factor for ischemic stroke but may also be one of the most significant among them [8, 9]. Dyslipidemia influences cognitive function in ischemic stroke patients by accelerating the progression of systemic atherosclerosis and is considered an important risk factor for cognitive impairment and even dementia [10, 11]. Previous lipid treatment guidelines have prioritized low-density lipoprotein cholesterol (LDL-C) as the primary target for stroke prevention and management [12–14]. Simultaneously, increasing evidence from studies and epidemiological investigations suggests that non-high-density lipoprotein cholesterol (NHDL-C) is more effective than LDL-C in predicting cardiovascular disease risk [15]. High-density lipoprotein cholesterol (HDL-C) possesses anti-inflammatory and antioxidant properties, which help regulate both innate and adaptive immune responses [16].

NHHR is an emerging composite indicator of atherosclerosis [17, 18]. Previous studies showed that NHHR exhibits superior predictive and diagnostic capabilities compared to traditional lipid parameters in assessing the risks of conditions, such as atherosclerosis, cardiovascular disease, non-alcoholic fatty liver disease, chronic kidney disease, insulin resistance, depression and metabolic syndrome [17, 19–22].

However, there have been no reports regarding the relationship between NHHR and cognitive function in patients with AIS. Existing studies [23] had primarily focused on single lipid markers, with limited exploration of composite parameters like NHHR in AIS cognitive outcomes. Therefore, we collected relevant data from our hospital to investigate the association between NHHR and acute cognitive impairment in patients with AIS, aiming to provide valuable reference.

Materials and methods

Study design and participants

This study included patients with AIS admitted to the Neurology Department of Liaocheng People's Hospital, China, between January 2023 and January 2025. All participants were first-ever stroke patients, diagnosed based on clinical criteria, neuroimaging (CT/MRI), and confirmation by two independent neurologists. The study protocol was approved by the Ethics Committee of Liaocheng People's Hospital (Approval No: 2024019). Because it was a retrospective study, written informed consent was not obtained from participants.

Data collection

Demographic data (age, sex, education level), lifestyle behaviors (smoking, alcohol consumption), and comorbidities (hypertension, diabetes, coronary heart disease (CHD)) were systematically recorded. All participants underwent blood tests (hematologic, hepatic, renal, lipid, glycemic, thyroid, and vitamin B12 profiles), cranial CT or MRI, and neuropsychological assessments.

Inclusion and exclusion criteria

Inclusion criteria:

1. Age > 18 years;
2. Diagnosis of acute ischemic stroke according to the China cerebral vascular disease guidelines [24], confirmed by two experienced neurologists through computed tomography (CT) and/or magnetic resonance imaging (MRI); first diagnosis of cerebral infarction; within 7 days of onset;
3. NIHSS ≤ 5 on admission, defined as mild ischemic stroke;
4. completed neuroimaging, laboratory tests, and cognitive assessments.

Exclusion criteria:

1. Consciousness disorders, severe aphasia, or motor deficits precluding cognitive testing;
2. History of cognitive impairment or psychiatric disorders;
3. Severe cardiac, pulmonary, hepatic, renal, endocrine, hematologic, or connective tissue diseases;

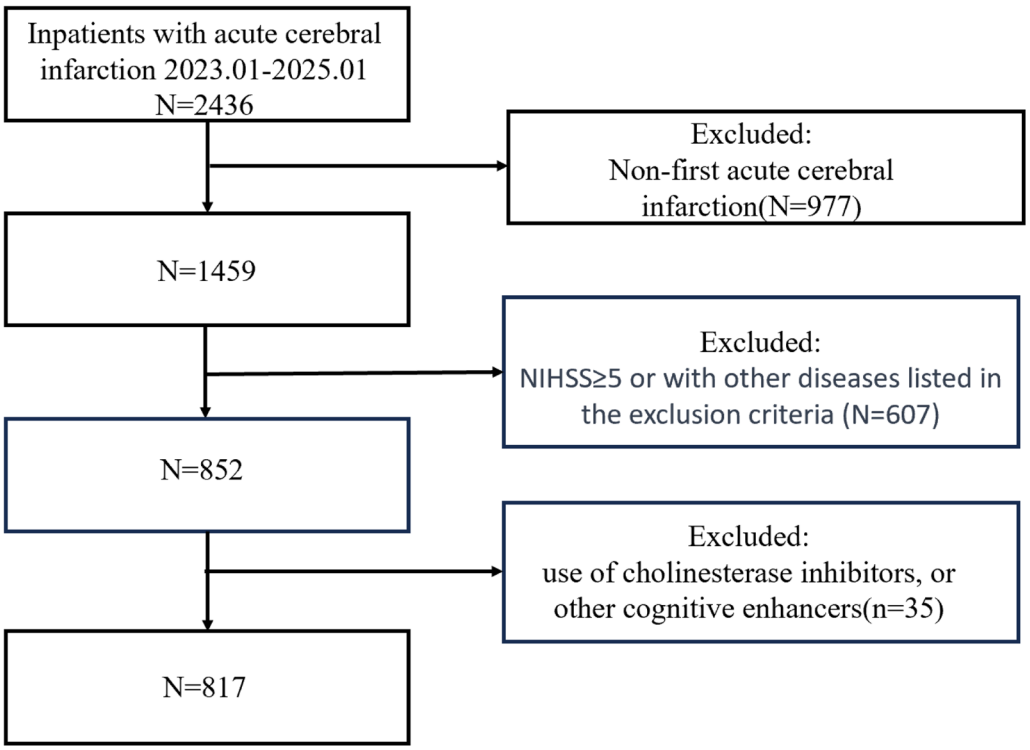

Fig. 1 Flow chart of the study participants

4. Use of cognitive-enhancing drugs within 3 months prior to enrollment.

According to the above criteria, a total of 817 patients were included. The screening process is shown in Fig. 1.

Cognitive function assessment

Cognitive function was evaluated within 2 weeks of acute cerebral infarction, using the MMSE, with Montreal Cognitive Assessment (MoCA) as a supplementary assessment. The total score of the MMSE is 30 points. In this study, < 18 was used to define cognitive impairment for participants who didn't receive any formal education, < 21 for participants who received 6 years of education or less, and < 25 for participants who received more than 6 years of education [25]. Specifically, for illiterate patients, oral testing was used during the assessment, and the results were culturally adjusted.

Assessment of NHHR

NHHR was used as an observational indicator and was calculated according to the method established in previous research [26]. NHHR was calculated as (total cholesterol—HDL-C)/HDL-C.

Statistical analysis

R version 4.2.0 was applied for all analyses, and statistical significance was defined as $P < 0.05$. Data normality was assessed using Shapiro–Wilk tests ($P > 0.05$), with normally distributed variables expressed as mean ± standard deviation. Categorical variables were analyzed using chi-square tests. Multivariate logistic regression analysis was performed to evaluate the risk factors of cognitive impairment, and the Cochran–Armitage trend test was used to assess dose–response relationships between NHHR quartiles. The ROC curve is used to assess the clinical applicability of predictive models.

Normally distributed data were presented as mean ± standard deviation.

Results

Characteristics of participants

A total of 817 patients with AIS were included in this study. 473 (57.9%) patients were identified as having cognitive impairment based on MMSE criteria. As shown in Table 1, the cognitive impairment group was significantly older than the control group (66.12 ± 9.62 vs. 59.54 ± 9.77 years, $P < 0.001$), and exhibited marked disparities in educational attainment ($P < 0.001$). Specifically, illiteracy rates were higher in the cognitive impairment group

Table 1 Comparison of baseline data of the two group patients

	Normal group ($n=344$)	Cognitive impairment group ($n=473$)	*P*
Age (years)	59.54 ± 9.77	66.12 ± 9.62	< 0.001*
Gender (male)	234 (68%)	312 (65%)	0.286
Education level			< 0.001*
Illiterate	40 (11.6%)	130 (27.5%)	
Elementary school	112 (32.6%)	141 (29.8%)	
Secondary education or higher	192 (55.8%)	202 (42.7%)	
BMI	25.89 ± 3.54	25.35 ± 3.67	0.31
Smoke	80 (23.26%)	106 (22.41%)	0.156
Drink	73 (21.22%)	96 (20.30%)	0.867
Hypertension	201 (58.43%)	309 (65.32%)	0.573
Diabetes	95 (27.61%)	119 (25.20%)	0.479
CHD	24 (6.98%)	44 (9.3%)	0.289

* means that there is a statistically significant difference between the two group. Normal group refers to patients with normal cognitive function; the cognitive impairment group represents the group of patients with cognitive impairment

Table 2 Comparison of NHHR between the two groups

	Normal group ($n=344$)	Cognitive impairment group ($n=473$)	*P*
HDL-C (mmol/L)	1.19 ± 0.34	1.161 ± 0.34	0.210
Total cholesterol (mmol/L)	4.50 ± 1.18	4.59 ± 1.18	0.279
NHHR	3.02 ± 1.43	3.24 ± 1.63	0.046*

* means a statistically significant difference compared to the Normal group, $P<0.05$

Table 3 NHHR quartiles and cognitive impairment

NHHR quartile	Total	Cognitive impairment	Cognitive impairment rate
Q1 (0.544–2.072)	205	106	51.7%
Q2 (2.072–2.904)	204	109	53.4%
Q 3 (2.904–3.918)	204	128	62.7%
Q 4 (3.918–15.591)	204	130	63.7%

Table 4 Multivariate logistic regression analysis

	β	OR	95% confidence interval	*P*
NHHR	0.127	1.13	1.12–1.25	0.018
Age	0.065	1.07	1.05–1.08	< 0.001
Education	−0.285	0.75	0.61–0.91	0.003

(27.5% vs. 11.6%), while fewer patients in this group had middle school or higher education (42.7% vs. 55.8%). No significant differences were observed between the two groups in gender distribution, BMI, smoking/alcohol history, or baseline comorbidities (hypertension, diabetes, coronary heart disease).The characteristics of participants are shown in Table 1.

Comparison of NHHR between the two groups

NHHR was significantly elevated in the cognitive impairment group compared to controls (3.24 ± 1.63 vs. 3.02 ± 1.43, $P=0.046$) (Table 2). Notably, although no significant intergroup differences were detected in HDL-C (1.16 ± 0.34 vs. 1.19 ± 0.34 mmol/L, $P=0.210$) or total cholesterol levels (4.59 ± 1.18 vs. 4.50 ± 1.18 mmol/L, $P=0.279$), NHHR emerged as a distinguishing factor.

Stratified analysis by NHHR quartiles

All patients were stratified by NHHR into quartiles, and the incidence of cognitive impairment was calculated in each stratum, along with conducting the Cochran–Armitage trend test. There was a significant dose–response relationship between the incidence of cognitive impairment and NHHR, with rates increasing from 51.7% in Q1 to 63.7% in Q4 (Cochran–Armitage trend test, $Z=2.31$, $P=0.021$). This trend underscored a direct association between elevated NHHR and cognitive impairment risk. The results were displayed in Table 3.

Association between NHHR and cognitive impairment

Multivariate logistic regression adjusted for confounders revealed that each unit increase in NHHR was independently associated with a 13.2% elevated risk of cognitive impairment (OR = 1.13, 95% confidence interval 1.02–1.25, $P=0.018$). Age (OR = 1.07 per year, 95% confidence

interval 1.05–1.08, $P < 0.001$) and lower educational attainment (OR = 0.75 for higher education, 95% confidence interval 0.61–0.91, $P = 0.003$) were also significant predictors of cognitive impairment (shown in Table 4).

Predictive model performance

Based on the results of the logistic regression analysis, we identified three key variables, age、education level and NHHR, to collaboratively construct the final predictive model. This model demonstrated moderate predictive performance (Fig. 2), with an AUC) of 0.71 (95% confidence interval 0.67–0.74), a sensitivity of 63.85%, and a specificity of 70.93%, at an optimal cutoff value of 0.5887 (shown in Fig. 2). These findings suggest that the model has potential as a clinical decision support tool.

Discussion

In this cross-sectional study involving 817 patients with AIS (NIHSS ≤5), we found that NHHR was independently associated with early cognitive impairment in patients with mild AIS. After thorough adjustments for age, education level, and vascular risk factors, each unit increase in NHHR was associated with a 13.2% increased risk of cognitive impairment. Notably, the significant dose–response relationship observed between the NHHR quartiles further strengthened the biological gradient of this association. These findings extend previous research on lipid–cognition relationships by introducing NHHR—a novel composite lipid parameter—as a superior predictor compared to traditional single-marker approaches.

Lipid metabolism abnormalities were common among patients with AIS and were closely related to the occurrence and progression of cerebral infarction [27–29].

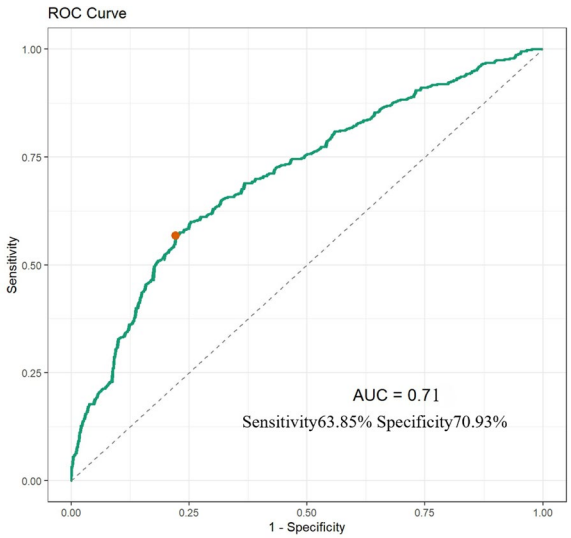

Fig. 2 ROC curve of the predictive model

NHHR demonstrated superior predictive ability compared to traditional lipid parameters. Previous studies [29] have mainly focused on single lipid indicators, such as LDL-C and non-HDL-C; however, NHHR's dual incorporation of pro-atherogenic (non-HDL-C) and anti-atherogenic (HDL-C) components better captures lipid-driven neurovascular injury. This mechanistic advantage is exemplified by our key observation: despite comparable HDL-C and total cholesterol levels between groups, NHHR remained significantly elevated in cognitive impairment patients (3.24 vs. 3.02, $P = 0.046$). This phenomenon was consistent with previous large-scale cohort studies [17, 30, 31], which indicate that NHHR was superior to single lipid markers in predicting atherosclerosis-related diseases.

The impact of NHHR on cognitive function may be associated with the following mechanisms. The atherogenic lipid burden, represented by non-HDL-C, which includes LDL, VLDL, and remnant cholesterol, could induce the production of reactive oxygen species and activate the NF-κB/NLRP3 pathways, lead to oxidative stress response, promoting beta-amyloid (Aβ) deposition [32]; In previous animal studies, lipid-modifying therapies were able to reduce the expression of proinflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukins IL-1β and IL-6 in the hippocampus, and also affected the expression of an oxidative stress-induced gene (heme oxygenase-1) [33]. Decreased functionality of HDL-C affected Aβ clearance [34]. Elevated NHHR caused the release of inflammatory factors, activating microglia and triggering neuroinflammation. Neuropathological studies further support this dual mechanism, demonstrating that a deficiency of HDL-C exacerbates blood–brain barrier permeability through the activation of MMP-9 [35], while elevated non-HDL-C accelerates β-amyloid deposition via APOE4-mediated pathways [32]. Some surface receptors of various lipoproteins were related to the processing of amyloid precursor protein into Aβ [36].

Notably, our dose–response result indicated that the risk of cognitive impairment ranged from 51.7 to 63.7% across the NHHR quartiles, suggesting that higher NHHR is associated with early cognitive dysfunction (HR = 1.21 for each SD increase). It was important to highlight the population specificity of this study, we selected patients with acute mild stroke, a high-risk subgroup that had been underestimated in previous lipid-cognition research. In such populations, early cognitive changes can easily be overlooked, significantly impacting other aspects of patient rehabilitation and compliance with secondary prevention. Our measurements of NHHR during the acute phase (within 14 day post-stroke) could capture lipid dynamics most relevant to early cognitive

impairment. These advancements addressed a critical gap in the assessment of early cognitive impairment following cerebral infarction.

In this study, the definition of cognitive impairment incorporated educational background for threshold stratification. MMSE and MoCA were commonly used to assess early cognitive impairment following an acute stroke [37]. In addition, some studies used another definition of cognitive impairment (a uniform MMSE cutoff of < 24) [37], which had certain limitations [38].

Our predictive model (AUC = 0.71) enabled rapid cognitive risk screening at admission using routine lipid assessments. High-risk patients could receive early cognitive training combined with intensified lipid treatment interventions.

Although this study provides new insights into the role of NHHR in early cognitive impairment, several key limitations warrant cautious interpretation. First, the study was a cross-sectional observation, preventing causal inference. It remained unclear whether elevated NHHR was a cause of cognitive decline or a consequence of stroke-induced metabolic dysregulation. Future longitudinal studies were needed to clarify this temporal relationship. In addition, the study was single-center, and the regional nature of the sample could affect the generalizability of the results, as indicated by the significant differences in mean age and illiteracy rate compared to [39, 40]. We focused on first-time AIS patients and excluded those with a history of previous strokes, which, while reducing the impact of factors on cognition, limited the generalizability of the results. Though hypertension prevalence did not reach statistical significance, the 6.9% absolute difference may still hold clinical relevance in larger cohorts. Future research could include larger sample sizes, a wider range of risk factors, and conduct multicenter and longitudinal studies to observe the relationship between changes in NHHR over time and cognitive function.

The potential of NHHR as a therapeutic target is worth exploring. First, NHHR was associated with the risk of various diseases, including cardiovascular disease and metabolic syndrome [17, 41, 42], which were often closely related to cognitive dysfunction. Targeting NHHR with lipid-modifying therapies may bring about the following positive effects. Lipid-modifying therapies aimed at NHHR could optimize lipid levels by reducing NHDL-C and increasing HDL-C. Such changes could help alleviate and oxidative stress [43], thereby improving blood flow and nutritional status in the brain, positively affecting cognitive function; Research indicated that dyslipidemia could lead to neuroinflammation, which was associated with cognitive impairment. By improving NHHR levels, it could help reduce the release of inflammatory factors and activate microglia, thus inhibiting neuroinflammation and enhancing cognitive function [33]; Changes in NHHR may be linked to the generation and clearance of Aβ, optimizing lipid levels might enhance Aβ clearance, reducing its accumulation in the brain and lowering the risk of dementia, such as Alzheimer's disease [44]; finally, targeting NHHR could lead to overall improvements in metabolic status, not just limited to changes in lipid levels, but also potentially affecting insulin sensitivity and inflammatory responses [41].Such comprehensive metabolic improvement could enhance patients'cognitive abilities and brain function. Therefore, lipid-modifying therapies targeting NHHR have the potential to become a new strategy for improving cognitive outcomes. However, this area requires more clinical trials and research to validate its efficacy and safety and to determine the best treatment protocols. Future explorations may provide new directions and hope for the treatment of cognitive disorders.

Conclusion

Our findings indicate a significant association between elevated NHHR and cognitive impairment in patients with acute mild ischemic stroke. The results underscore the importance of NHHR as a potential biomarker for cognitive decline in this patient population. Furthermore, the identification of age and educational attainment as additional risk factors highlights the complexity of cognitive impairment and the need for comprehensive assessment strategies in clinical practice. The predictive model we developed demonstrates moderate accuracy, providing a new direction for investigating treatment for cognitive impairment after AIS.

Abbreviations

NHHR	Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio
AIS	Acute ischemic stroke
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
LDL-C	Low-density lipoprotein cholesterol
HDL	High-density lipoprotein cholesterol
Non HDL-C	Non-high-density lipoprotein cholesterol
ROC Curve	Receiver Operating Characteristic Curve
AUC	Area under the ROC curve
TC	Cholesterol
BMI	Body mass index
CHD	Coronary heart disease

Author contributions

HW: writing—original draft, writing—review & editing, funding acquisition; JW: writing—original draft, writing—review & editing; DF: data curation, writing—review & editing;LW: writing—original draft, writing—review & editing; JZ: writing—original draft, writing—review & editing.All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All procedures involving human participants in this study complied with the ethical standards set by relevant institutions and/or national research committees, as well as the principles outlined in the Helsinki Declaration of 1964 and its later amendments or similar ethical standards. The research had obtained approval from the Ethics Review Committee of Liaocheng People's Hospital [approval no: 2024019]. The data sets generated and/or analyzed during the current study are available from the corresponding author.

Competing interests
The authors declare no competing interests.

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