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ORIGINAL RESEARCH

HDL-C/LDL-C and Risk of Cerebral White Matter Hyperintensities: A Cross-Sectional Study

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Background and Purpose: At present, there is still a lack of metabolic indices to predict white matter hyperintensities. This study aimed to explore the correlations of the high-density lipoprotein cholesterol (HDL-C)/low-density lipoprotein cholesterol (LDL-C) ratio with the risk of white matter hyperintensities.

Methods: Hospitalized patients who underwent inpatient treatment or physical examination due to various chronic diseases between January 18, 2018, and March 20, 2023, were enrolled. Fazekas scores were used to assess the severity of white matter hyperintensities. Logistic regression analysis was used to adjust for possible confounders.

Results: Of the 1162 enrolled patients, 770 (66.27%) patients were classified as having no or mild WMHs, and 392 (33.73%) were classified as having moderate or severe WMHs. After adjusting for covariates, the logistic regression analysis indicated that the ratio of HDL-C to LDL-C was related to the severity of WMHs (Model 1, OR = 0.23, 95% CI: 0.07–0.73, P=0.012; Model 2, OR = 2.03, 95% CI: 1.12–3.67, P=0.019).

Conclusion: Our findings suggest that the ratio of HDL-C to LDL-C is related to the severity of WMHs and that a high ratio of HDL-C to LDL-C is a protective factor against WMHs. This suggests that the ratio of HDL-C to LDL-C could be used as a metabolic prediction index of WMH severity.

Keywords: high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, white matter hyperintensities, risk, Fazekas scale

Introduction

White matter hyperintensities (WMHs) are very common in older individuals and confer an increased risk of stroke, dementia and death.[1,2] Existing studies suggest that WMHs are indicative of cerebral small vessel disease and are associated with age and hypertension.[3,4] In recent years, the relationship between abnormal lipid metabolism and WMHs has attracted increasing attention from scholars. A multicenter, large-sample cohort study used circulating metabolomic measures to show that multiple lipid measures (eg, lysophosphatidylcholines, hydroxysphingomyelin, low-density lipoprotein size and composition) were associated with WMHs in a general population of middle-aged and older adults.[5] Another study revealed strong associations of metabolic syndrome with WMHs and cognitive deficits.[6]

At present, there is still a lack of metabolic indices to predict WMHs. Both high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) are indicators of lipid metabolism and are related to the risk of cardiovascular and cerebrovascular diseases. As a new marker of lipid metabolism, the HDL-C/LDL-C ratio can better reflect the balance of atherogenic and antiatherogenic cholesterol than HDL-C or LDL-C alone and is a predictor of the risk of atherosclerosis and cardiovascular and cerebrovascular diseases.[7] A recent study showed that an HDL-C/LDL-C ratio of 0.4–0.6 was correlated with lower MI risk, all-cause mortality, hemorrhagic stroke and ischemic stroke.[8] Therefore, we designed a cross-sectional study to explore the correlations of the HDL-C/LDL-C ratio with the risk of WMHs.

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Methods

Study Population

In our cross-sectional study, the study group consisted of hospitalized patients who underwent inpatient treatment or physical examination due to various chronic diseases in the Department of Neurology, Affiliated Jiangning Hospital of Nanjing Medical University between January 18, 2018, and March 20, 2023. The inpatient medical record system contains data on patient demographics, clinical and imaging features and treatment details. Data on patient demographics, clinical history, and clinical presentation were collected. The inclusion criteria were as follows: 1) aged 45 or older and 2) underwent cerebral MRI. The exclusion criteria were as follows: participants with severe head injury; severe cerebral infarction, defined as an NIH Stroke Scale score ≥ 14; severe cerebral hemorrhage, defined as a baseline intraparenchymal hemorrhage volume ≥ 30 mL or intraventricular hemorrhage; vascular malformation or brain malignancy; or the presence of multiple sclerosis or a lack of complete clinical data. A total of 1766 middle-aged and elderly inpatients with various chronic diseases or who were physically examined were enrolled in the study. All patients provided informed consent and were enrolled if all inclusion criteria and none of the exclusion criteria were met. At the end of the study, 1162 eligible patients were analyzed, and a detailed study flowchart is shown in Figure 1.

Data Collection

To assess relevant risk factors at baseline, we examined patient demographic characteristics (age, sex, body mass index (BMI) and medical history), history of hypertension, history of diabetes mellitus, presence of coronary heart disease, history of atrial fibrillation, history of cerebral hemorrhage, history of ischemic stroke, past or present cigarette or alcohol use, and antiplatelet or statin treatment. Patients underwent a physical examination, systolic and diastolic blood pressure (SBP & DBP) was measured, and laboratory examinations including tests for glucose (white blood cell counts, D-dimer, fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c), homocysteine (HCY), total cholesterol (TC), high-density

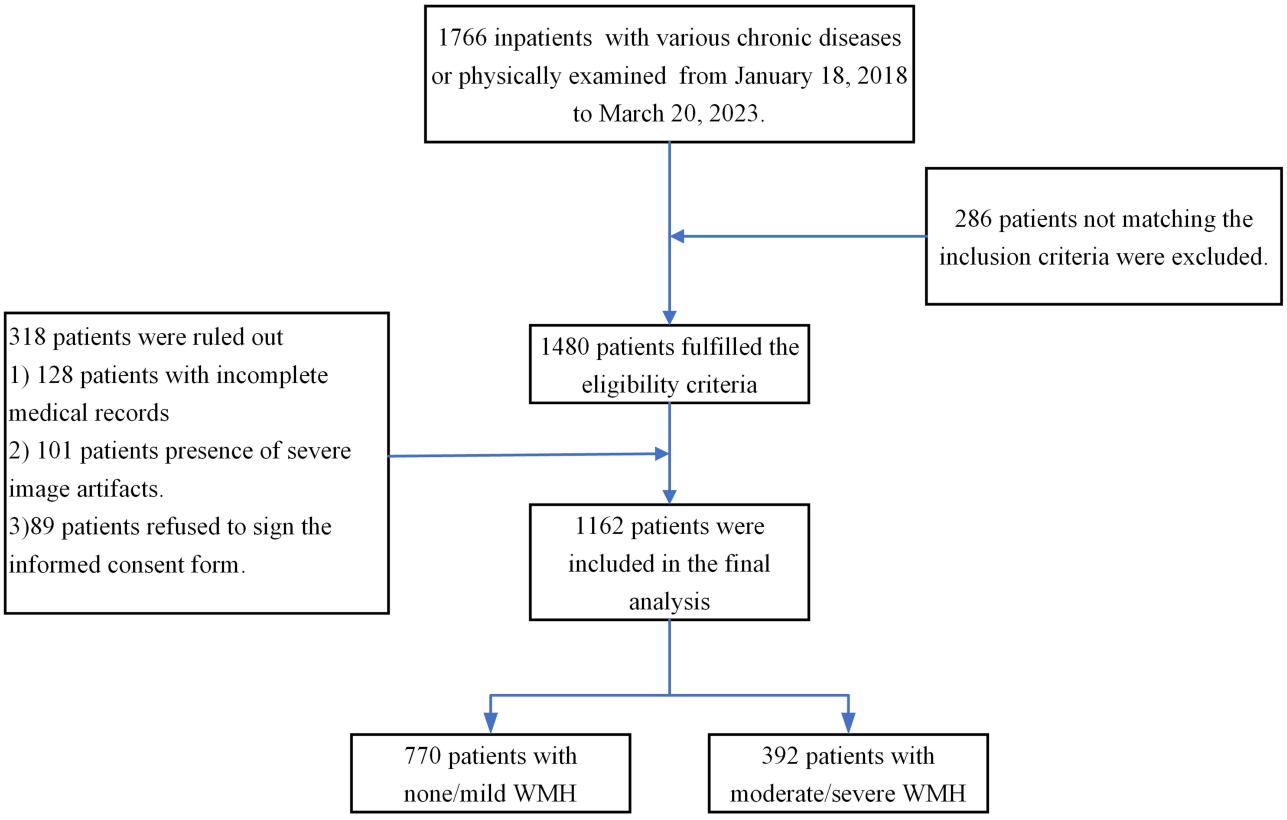

Figure 1 Flow chart of patient inclusion for this study.

lipoprotein cholesterol (HDL), triglyceride (TG), low-density lipoprotein (LDL), lipoprotein-a (LP-A), creatinine (Cr) and uric acid (UA) were performed.

MRI Acquisition

Enrolled patients underwent a brain MRI examination with a 3.0 T scanner (Philips Medical Systems, the Netherlands) with an 8-channel receiver array head coil. Standardized parameters of the MRI sequences, including T1-weighted, T2-weighted and fluid-attenuated inversion recovery images, were obtained. Detailed parameters of the MRI scans were reported in our previous study.[9,10]

Fazekas Scores for Assessment of the Severity of WMHs

The Fazekas scale divides the white matter into periventricular and deep white matter, and each region is given a grade depending on the size and confluence of lesions:[11] (1) periventricular white matter hyperintensities (PVWMHs), for which 0 = absent, 1 = "caps" or pencil-thin lining, 2 = smooth "halo", and 3 = irregular periventricular signal extending into the deep white matter; and (2) deep white matter hyperintensities (DWMHs), for which 0 = absent, 1 = punctate foci, 2 = beginning confluence, and 3 = large confluent areas. Two experienced neurologists and a neuroradiologist participated in the evaluation of the MRI results. WMHs were analyzed as none/mild (Fazekas score 0–1) vs moderate/severe (Fazekas score 2–3) according to Fazekas scores. If scores for the two samples were discordant, the final score for the classification was upgraded to the higher score.

Statistics

Continuous data are summarized as the mean values with SDs for data with a normal distribution or the median values with interquartile ranges for data with a skewed distribution. Categorical data are presented as frequencies with proportions. A two-sample *t* test was used to compare continuous data. Categorical data were analyzed using the chi-square test. Multivariable logistic regression analysis was used to adjust for possible confounding factors. All statistical analyses were performed using SPSS 25.0 software (SPSS, Chicago, IL).

Results

Of the 1162 enrolled patients, 770 (66.27%) patients were classified as having no or mild WMHs, and 392 (33.73%) were classified as having moderate or severe WMHs. Patients with no or mild WMHs were younger (62.67±9.93 vs 70.72 ±9.43, y, P <0.001) than those with moderate or severe WMHs. In addition, the asymptomatic or mild-illness patient groups had a lower ratio of hypertension (60.78% vs 78.32%; P<0.001), diabetes (23.25% vs 30.87%; P=0.007), previous cerebral hemorrhage (1.69% vs 4.59%; P=0.041), previous ischemic stroke (36.36% vs 47.19%; P<0.001), atrial fibrillation (2.21% vs 4.59%; P=0.023), oral antiplatelet drugs (50.39% vs 62.76%; P <0.001) and oral statins (47.79% vs 54.85%; P =0.031) than the group of patients with moderate or severe WMHs. Moreover, patients with no or mild WMHs presented with lower levels of SBP (136.99±20.25 vs 147.44±22.71, mmHg, P<0.001), DBP (80.46±12.89 vs 82.82±12.73, mmHg, P=0.006), pulse pressure (56.13±16.61 vs 64.45±18.31, mmHg, P<0.001), D-dimer (0.49±0.82 vs 0.96±0.72, mg/L, P<0.001), glycated hemoglobin (5.99±1.30 vs 6.26±1.55, %, P=0.009), lipoprotein(a) (233.76 ±223.61 vs 266.50±254.88, mg/dL, P=0.028), creatinine (64.54±20.86 vs 72.27±27.23, μmmol/L, P<0.001), uric acid (308.50±87.69 vs 321.42±92.02, μmmol/L, P=0.020) and homocysteine (13.30±6.96 vs 17.23±10.05, μmmol/L, P<0.001) than patients with moderate or severe WMHs. However, patients with no or mild WMHs had higher levels of HDL-C (1.25±0.49 vs 1.08±0.30, mmol/L, P<0.001) and a higher ratio of HDL-C to LDL-C (0.65±0.54 vs 0.50±0.25, P<0.001) than control subjects. The details are presented in Table 1.

After adjusting for covariates, the logistic regression analysis indicated that the ratio of HDL-C to LDL-C was related to the severity of WMHs (Model 1, OR = 0.23, 95% CI: 0.07–0.73, P=0.012). In addition, age (OR = 1.07, 95% CI: 1.04–1.09, P<0.001), history of cerebral hemorrhage (OR = 3.26, 95% CI: 1.07–9.97, P=0.038), history of ischemic stroke (OR = 1.87, 95% CI: 1.22–2.87, P=0.004) and oral antiplatelet drugs (OR = 1.78, 95% CI: 1.09–2.89, P=0.020) were also associated with a risk of severe WMHs (Table 2).

Table 1 Clinical Characteristics of the Included Patients (n=1162). WMHs Were Analyzed as None/Mild vs Moderate/Severe Signal Attenuation

Variables	None/Mild WMH (n=770)	Moderate/Severe WMH (n=392)	*P* value
Demographic characteristics			
Age, y, mean ± SD	62.67±9.93	70.72±9.43	<0.001
Male, n (%)	417 (54.16)	233 (59.44)	0.078
BMI, kg/m^2	24.46±3.20	24.67±3.12	0.445
Blood pressure and heart rate, mean ± SD			
SBP, mmHg	136.99±20.25	147.44±22.71	<0.001
DBP, mmHg	80.46±12.89	82.82±12.73	0.006
Pulse pressure, mmHg	56.13±16.61	64.45±18.31	<0.001
History of diseases, n (%)			
Hypertension	468 (60.78)	307 (78.32)	<0.001
Diabetes	179 (23.25)	121 (30.87)	0.007
Coronary artery disease	72 (9.35)	38 (9.69)	0.927
Previous cerebral hemorrhage	13 (1.69)	18 (4.59)	0.041
Previous ischemic stroke	280 (36.36)	185 (47.19)	<0.001
Atrial fibrillation	17 (2.21)	18 (4.59)	0.023
Bad habits, n (%)			
Current smoker	163 (21.17)	70 (17.86)	0.168
Current alcohol user	109 (14.16)	51 (13.01)	0.592
Oral medications, n (%)			
Oral antiplatelet drugs	388 (50.39)	246 (62.76)	<0.001
Oral statins	368 (47.79)	215 (54.85)	0.031
Laboratory examinations, mean ± SD			
White blood cell counts, *10^9/L	5.71±1.76	6.00±2.24	0.571
D-dimer, mg/L	0.49±0.82	0.96±0.72	<0.001
Fasting blood glucose, mmol/L	5.72±1.95	5.76±1.84	0.774
Glycated hemoglobin, %	5.99±1.30	6.26±1.55	0.009
Total cholesterol, mmol/L	4.31±1.12	4.20±2.62	0.353
Triglyceride, mmol/L	1.64±1.20	1.56±0.93	0.166
LDL-C, mmol/L	2.41±0.94	2.45±0.88	0.387
HDL-C, mmol/L	1.25±0.49	1.08±0.30	<0.001
Lipoprotein(a), mg/dL	233.76±223.61	266.50±254.88	0.028
Creatinine, μmmol/L	64.54±20.86	72.27±27.23	<0.001
Uric acid, μmmol/L	308.50±87.69	321.42±92.02	0.020
Homocysteine, μmmol/L	13.30±6.96	17.23±10.05	<0.001
HDL-C/LDL-C	0.65±0.54	0.50±0.25	<0.001

Notes: Continuous variables are shown as the mean ± standard deviation (SD), and categorical variables are shown as numbers combined with percentages (%). Pulse pressure means the difference between the systolic and diastolic pressures.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

After adjusting for sex, age, SBP, DBP, previous cerebral hemorrhage, previous ischemic stroke, atrial fibrillation, oral antiplatelet drugs, oral statins, D-dimer, glycated hemoglobin, lipoprotein(a), creatinine, uric acid and homocysteine, the logistic regression analysis also indicated that a high ratio of HDL-C to LDL-C was a protective factor against WMHs (Model 2, OR = 0.19, 95% CI: 0.04–0.86, *P*=0.031). In addition, age (OR = 1.05, 95% CI: 1.02–1.08, *P*=0.001), previous cerebral hemorrhage (OR = 4.79, 95% CI: 1.35–16.91, *P*=0.015), previous ischemic stroke (OR = 1.75, 95% CI: 1.04–2.93, *P*=0.035) and oral antiplatelet drugs (Model 2, OR = 2.03, 95% CI: 1.12–3.67, *P*=0.019) were also associated with a risk of severe WMHs (Table 3).

Table 2 Correlation Between the Severity of WMHs and Risk Factors in Model 1

Variables	β	Wald	OR (95% CI)	*P* value
Gender	−0.271	1.796	0.736 (0.51–1.13)	0.180
Age	0.063	32.488	1.07 (1.04–1.09)	<0.001
Hypertension	0.333	2.180	1.40 (0.90–2.17)	0.140
Diabetes	0.245	1.075	1.28 (0.80–2.03)	0.300
Previous cerebral hemorrhage	1.182	4.306	3.26 (1.07–9.97)	0.038
Previous ischemic stroke	0.627	8.195	1.87 (1.22–2.87)	0.004
Atrial fibrillation	−21.986	0.001	0.01 (0.00–0.01)	0.998
Oral antiplatelet drugs	0.575	5.376	1.78 (1.09–2.89)	0.020
Oral statins	0.021	0.009	1.02 (0.66–1.59)	0.926
HDL-C/LDL-C	−1.463	6.242	0.23 (0.07–0.73)	0.012

Notes: Model 1 adjusted for sex, age, hypertension, diabetes, previous cerebral hemorrhage, previous ischemic stroke, atrial fibrillation, oral antiplatelet drugs and oral statins.
Abbreviations: OR, odds ratio; CI, confidence interval.

Table 3 Correlation Between the Severity of WMHs and Risk Factors in Model 2

Variables	β	Wald	OR (95% CI)	*P* value
Gender	−0.012	0.002	0.99 (0.56–1.75)	0.966
Age	0.050	10.789	1.05 (1.02–1.08)	0.001
SBP	0.003	0.188	1.00 (0.99–1.02)	0.665
DBP	0.023	3.570	1.02 (1.00–1.05)	0.059
Previous cerebral hemorrhage	1.566	5.908	4.79 (1.35–16.91)	0.015
Previous ischemic stroke	0.558	4.459	1.75 (1.04–2.93)	0.035
Atrial fibrillation	−22.004	0.001	0.01 (0.00–0.01)	0.998
Oral antiplatelet drugs	0.708	5.511	2.03 (1.12–3.67)	0.019
Oral statins	0.118	0.179	1.13 (0.65–1.94)	0.673
D-dimer	0.223	0.927	1.25 (0.79–1.97)	0.336
Glycated hemoglobin	0.014	0.017	1.01 (0.82–1.25)	0.897
Lipoprotein(a)	0.001	1.147	1.00 (1.00–1.01)	0.284
Creatinine	0.014	2.394	1.01 (0.99–1.03)	0.122
Uric acid	0.001	0.052	1.00 (1.00–1.01)	0.820
Homocysteine	0.030	3.138	1.03 (1.00–1.07)	0.077
HDL-C/LDL-C	−1.682	4.650	0.19 (0.04–0.86)	0.031

Notes: Model 2 adjusted for sex, age, SBP, DBP, previous cerebral hemorrhage, previous ischemic stroke, atrial fibrillation, oral antiplatelet drugs, oral statins, D-dimer, glycated hemoglobin, lipoprotein(a), creatinine, uric acid and homocysteine.
Abbreviations: OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure.

We then compared the distribution of HDL-C/LDL-C between patients with no or mild and moderate or severe WMHs by univariate analysis. The results showed that the ratios of HDL-C to LDL-C were significantly higher in patients with no or mild WMHs than in those with moderate or severe illness (Figure 2).

Discussion

This study revealed that the ratio of HDL-C to LDL-C was related to the severity of WMHs and that a high ratio of HDL-C to LDL-C was a protective factor against WMHs. This suggests that the ratio of HDL-C to LDL-C could be used as a metabolic prediction index of WMH severity.

Hyperlipidemia, especially increased LDL-C levels and decreased HDL levels, are major risk factors for atherosclerosis.[12] Studies have shown that the ratio of HDL-C to LDL-C can better reflect the balance of atherogenic

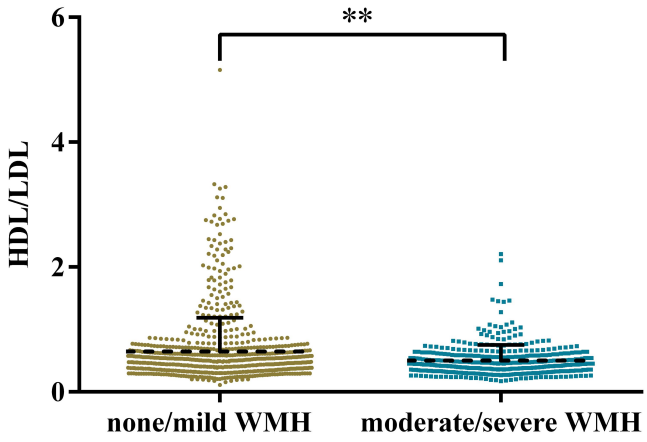

Figure 2 Comparison of HDL/LDL distribution between the two groups. Asterisks "**" represent $P < 0.01$ compared with the control group.

and antiatherogenic cholesterol than HDL-C or LDL-C alone, and a decreased HDL-C/LDL-C ratio is an important risk factor for coronary heart disease.[13,14] Our study suggested that the ratio of HDL-C to LDL-C can also predict the severity of WMHs even after adjusting for covariates.

We speculate that this may be caused by the following circumstances. First, WMHs are a common condition that often occurs in elderly individuals and shares common risk factors with cardiovascular and cerebrovascular diseases. Our previous research also suggested that hyperuricemia and small low-density lipoprotein cholesterol may increase the risk of WMHs.[15,16] A reduced ratio of HDL-C to LDL-C is a risk factor for cardiovascular and cerebrovascular diseases, which can also lead to increased WMH risk.[17] Second, low levels of HDL-C could cause lipid oxidation, hence inducing inflammation and accentuating tissue damage, and importantly, decreased HDL levels may further increase inflammation, thus perhaps eventually leading to small blood vessel damage, resulting in WMHs.[18,19] Third, LDL-C tends to deposit in the walls of arteries, leading to plaque buildup in the artery wall, eventually blocking the artery. Plaque buildups can lead to heart attacks and dangerous blood clots. The accumulation of LDL-C inside the blood vessels serves as a major cause of arteriosclerosis, and even slightly elevated LDL cholesterol may have a negative impact on cardiovascular risk.[20,21] Therefore, the ratio of HDL-C to LDL-C can better reflect the severity of inflammation, lipid metabolism and arteriosclerosis, all of which may be related to the risk of WMHs.

To the best of our knowledge, this is the first large-sample study demonstrating the relationship between HDL-C/LDL-C and the severity of WMHs. All data were subjected to rigorous quality controls, and rigorous statistical analyses were performed. Meanwhile, to further understand the relationship between HDL-C/LDL-C and WMHs, we performed logistic regression to adjust for confounding factors. This finding will encourage scholars to further understand the relationship between WMHs and metabolic indices. However, there are some limitations in the current study, which are listed as follows. First and most importantly, this study is based on clinical research and does not explore the mechanism. Second, this study is a single-center study involving individuals in the Han population in the same region. Therefore, further multicenter and in-depth mechanistic studies are needed to overcome the above limitations.

Taken together, our findings suggest that the HDL-C to LDL-C ratio was related to the severity of WMHs and that a high ratio of HDL-C to LDL-C was a protective factor against WMHs. Moreover, a longer follow-up period is needed to evaluate the relationship between WMHs and metabolic indices.

Abbreviations

WMHs, white matter hyperintensities; PVWMHs, periventricular white matter hyperintensities; DWMHs, deep white matter hyperintensities; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HCY, homocysteine; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; LP-A, lipoprotein(a); Cr, creatinine; UA, uric acid; SD, standard deviation; OR, odds ratio; CI, confidence interval.

Data Sharing Statement

Study data are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

We obtained ethical approval for this study from the ethics committee of the Affiliated Jiangning Hospital of Nanjing Medical University and performed in accordance with the Declaration of Helsinki (reference number, 202203023K01). Written informed consent was obtained from all study participants.

Consent for Publication

All patients gave informed consent for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis 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.

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Disclosure

The author declares no competing financial interests.

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