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Association of novel lipid indices with the white matter hyperintensities in cerebral small vessel disease: a cross-sectional study

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Abstract

Background Lipids are associated with atherosclerosis, and novel lipid indices have been recently identified to be closely linked to cardiovascular diseases. This study explored the association between four novel lipid indices and the white matter hyperintensities (WMHs) in patients diagnosed with cerebral small vessel disease (CSVD).

Methods Between January 2023 and February 2024, 219 patients were recruited, including 165 patients with CSVD WMHs and 54 healthy controls. Based on WMHs severity, patients with CSVD were categorised into mild and moderate-to-severe cohorts using the Fazekas rating scale. The plasma levels of four novel lipid indices (low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio [LDL-C/HDL-C], triglyceride/high-density lipoprotein cholesterol ratio [TG/HDL-C], total cholesterol/high-density lipoprotein cholesterol ratio [TC/HDL-C], and non-high-density lipoprotein cholesterol [Non-HDL-C]), were rigorously monitored in the enrolled patients.

Results A total of 165 patients with CSVD WMHs were enrolled, including 94 with mild WMHs and 71 with moderate-to-severe WMHs. Multivariable logistic regression analysis revealed that LDL-C/HDL-C, TG/HDL-C, TC/HDL-C, and Non-HDL-C levels were significantly associated with WMHs (all $P \leq 0.001$). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of plasma lipid levels for WMHs in patients with CSVD. The novel lipid indicators outperformed traditional lipid indicators in assessing the diagnostic capability of WMHs. The combined index of the four blood lipid indices had an optimal cutoff point (OCP) of 0.489, with 88.3% sensitivity and 60.6% specificity. The area under the curve (AUC) is 0.800 (95% confidence interval [CI], 0.731–0.869; $P < 0.001$). Compared with males (OR = 1.126, 95% CI = 0.779–1.628), females (OR = 2.484, 95% CI = 1.398–4.414; P for interaction = 0.023) had a higher risk of developing WMHs.

Conclusion This study demonstrates a significant association between four novel lipid indices and the cerebral WMHs in CSVD, highlighting the potential of these markers as novel plasma biomarkers and predictive indicators for assessing CSVD progression and guiding clinical management.

Keywords Blood lipid, Cerebral small vessel disease (CSVD), Novel lipid indices, White matter hyperintensities (WMHs)

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Background

Cerebral small vessel disease (CSVD) is a prevalent cerebrovascular disorder, particularly affecting middle-aged and older adults. It constitutes a primary cause of vascular cognitive impairment and potentially contributes to up to 45% of cases of vascular dementia or mixed dementia with Alzheimer's disease [1, 2]. The clinical presentation of CSVD exhibit significant heterogeneity, including gait disorders, neuropsychiatric symptoms, speech and motor impairments, and urinary incontinence, all of which significantly affect the quality of life for both patients and their families [1, 2]. The onset of the disease is insidious in most patients, making neuroimaging crucial for diagnosing CSVD and monitoring its progression. The primary neuroimaging features of CSVD include vascular-origin lacunes (LI), white matter hyperintensities (WMHs), cortical microinfarcts (CMB), enlarged perivascular spaces (EPVS), microbleeds, and brain atrophy [3]. Brain WMHs associated with CSVD are notably common among middle-aged and older populations, affecting approximately 11–15% of these individuals [4]. The prevalence of these lesions escalates with advancing age, with rates soaring to 90% among individuals aged 80 and older [4]. Previous studies have indicated that the progression of WMHs associated with CSVD is closely linked to adverse functional outcomes, including cognitive decline, gait abnormalities, and increased risk of stroke [5]. Therefore, the identification of rapid and effective biomarkers in the early stages of CSVD to predict the extent and likelihood of WMHs development is crucial for its prevention.

In recent years, numerous researchers have used animal models and conducted clinical studies to investigate the pathophysiological mechanisms underlying CSVD. Atherosclerosis of the blood vessels serves as a crucial basis for inducing endothelial dysfunction of cerebral blood vessels, which can further lead to the occurrence of CSVD by inducing neuroinflammation and blood-brain barrier (BBB) damage [6]. Dyslipidaemia is a crucial pathogenic factor in the progression of atherosclerosis.

Novel lipid indices have attracted widespread attention with the evolution of research techniques. Past epidemiological studies and clinical trials have emphasised that novel lipid indices may have more predictive value in promoting the occurrence of atherosclerosis and advancement of cardiovascular and cerebrovascular disorders than traditional lipid indicators such as low-density lipoprotein cholesterol (LDL-C) [7, 8].Despite extensive research on the underlying mechanisms of CSVD, the specific role of these novel lipid indices in the disease remains unclear. This study has investigated the association between novel lipid indices and CSVD-related WMHs, with an emphasis on ratios such as low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio (LDL-C/HDL-C), triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-C), total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDL-C), and non-high-density lipoprotein cholesterol (Non-HDL-C). The primary aim is to elucidate the potential mechanisms underlying the significance of novel lipid indices associated with the onset of CSVD, ultimately contributing to the advancement of novel clinical strategies for early disease detection, prompt treatment, and effective prevention.

Materials and methods

Study subjects

The study included non-acute stroke patients diagnosed with CSVD and exhibiting Magnetic resonance imaging (MRI)-WMH imaging markers, as well as healthy subjects who visited the Neurology Department at the First Affiliated Hospital of Anhui University of Science and Technology. (Fig. 1)

WMHs group patients Selection Criteria:

1. Age ≥ 40 years old;
2. Underwent cranial MRI examination and met the imaging diagnostic criteria for CSVD (Primarily characterized by WMHs with vascular origin, with or without accompanying lacunar infarcts or perivascular spaces.) [3].
3. The MRI exhibits: mild WMHs (Fazekas score for deep white matter = 1 or periventricular = 2); moderate to severe WMHs (Fazekas score for deep white matter > 1 or periventricular > 2);
4. Completed blood and plasma lipid tests;
5. Patients with impaired or failing important organ functions, such as heart, lung, liver, kidney, etc.;

WMHs group patients Exclusion Criteria:

1. Acute stroke patients;
2. Individuals with WMHs caused by metabolic, immune, infectious, hypoxic, toxic, genetic, or other factors;.
3. Patients with malignant tumours and severe neurological impairments such as visual, auditory, or comprehension impairments;
4. Intracranial or extracranial arterial occlusion or stenosis > 50%;
5. Patients with impaired or failing important organ functions, such as heart, lung, liver, kidney, etc.
6. Individuals unable to undergo cranial MRI scanning.
7. Patients regularly taking lipid-lowering drugs (e.g., atorvastatin, rosuvastatin) before blood lipid test.

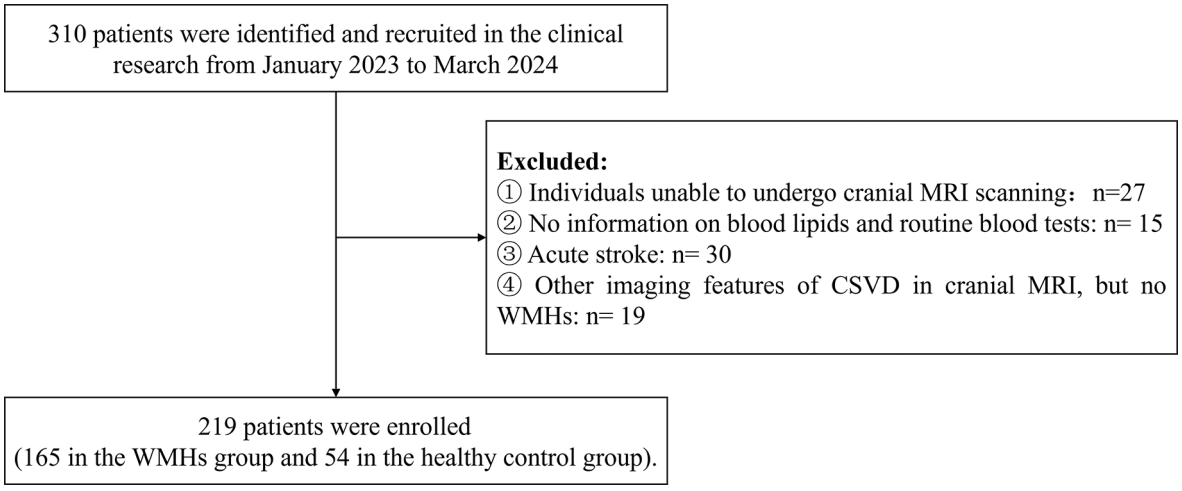

Fig. 1 Study recruitment profile

8. Patients with metabolic diseases that affect blood lipids, such as thyroid diseases (e.g., hypothyroidism), kidney diseases (e.g., nephrotic syndrome), obesity, and liver diseases.

Control group patients Selection Criteria:

1. Members who visit the hospital concurrently with the WMHs group, are age-matched, and have signed the informed consent form;
2. Completion of relevant blood tests and cranial MRI examinations to confirm the absence of imaging manifestations of CSVD such as WMHs, LI, CMB, etc.

Control group patients Exclusion Criteria:

1. Individuals with a previous medical history of cerebrovascular diseases, neurological diseases, cardiovascular diseases, etc.;
2. Individuals unable to undergo cranial MRI scanning;
3. Patients regularly taking lipid-lowering drugs before blood lipid test;
4. Patients with metabolic diseases that affect blood lipids.

Gathering of demographic and clinical information

Key demographic information, including age and sex, were collected for all enrolled patients, along with vascular risk factors such as diabetes, hypertension, prior heart disease, smoking, and alcohol history. Clinical variables recorded at admission included white blood cell count (WBC), red blood cell count (RBC), haemoglobin (HB), platelet count (PLT), neutrophil percentage (NEUT%), lymphocyte percentage (LY%), glucose (GLU), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), homocysteine (HCY), fibrinogen (FIB), C-reactive protein (CRP), acetylglucosaminidase (NAG), cystatin C (Cys-C), total cholesterol (TC), total triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A (ApoA), and apolipoprotein B (ApoB). The focus was novel lipid indices (LDL-C/HDL-C, TG/HDL-C, TC/HDL-C, and Non-HDL-C). The formula for Non-HDL-C=TC - (HDL-C) [9].

Imaging evaluation

Magnetic resonance imaging (MRI) examinations utilised either a 1.5T GE HDxt or a 3.0T GE DISCOVERY MR750w system, both of which were sourced from the United States. The imaging sequences included axial T1-weighted, T2-weighted, Fluid-Attenuated Inversion Recovery (FLAIR), and diffusion-weighted imaging (DWI). Magnetic Resonance Angiography (MRA) was performed to evaluate the intracranial arterial vasculature precisely. According to the CSVD diagnostic criteria [3], the head MRI results of patients in the WMHs group were recorded as follows: (1) WMHs imaging manifestations: On MRI images, WMHs appeared as isosignals or low signals on T1 sequences and as high signals on T2WI and FLAIR sequences. (2) LI imaging manifestations: Liquid-filled cystic lacunae, with diameters ranging from 3 to 15 mm, were observed as circular or oval areas surrounded by high signal intensity on FLAIR images. (3) EPVS imaging manifestations: Enlarged cerebrospinal fluid-filled spaces accompanying small cerebral vessels, observed in certain situations, appear as low signals on T1 and FLAIR sequences, and as high signals on T2 sequences from MRI. These spaces are commonly

found in the central semiovale and the basal ganglia. The Fazekas scale was employed to precisely grade periventricular and deep WMHs, guaranteeing a professional and unerring assessment [10]. Based on the severity of WMHs, patients in the WMHs group were further classified into two distinct groups: the mild WMHs group (Fazekas scores 1–2) and the moderate-to-severe WMHs group (Fazekas scores 3–6). Imaging diagnosis and Fazekas scoring were jointly performed by two neurologists who had undergone unified training and had rich experience. When disagreements arose, further discussions were held to reach an agreement. If an agreement could not be reached through discussion, a third independent neurologist was introduced for the final adjudication.

Statistical analysis

Data were analysed using SPSS 26.0, and graphical representations were created using GraphPad Prism 9.5.0. Categorical data are presented as percentages and were statistically analysed using either the chi-square or Fisher's exact test. Statistically compared normal distribution variables using mean ± SD and t-test. For the non-normal data, the median (IQR) and Mann-Whitney U tests were used for the analysis. Logistic regression modelling was conducted across the three models to identify the predictors of WMHs in patients with CSVD. Three models were used: Model 1 (sex and age), Model 2 (Model 1 + hazards such as diabetes, coronary heart disease, hypertension, smoking, and alcohol consumption), and Model 3 (Model 2 refined with $P<0.01$ variables from univariable logistic regression). The associations between WMHs of different severity levels and novel lipid indicators were assessed using a logistic regression model. A subgroup analysis based on age, sex, and hypertension status was conducted to explore their impact on WMHs. Relationships were assessed using odds ratios (OR) and corresponding 95% CI. Additionally, Receiver operating characteristic curve (ROC) analysis was performed to establish the optimal cutoff point (OCP) for predicting WMHs in patients with CSVD using lipid indices. The accuracy of the test was evaluated by the area under the curve (AUC), with *P*-value cutoff of 0.05.

Results

Between January 2023 and March 2024, 310 participants were screened. After excluding 27 subjects without MRI, 15 who did not undergo blood lipid and routine blood tests, 30 patients with CSVD accompanied by acute stroke, and 19 patients with CSVD without imaging manifestations of WMHs, 165 patients with CSVD and 54 healthy controls were recruited. Among the patients with CSVD, 64 (38.79%) were women, and 101 (61.21%) were men. Based on the joint evaluation of cranial MRI by two neurologists (Cohen's kappa = 0.841), patients in the WMHs group were further categorised into two groups using the Fazekas scale: 94 patients (56.97%) with mild WMHs (Fazekas scores 1–2), and 71 patients (43.03%) with moderate-to-severe WMHs (Fazekas scores 3–6).

Comparisons between healthy controls and patients with CSVD revealed distinct variations in age ($P<0.001$), male proportion ($P=0.008$), and vascular predisposing factors such as smoking history ($P=0.012$), diabetes ($P=0.002$), and hypertension ($P<0.001$). In contrast to the control group, individuals with CSVD displayed considerably augmented levels of several laboratory parameters, including WBC ($P=0.002$), RBC ($P=0.014$), NEUT% ($P=0.021$), GLU ($P=0.001$), AST ($P=0.031$), ALP ($P=0.007$), urea nitrogen ($P=0.008$), Cr ($P=0.008$), UA ($P=0.008$), CRP ($P=0.004$), and others such as HCY, FIB, GGT, Cys-C and NAG (all $P<0.001$). Furthermore, lipid parameters, such as lipoprotein A, TG, TC, LDL (all $P<0.001$), and HDL ($P=0.002$), were remarkably elevated in patients with CSVD compared to those in the control group. Notably, patients with CSVD also exhibited markedly elevated LDL-C/HDL-C, TG/HDL-C, TC/HDL-C, and Non-HDL-C ratios (all $P<0.001$). (Table 1)

A comparative assessment of baseline characteristics among patients with CSVD revealed significant associations between WMHs severity and age ($P<0.001$), history of alcohol consumption ($P=0.020$), hypertension ($P=0.011$), diabetes ($P=0.005$), creatinine ($P=0.018$), homocysteine ($P=0.004$), FIB ($P<0.001$), and Cys-C levels ($P<0.001$). Additionally, significant associations were observed between elevated levels of conventional lipids (TC and LDL) and novel lipid indices (LDL-C/HDL-C, TG/HDL-C, TC/HDL-C, and Non-HDL-C), all of which were positively correlated with WMHs severity ($P\leq0.001$, except for TG/HDL-C at $P=0.010$). (Table 2)

A logistic regression model was used to evaluate the association between new lipid indices and WMHs. Even after adjusting for age, sex, vascular risk factors such as hypertension, coronary heart disease, diabetes, smoking, alcohol consumption history, and potential confounding factors such as creatinine, homocysteine, fibrinogen, and C-reactive protein levels, these new lipid indicators were still significantly associated with WMHs (all $P<0.05$). (Table 3) However, when a logistic regression model was used to explore the relationship between lipid indicators and the severity of WMHs, only HDL-C ($P=0.017$) and TG/HDL-C ($P=0.005$) were associated with the mild WMHs Group. However, after adjusting for potential confounding factors, TG (OR = 2.371, 95% CI = 1.023–5.494; $P=0.044$) and the TG/HDL-C ratio (OR = 2.371, 95% CI = 1.288–6.543; $P=0.010$) were associated with the mild WMHs Group. The remaining indicators were not associated with the WMH severity. (Table 4)

ROC analysis was used in order to verify the diagnostic capacity of blood lipid indices in evaluating patients with

Table 1 Demographic and clinical characteristics of the Control Group and enrolled CSVD patients

Variables	Control Group ($n=54$)	WMHs Group ($n=165$)	*P*-value
Demographic characteristics			
Age, median (IQR)	57.00 (51.75, 61.25)	64.00 (56.00, 74.00)	< 0.001
Sex, male (%)	22 (40.7%)	101 (61.2%)	0.008
Vascular risk factors			
Smoking, n (%)	7 (13.0%)	50 (30.3%)	0.012
Alcohol consumption, n (%)	7 (13.0%)	35 (21.2%)	0.181
Hypertension, n (%)	15 (27.8%)	110 (66.7%)	< 0.001
Diabetes, n (%)	3 (5.6%)	41 (24.8%)	0.002
Coronary heart disease, n (%)	2 (3.7%)	15 (9.1%)	0.322
Laboratory data			
WBC, 10^9/L, median (IQR)	5.27 (4.43, 5.99)	6.07 (4.91, 7.45)	0.002
RBC, 10^{12}/L, median (IQR)	4.39 (4.09, 4.63)	4.62 (4.18, 4.88)	0.014
HB, g/L, median (IQR)	128.50 (116.00, 139.50)	134.00 (125.00, 141.00)	0.055
PLT, 10^9/L, mean (SD)	219.37 ± 66.72	212.96 ± 50.09	0.518
NEUT %, median (IQR)	56.04 (51.68, 63.01)	61.40 (54.85, 67.70)	0.021
LY %, median (IQR)	32.50 (27.96, 38.24)	27.30 (22.90, 33.55)	0.002
GLU, mmol/L, median (IQR)	5.10 (4.68, 5.60)	5.50 (4.90, 6.80)	0.001
ALT, U/L, median (IQR)	19.00 (15.00, 27.25)	21.00 (16.50, 29.00)	0.173
AST, U/L, median (IQR)	21.00 (16.00, 26.25)	24.00 (19.00, 28.00)	0.031
ALP, U/L, median (IQR)	66.00 (56.75, 80.00)	77.00 (63.00, 88.00)	0.007
GGT, U/L, median (IQR)	21.50 (13.75, 35.75)	24.00 (17.00, 35.00)	0.211
BUN, mmol/L, median (IQR)	5.21 (4.25, 5.90)	5.60 (4.34, 7.00)	0.033
Cr, umol/L, median (IQR)	64.00 (53.68, 72.40)	77.00(65.50, 91.00)	< 0.001
UA, umol/L, median (IQR)	257.50 (205.75, 311.50)	307.00 (264.00, 362.50)	< 0.001
HCY,μmol/L, median (IQR)	8.98 (7.75, 10.93)	13.15 (10.50, 18.92)	< 0.001
FIB ,μg/ml, median (IQR)	2.63 (2.29, 3.12)	3.13 (2.76, 3.69)	< 0.001
CRP, mg/L, median (IQR)	0.05 (0.00, 1.000)	1.00 (0.00, 3.20)	0.004
NAG, U/L, median (IQR)	12.70 (10.68, 16.30)	17.00 (14.15, 20.55)	< 0.001
Cys-C, mg/L, median (IQR)	0.89 (0.80, 1.05)	1.19 (1.00, 1.39)	< 0.001
Lipid parameter			
TG, mmol/L, median (IQR)	0.98 (0.77, 1.15)	1.65 (1.14, 2.50)	< 0.001
TC, mmol/L, median (IQR)	3.72 (3.45, 4.05)	4.47 (3.59, 5.24)	< 0.001
LDL-C, mmol/L, median (IQR)	2.13 (1.83, 2.48)	3.19 (2.60, 3.81)	< 0.001
HDL-C, mmol/L, median (IQR)	1.13 (0.85, 1.29)	0.98 (0.81, 1.11)	0.002
Apo A, g/L, mean (SD)	1.23 ± 0.18	1.26 ± 0.25	0.361
Apo B, g/L, median (IQR)	0.83 (0.67, 0.91)	0.83 (0.67, 1.02)	0.750
LDL-C/HDL-C, median (IQR)	1.87 (1.45, 2.64)	3.25 (2.77, 4.09)	< 0.001
TG/HDL-C, median (IQR)	0.89 (0.74, 1.09)	1.78 (1.22, 2.71)	< 0.001
TC/HDL-C, median (IQR)	3.28 (2.88, 4.26)	4.49 (3.57, 5.71)	< 0.001
Non-HDL-C, median (IQR)	2.64 (2.30, 2.91)	3.43 (2.68, 4.18)	< 0.001

Abbreviations CSVD, Cerebral Small Vessel Disease; WBC, Leukocyte; RBC, Red Blood Cell; HB, Haemoglobin; PLT, Platelet Count; NEUT%, Neutrophil Percentage; LY%, Lymphocyte Percentage; GLU, Glucose; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; GGT, Gamma-glutamyl Transferase; BUN, Blood Urea Nitrogen; Cr, Creatinine; UA, Uric Acid; HCY, Homocysteine; FIB, Fibrinogen; CRP, C-reactive Protein; NAG, Acetylglucosaminidase; Cys-C, Cystatin C; TC, Total Cholesterol; TG, Total Triglyceride; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; ApoA, Apolipoprotein A; ApoB, Apolipoprotein B; LDL-C/HDL-C, Low-Density Lipoprotein Cholesterol to High-Density Lipoprotein Cholesterol Ratio; TG/HDL-C, Triglyceride to High-Density Lipoprotein Cholesterol Ratio; TC/HDL-C, Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio; Non-HDL-C, Non-High-Density Lipoprotein Cholesterol

WMHs. Novel lipid indices outperformed traditional indices, with the combined use of four novel indices providing the best diagnostic capabilities. The OCP was 0.489, yielding a sensitivity of 88.3% and a specificity of 60.6%. The AUC was 0.800 (95% confidence interval [CI], 0.731–0.869; $P<0.001$).(Fig. 2).

A subgroup analysis was performed to investigate the association between age, sex, hypertension characteristics, and novel lipid markers. The study found that the TG/HDL cholesterol ratio was not statistically significant in males, individuals aged < 65 years, and those without hypertension. However, the remaining novel lipid indices were significantly associated with age, sex,

Table 2 Clinical and demographic characteristics of CSVD patients with different degrees of WMHs

Variables	mild Group ($n=94$)	moderate to severe Group ($n=71$)	*P*-value
Demographic characteristics			
Age, median (IQR)	59.50 (54.00, 69.00)	71.00 (60.00, 78.00)	< 0.001
Sex, male, n (%)	59 (62.8%)	42 (59.2%)	0.637
Vascular risk factors			
Smoking, n (%)	33 (35.1%)	17 (23.9%)	0.122
Alcohol consumption, n (%)	26 (27.7%)	9 (12.7%)	0.020
Hypertension, n (%)	55 (58.5%)	55 (77.5%)	0.011
Diabetes, n (%)	31 (33.0%)	10 (14.1%)	0.005
Coronary heart disease, n (%)	7 (7.4%)	8 (11.3%)	0.398
Laboratory data			
WBC, 10^9/L, median (IQR)	6.10 (5.07, 7.51)	5.68 (4.82, 7.35)	0.535
RBC, 10^{12}/L, median (IQR)	4.62 (4.17, 4.88)	4.60 (4.29, 4.94)	0.689
HB, g/L, median (IQR)	135.50 (124.00, 144.00)	132.00 (126.00, 137.00)	0.085
PLT, 10^9/L, mean (SD)	214.57 ± 51.88	210.82 ± 47.90	0.635
NEUT %, median (IQR)	59.25 (53.28, 67.05)	64.60 (57.60, 68.40)	0.064
LY%, median (IQR)	28.30 (23.38, 33.58)	25.70 (22.60, 33.60)	0.474
GLU, mmol/L, median (IQR)	5.40 (4.90, 6.45)	5.80 (4.90, 7.10)	0.130
ALT, U/L, median (IQR)	21.00 (16.75, 28.00)	22.00 (16.00, 33.00)	0.421
AST, U/L, median (IQR)	23.50 (18.75, 28.00)	24.00 (20.00, 31.00)	0.096
ALP, U/L, median (IQR)	75.50 (63.00, 87.50)	78.00 (61.00, 88.00)	0.495
GGT, U/L, median (IQR)	23.00 (17.00, 41.25)	24.00 (17.00, 31.00)	0.519
BUN, mmol/L, median (IQR)	5.40 (4.20, 7.19)	5.80 (4.50, 6.90)	0.668
Cr, umol/L, median (IQR)	76.10 (62.85, 87.25)	79.20 (68.00, 98.00)	0.018
UA, umol/L, median (IQR)	304.50 (267.00, 354.25)	312.00 (255.00, 399.00)	0.316
HCY, μmol/L, median (IQR)	12.23 (9.75, 16.72)	15.18 (11.60, 24.33)	0.004
FIB, μg/ml, median (IQR)	2.91 (2.60, 3.51)	3.37 (2.97, 4.21)	< 0.001
CRP, mg/L, median (IQR)	1.00 (0.00, 3.00)	1.00 (0.00, 4.00)	0.121
NAG, U/L, median (IQR)	16.75 (14.35, 19.33)	17.60 (13.20, 22.80)	0.169
Cys-C, mg/L, median (IQR)	1.12 (0.88, 1.29)	1.26 (1.10, 1.52)	< 0.001
Lipid parameter			
TG, mmol/L, median (IQR)	1.61 (1.12, 2.20)	1.72 (1.17, 2.81)	0.107
TC, mmol/L, median (IQR)	4.12 (3.42, 4.68)	4.86 (4.09, 5.82)	< 0.001
LDL-C, mmol/L, median (IQR)	3.01 (2.38, 3.53)	3.43 (3.11, 4.32)	< 0.001
HDL-C, mmol/L, median (IQR)	0.98 (0.85, 1.12)	0.93 (0.78, 1.07)	0.086
ApoA, g/L, mean (SD)	1.25 ± 0.21	1.28 ± 0.30	0.504
ApoB, g/L, median (IQR)	0.82 (0.65, 1.02)	0.83 (0.68, 0.93)	0.893
LDL-C/HDL-C, median (IQR)	1.57 (1.13, 2.48)	1.98 (1.35, 2.95)	0.010
TG/HDL-C, median (IQR)	4.02 (3.28, 5.00)	5.17 (4.17, 7.12)	< 0.001
TC/HDL-C, median (IQR)	3.07 (2.38, 3.77)	3.98 (3.11, 4.81)	< 0.001
Non-HDL-C, median (IQR)	0.22 (-0.51, 0.67)	0.47 (-0.62, 1.55)	0.093

Abbreviations CSVD, Cerebral Small Vessel Disease; WBC, Leukocyte; RBC, Red Blood Cell; HB, Haemoglobin; PLT, Platelet Count; NEUT%, Neutrophil Percentage; LY%, Lymphocyte Percentage; GLU, Glucose; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; GGT, Gamma-glutamyl Transferase; BUN, Blood Urea Nitrogen; Cr, Creatinine; UA, Uric Acid; HCY, Homocysteine; FIB, Fibrinogen; CRP, C-reactive Protein; NAG, Acetylglucosaminidase; Cys-C, Cystatin C; TC, Total Cholesterol; TG, Total Triglyceride; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; ApoA, Apolipoprotein A; ApoB, Apolipoprotein B; LDL-C/HDL-C, Low-Density Lipoprotein Cholesterol to High-Density Lipoprotein Cholesterol Ratio; TG/HDL-C, Triglyceride to High-Density Lipoprotein Cholesterol Ratio; TC/HDL-C, Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio; Non-HDL-C, Non-High-Density Lipoprotein Cholesterol

and hypertension (all $P<0.05$). Compared with males (OR=1.126, 95% CI=0.779–1.628), females (OR=2.484, 95% CI=1.398–4.414; P for interaction=0.023) had a higher risk of developing WMHs. (Fig. 3)

Discussion

This study, a small-sample cross-sectional investigation of a population with CSVD but without acute stroke events, revealed significant associations between novel lipid indices and WMHs. While only the TG/HDL-C ratio showed a clear association with mild WMHs, this finding alone highlights the potential value of novel lipid

Table 3 Logistic regression model of novel lipid indices and CSVD WMHs

	HR (95%CI)			
	Unadjusted model	Model 1	Model 2	Model 3
LDL-C/HDL-C				
LDL-C/HDL-C (quartile)	1.661 (1.284, 2.149)	1.650 (1.262, 2.156)	1.627 (1.229, 2.154)	1.790 (1.309, 2.449)
P-value	< 0.001	< 0.001	< 0.001	< 0.001
TG/HDL-C				
TG/HDL-C (quartile)	1.499 (1.132, 1.983)	1.549 (1.145, 2.095)	1.625 (1.160, 2.275)	1.569 (1.079, 2.281)
P-value	0.005	0.005	0.005	0.018
TC/HDL-C				
TC/HDL-C (quartile)	1.586 (1.288, 1.952)	1.602 (1.278, 2.008)	1.639 (1.295, 2.074)	1.602 (1.236, 2.076)
P-value	< 0.001	< 0.001	< 0.001	< 0.001
Non-HDL-C				
Non-HDL-C (quartile)	2.102 (1.532, 2.883)	2.183 (1.542, 3.091)	2.264 (1.557, 3.293)	2.030 (1.352, 3.050)
P-value	< 0.001	< 0.001	< 0.001	< 0.001

Notes Model 1 accounted for sex and age, while Model 2 was built upon Model 1 by adjusting for risk factors such as hypertension, diabetes, coronary heart disease, and history of smoking and alcohol consumption. Model 3 was refined by including variables with statistical significance ($P < 0.01$) from the univariable logistic analysis (age, history of drinking, hypertension, AST, Cr, HCY, FIB, CRP, and NAG)

Abbreviations CSVD, Cerebral Small Vessel Disease; OR odds ratio; CI, confidence interval; LDL-C/HDL-C, Low-Density Lipoprotein Cholesterol to High-Density Lipoprotein Cholesterol Ratio; TG/HDL-C, Triglyceride to High-Density Lipoprotein Cholesterol Ratio; TC/HDL-C, Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio; Non-HDL-C, Non-High-Density Lipoprotein Cholesterol

indices in assessing WMHs risk. Notably, after accounting for potential confounding factors, this study revealed that individuals with elevated LDL-C/HDL-C, TG/HDL-C, TC/HDL-C, and non-HDL-C levels have a markedly increased risk of WMHs.

Dyslipidaemia is widely recognised as a fundamental contributor to atherosclerosis and is a modifiable risk factor closely associated with CSVD. High Atherosclerotic Index of Plasma (AIP) is strongly linked to WMHs and lacunar lesions in CSVD [11]. Extensive research has focused on traditional lipid markers, particularly LDL-C, which is generally considered the primary target for interventions in cardiovascular and cerebrovascular diseases [12, 13]. However, some clinical studies suggest that despite aggressive lipid-lowering therapies aimed at reducing LDL-C levels, there remains a notable risk of cardiovascular and cerebrovascular diseases [14, 15]. This implies that lowering the LDL-C levels alone may not be sufficient to effectively manage the risk of these diseases. The past few years have witnessed a growing interest in novel lipid indices derived from conventional

Table 4 Logistic regression model of lipid indices and CSVD different degrees of WMHs

	Unadjusted model		adjusted model	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
TG				
mild Group	1.624 (0.945, 2.790)	0.079	2.371 (1.023, 5.494)	0.044
moderate to severe Group	0.691 (0.473, 1.008)	0.055	0.858 (0.505, 1.460)	0.573
TC				
mild Group	0.821 (0.527, 1.281)	0.385	0.927 (0.498, 1.729)	0.813
moderate to severe Group	0.916 (0.709, 1.183)	0.499	0.877 (0.584, 1.317)	0.528
LDL				
mild Group	0.945 (0.628, 1.422)	0.789	1.191 (0.684, 2.071)	0.537
moderate to severe Group	0.991 (0.672, 1.463)	0.965	0.977 (0.553, 1.727)	0.937
HDL				
mild Group	0.090 (0.013, 0.645)	0.017	0.184 (0.024, 1.411)	0.103
moderate to severe Group	0.115 (0.011, 1.211)	0.072	0.231 (0.007, 7.977)	0.418
LDL-C/HDL-C				
mild Group	1.350 (0.905, 2.015)	0.141	1.501 (0.853, 2.643)	0.159
moderate to severe Group	1.217 (0.887, 1.669)	0.223	1.145 (0.727, 1.806)	0.559
TG/HDL-C				
mild Group	2.167 (1.267, 3.705)	0.005	2.903 (1.288, 6.543)	0.010
moderate to severe Group	0.786 (0.552, 1.118)	0.180	0.903 (0.567, 1.437)	0.666
TC/HDL-C				
mild Group	1.320 (0.954, 1.828)	0.094	1.458 (0.925, 2.300)	0.105
moderate to severe Group	1.098 (0.901, 1.337)	0.356	1.025 (0.725, 1.450)	0.888
Non-HDL-C				
mild Group	0.978 (0.628, 1.521)	0.920	1.146 (0.603, 2.179)	0.677
moderate to severe Group	0.940 (0.726, 1.218)	0.641	0.892 (0.592, 1.344)	0.585

Notes The adjusted model was refined by including variables with statistical significance ($P < 0.01$) from the univariable logistic analysis (age, history of drinking, hypertension, AST, Cr, HCY, FIB, CRP, and NAG)

Abbreviations CSVD, Cerebral Small Vessel Disease; OR odds ratio; CI, confidence interval; TG, Triglyceride; TC, Total Cholesterol; LDL, Low-Density Lipoprotein Cholesterol; HDL, High-Density Lipoprotein Cholesterol; LDL-C/HDL-C, Low-Density Lipoprotein Cholesterol to High-Density Lipoprotein Cholesterol Ratio; TG/HDL-C, Triglyceride to High-Density Lipoprotein Cholesterol Ratio; TC/HDL-C, Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio; Non-HDL-C, Non-High-Density Lipoprotein Cholesterol

lipid measurements, which are considered alternative, convenient, and reliable targets. Emerging evidence has indicated that these non-traditional lipid indicators may outperform LDL-C in predicting vascular risks. For instance, Zheng found that elevated levels of these

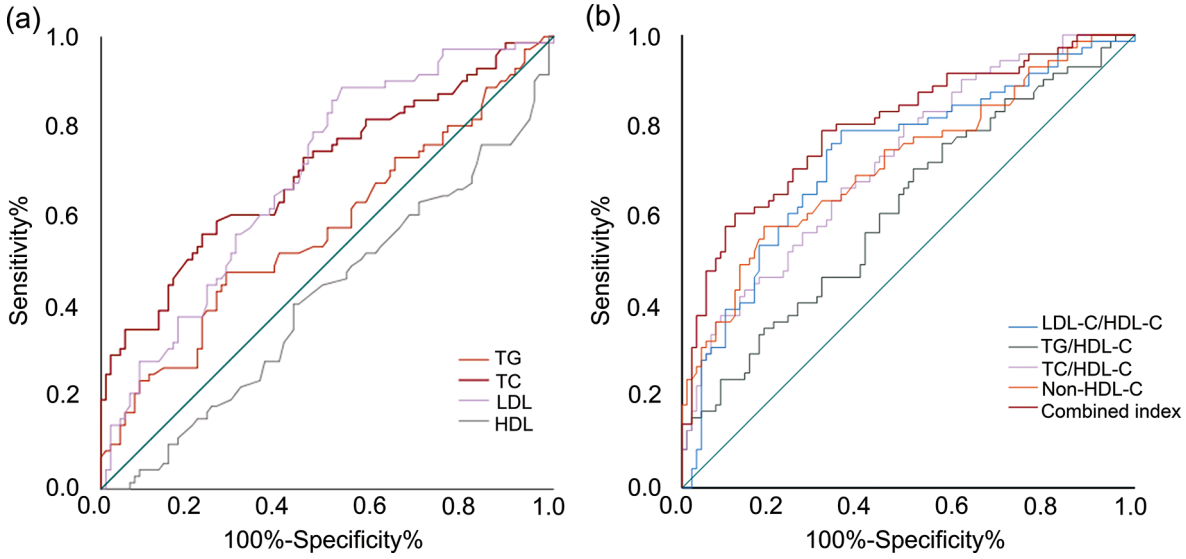

Fig. 2 Diagnostic performance of lipid parameters and lipid indices using ROC analyses. The predictive value of traditional lipid indices (TG, TC, LDL, HDL), as well as novel lipid indices (including LDL-C/HDL-C, TG/HDL-C, TC/HDL-C, Non-HDL-C, and combined index), for WMHs in CSVD patients was assessed. The AUC was 0.573 (95%CI, 0.483–0.663; $P=0.107$) for TG, 0.703 (95%CI, 0.621–0.785; $P<0.001$) for TC, 0.693 (95%CI, 0.613–0.773; $P<0.001$)) for LDL, 0.422 (95%CI, 0.334–0.501; $P=0.086$) for HDL, 0.729 (95%CI, 0.650–0.809; $P<0.001$) for LDL-C/HDL-C, 0.617 (95%CI, 0.530–0.703; $P=0.010$) for TG/HDL-C, 0.724 (95%CI, 0.647–0.801; $P<0.001$) for TC/HDL-C, 0.719 (95% CI, 0.639–0.799; $P<0.001$) for Non-HDL-C, and 0.800 (95% CI, 0.731–0.869; $P<0.001$) for the Joint Indicators. *Abbreviation* CSVD, Cerebral Small Vessel Disease; ROC, Receiver Operating Characteristic Curve; AUC, Area Under Curve; CI, confidence interval; TG, Triglyceride; TC, Total Cholesterol; LDL, Low-Density Lipoprotein Cholesterol; HDL, High-Density Lipoprotein Cholesterol; LDL-C/HDL-C, Low-Density Lipoprotein Cholesterol to High-Density Lipoprotein Cholesterol Ratio; TG/HDL-C, Triglyceride to High-Density Lipoprotein Cholesterol Ratio; TC/HDL-C, Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio; Non-HDL-C, Non-High-Density Lipoprotein Cholesterol

four novel lipid indices were positively correlated with a heightened risk of cerebrovascular disease in patients with hypertension [16, 17]. Studies have suggested that maintaining a lower lipid ratio could be beneficial in preventing cerebrovascular disease. As expected, this study found that these four novel lipid indices were closely related to CSVD and it demonstrated a direct positive correlation with the risk of cerebral WMHs. Patients with higher lipid levels may be at greater risk of developing WMHs, particularly CSVD.

It remains unclear how LDL-C/HDL-C, TG/HDL-C, TC/HDL-C, and Non-HDL-C promote WMHs in patients with CSVD. The following mechanisms may explain this phenomenon: first, these lipid ratios encompass both atherogenic and anti-atherogenic effects, which may provide a more comprehensive prediction of residual risk than single indicators [18]. A higher ratio may indicate an increased risk of atherosclerosis, which could subsequently affect the cerebrovascular health. For instance, high levels of LDL may stimulate microglial activation, exacerbating the breakdown of the BBB, and causing damage to WMHs [19]. Elevated levels of TG levels may lead to insufficient cerebral blood flow by triggering inflammation and damage to microvessels, or by affecting blood flow in cerebral vessels, ultimately promoting the formation of WMHs [20]. Lower levels of HDL levels may be linked to larger WMHs volumes, potentially because they can induce inflammation, promote intracranial small vessel damage, and increase the risk of WMHs [21, 22].

Second, the accumulation of cholesterol in cells can trigger an inflammasome response and result in the production of inflammatory mediators, like interleukin (IL)-1β [23]. This may also be related to the interaction of various mechanisms that influence CSVD progression, atherosclerosis, promote inflammatory responses and oxidative stress, impair endothelial function, increase thrombus formation and plaque instability, and affect vascular autoregulation, all of which exacerbate BBB damage. Additionally, endothelial dysfunction can affect cerebral perfusion, leading to myelin damage and changes in the microstructure of the cerebral white matter, ultimately progressing to what is observed on imaging as WMHs [19, 24, 25]. Overall, the novel lipid indices play a central role in the formation and progression of CSVD, affecting the cerebral white matter.

This cross-sectional retrospective study comprehensively examined the association between novel lipid indices and CSVD-related WMHs. Notably, this study marks the initial discovery of an association between novel lipid indices and WMHs associated with CSVD. Given the aging population, the high incidence of CSVD, and its severe consequences, screening high-risk populations has become a crucial preventive measure. Compared to traditional lipid indices such as LDL-C, novel lipid indices offer a more comprehensive profile of lipid metabolism.

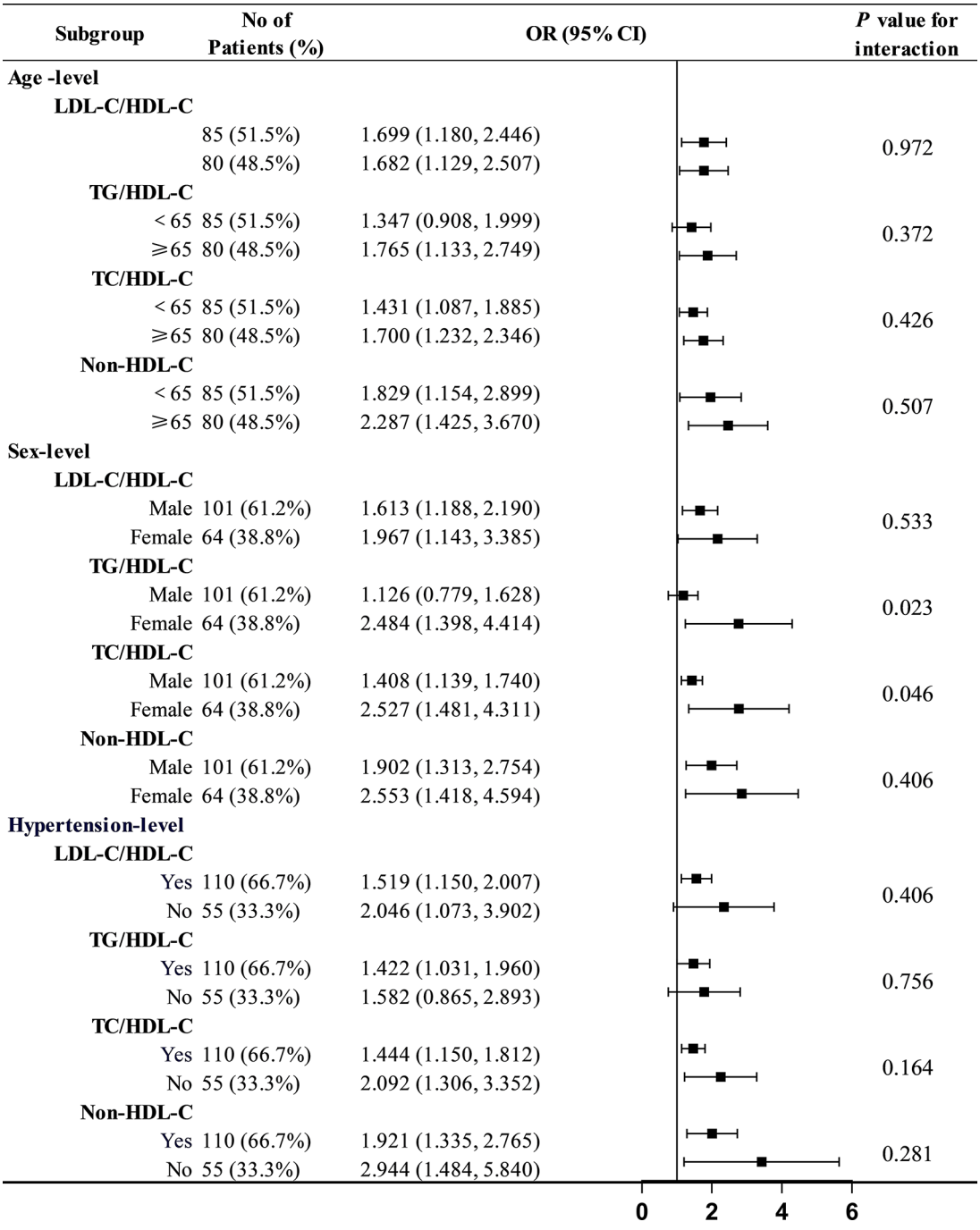

Fig. 3 Graph of WMHs subgroup analysis by age, gender, and hypertension status. *Abbreviation* OR odds ratio; CI, confidence interval; TG, Triglyceride; TC, Total Cholesterol; LDL, Low-Density Lipoprotein Cholesterol; HDL, High-Density Lipoprotein Cholesterol; LDL-C/HDL-C, Low-Density Lipoprotein Cholesterol to High-Density Lipoprotein Cholesterol Ratio; TG/HDL-C, Triglyceride to High-Density Lipoprotein Cholesterol Ratio; TC/HDL-C, Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio; Non-HDL-C, Non-High-Density Lipoprotein Cholesterol.

They accurately reflect the degree of dyslipidaemia and demonstrate high sensitivity and specificity in assessing the onset and progression of CSVD-related WMHs. By identifying novel lipid markers associated with WMHs risk, this study aims to identify new biomarkers for early disease diagnosis, offering valuable tools for risk assessment and stratification of patients with CSVD. This facilitated accurate identification and intervention in the early stages. Furthermore, novel lipid markers can assist clinicians in more accurately assessing the progression and prognosis of patients' diseases, enabling the development of personalised and precise treatment strategies.

This cross-sectional retrospective study comprehensively explored the significant relationship present between WMHs and novel lipid markers in patients with CSVD. This is a novel and inadequately explored area of research. Previous studies have primarily focused on traditional lipid markers, whereas the present study extended these to novel lipid markers, offering new perspectives for understanding the pathogenesis of WMHs.

Strengths and limitations

The remarkable contribution of this study is that it is the first to reveal that compared to traditional lipid indicators, novel lipid indices may have a greater impact on increasing the risk of WMHs. This finding sheds light on the probable influence of lipid metabolism abnormalities on the development of WMHs associated with CSVD, and presents new clues for delving into the complex pathophysiological mechanisms of this condition. In addition, this study paves the way for early disease identification and risk assessment. Although these findings strongly support the link between novel lipid indices and CSVD-related WMHs, several limitations must be acknowledged. First, the measurement of lipid levels was limited to a single time point upon admission, restricting the examination of the dynamic relationship between the temporal variations in non-conventional parameters and CSVD-related WMHs. This limitation impedes a comprehensive assessment of the temporal relationships and causality between them. Additionally, the study was confined to a small, single-centre, cross-sectional, retrospective sample of the population in a specific region of China. To ensure the universal applicability and clinical relevance of the conclusions, future research endeavours must aspire to broader horizons, embracing larger-scale, geographically diverse, and multi-centre platforms. By incorporating a wider spectrum of clinically representative samples, these studies enable a comprehensive evaluation of the performance of these lipid indicators across diverse populations and their intricate relationship with CSVD.

Conclusion

This study identified a significant association between elevated levels of novel lipid indices and cerebral WMHs in CSVD, emphasising the potential of these four markers as novel plasma biomarkers for CSVD. This crucial finding provides important insights for early risk identification, personalised treatment, and innovative therapy.

Abbreviations

CSVD	cerebral small vessel disease
WMHs	white matter hyperintensities
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TG	Triglyceride
TC	Total cholesterol
LDL-C/HDL-C	Low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio
TG/HDL-C	Triglyceride/high-density lipoprotein cholesterol ratio
TC/HDL-C	Total cholesterol/high-density lipoprotein cholesterol ratio
Non-HDL-C	Non-high-density lipoprotein cholesterol
OCP	Optimal cutoff point
AUC	Area under the curve
ROC	Receiver operating characteristic curves

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Author contributions

Chen Rao and Lei Zhu conceived the study and designed the experiments, with input from Chuanqin Yu. Zhiwen Zha, Tong Gu, Xuke Zhang, and Meihai Wen collected and assembled the data. Data analysis was performed by Chen Rao and Simin Zhang. Chen Rao and Lei Zhu wrote the manuscript, which was approved by all authors: Chen Rao, Lei Zhu, Chuanqin Yu, Simin Zhang, Zhiwen Zha, Tong Gu, Xuke Zhang, and Meihai Wen.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Science and Technology. All participants provided written informed consent after being fully briefed on the study's objectives and procedures. (Approval No. 2019B20,2019-1-1).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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