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U-shaped Relationship between high-density lipoprotein cholesterol levels and intracranial aneurysm rupture: a retrospective cross-sectional study in the Chinese population

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Abstract

Background Previous results on the association between HDL (high-density lipoprotein cholesterol) levels and intracranial aneurysm (IA) rupture were controversial. We aimed to investigate the association between HDL levels and the risk of IA rupture.

Methods Medical records of patients with solitary IA diagnosed at West China Hospital of Sichuan University were reviewed and analyzed between December 2008 and March 2023. Univariable and multivariable logistic regression analyses were performed to determine the effects of HDL levels on IA rupture risk. A three-piece-wise logistic regression model with smoothing was used to analyze different association thresholds between HDL and the risk of IA rupture after adjusting for confounding factors.

Results Univariable and multivariable logistic regression analysis showed the independent association between HDL and IA rupture. After being adjusted for confounders, different U-shaped relationships were found between HDL levels and the risk of IA in males, females, and all patients. Compared to HDL in the range of 0.9 ~ 1.3 mmol/L, patients had 79% [OR (95%CI):1.79(1.16 ~ 2.78), $p = 0.009$] increase of rupture when lower than 0.9 mmol/L, 60% [OR (95%CI):1.6(1.19 ~ 2.17), $p = 0.002$] increase when higher than 1.3 mmol/L before or after adjusted confounders. We found gender differences in the HDL range of IA rupture; the lowest range of HDL was 1.1 ~ 1.4 mmol/L in females and 0.8 ~ 1.1 mmol/L in males.

Conclusions There was a U-shaped relationship between HDL levels and the risk of IA rupture. People with HDL levels between 0.9 and 1.3 mmol/L are least likely to experience IA rupture in the Chinese population.

Keywords high-density lipoprotein cholesterol, intracranial aneurysm, U-shaped

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Introduction

Spontaneous subarachnoid hemorrhage (SAH) is ranked as the third most widespread type of stroke and is often associated with the rupture of an aneurysm [1]. Almost 500,000 patients are globally affected by aneurysmal SAH (aSAH) annually [2], characterized by high mortality and morbidity [3]. Understanding the risk factors is paramount to comprehend the risk of developing aSAH.

Previous studies investigating the relationship between HDL (high-density lipoprotein cholesterol) levels and the risk of intracranial aneurysm (IA) rupture have yielded conflicting results. While some research has suggested an inverse association between HDL and IA rupture [4, 5], others have found no significant relationship [6] or even a positive correlation at higher HDL levels [7]. Methodological differences may partly explain these discrepancies. For instance, many studies did not exclude patients with multiple intracranial aneurysms (MIAs), which are associated with a higher risk of rupture due to familial susceptibility [4, 5]. Additionally, the timing of patient onset to hospital admission was often unspecified, potentially affecting the accuracy of HDL measurements [7]. Sample size limitations in earlier studies may have further restricted their ability to detect nuanced associations [6]. Moreover, most prior research was conducted in Western populations, limiting the generalizability of findings to other ethnic groups [4, 6]. To address these gaps, our study focuses on a large cohort of 1368 ethnically Chinese adults with solitary IA, employing strict exclusion criteria and robust statistical methods to explore the relationship between HDL levels and IA rupture risk.

Methods

Study design and population

This retrospective cross-sectional study was conducted at West China Hospital of Sichuan University in Sichuan Province from Dec 31, 2008, to Mar 31, 2023. Data were extracted from the hospital's Electronic Medical Record System, including demographic information such as age, sex, height, weight, and comorbidities such as hypertension, diabetes mellitus (DM), coronary artery disease (CAD), and atrial fibrillation (AF). Additional data on current tobacco and alcohol use and the size, location, and presence or absence of IA rupture were also collected. Serum samples were collected upon admission, within 48 h of symptom onset, and before any medical intervention. This timing was chosen to ensure that lipid levels reflected baseline concentrations rather than being influenced by treatment or prolonged acute-phase changes. All blood samples were processed within 2 h of collection, following standardized laboratory protocols to ensure the consistency of HDL measurements.

The IA was confirmed through imaging techniques such as computed tomography angiography (CTA), magnetic resonance angiography (MRA), digital subtraction angiography (DSA), or intraoperative examination by a neurosurgeon. Our exclusion criteria are as follows: (1) age below 18 years, (2) pregnancy, (3) presentation more than 48 h after onset of aSAH, presence of a postoperative IA, a family history of IA, blood blister-like aneurysms, serpentine or dissecting aneurysms, intracranial pseudoaneurysms, MIAs, or undetermined location of the IA, (4) coexisting conditions such as brain arteriovenous malformations(AVM), dura mater arteriovenous fistulas(DAVF), moyamoya disease(MMD), intracranial fusiform aneurysms, tumors, and cerebral hemorrhage in the basal ganglia or lobar hemorrhage, (5) coagulation disorders or thrombocytopenia, and (6) missing data regarding lipids. The flowchart of the study population is presented in Fig. 1.

This study was approved by the Biomedical Ethics Review Committee of West China Hospital of Sichuan University and was registered with the Chinese Clinical Trials Registry (ChiCTR2300071616). Following national legislation and institutional requirements, informed consent was not necessary for participation in this study.

Statistical analysis

The analysis included measures such as the mean, median, standard deviation, range, and quartiles for continuous variables and frequency tables for categorical variables. Normality tests were performed to assess the data distribution, and appropriate descriptive statistical methods were applied to both normally and non-normally distributed variables. A list of missing data for the present study is included in the supplementary information (Table S1). To address any missing data, multiple imputations were conducted to obtain accurate results. Multiple imputations were performed to handle missing data, ensuring the robustness of the analyses. Sensitivity analyses confirmed that the results remained consistent despite the missing values. Initially, data were collected on the presence or absence of IA rupture and potential influencing factors such as demographic, clinical, and laboratory variables.

We evaluated the association between individual factors, such as age, sex, height, weight, body mass index (BMI), hypertension, DM, CAD, AF, current tobacco use, current alcohol use, aneurysm size, aneurysm location, HDL as a continuous variable, and HDL as a categorical variable, and the presence of IA rupture. We conducted a univariable logistic regression analysis to identify factors that potentially correlate with the presence of IA rupture.

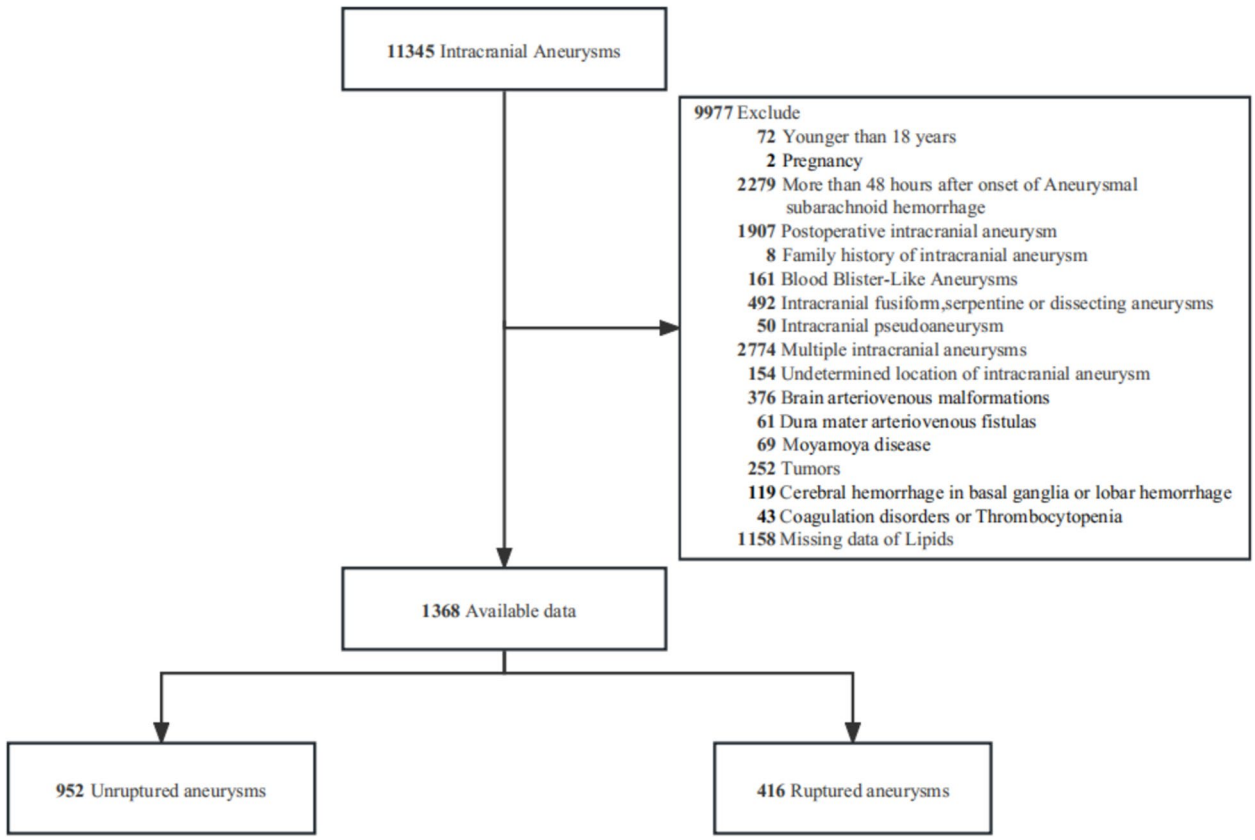

Fig. 1 Flowchart of study

Thirdly, a multivariable logistic regression analysis was performed to identify independent factors significantly associated with IA rupture while adjusting for potential confounders such as age, sex, BMI, hypertension, DM, CAD, AF, current tobacco use, current alcohol use, size, and location. All factors were entered into the model to identify the endpoint event's independent predictors that were statistically significant between groups with a p-value < 0.05 in the univariable regression analysis and relevant to the clinical outcome.

We used restricted cubic spline (RCS) to examine the correlation between HDL levels and IA rupture risk, focusing on potential nonlinear relationships. The RCS model was constructed with 4 knots at the 5th, 35th, 65th, and 95th percentiles of the HDL distribution. The cutoff value was defined as the point where the odds ratio (OR) curve intersected with 1 on the vertical axis, indicating no increased or decreased risk. Our findings revealed that the lowest interval of ruptured risk was approximately between 0.9 and 1.3 mmol/L. We utilized the HDL range of 0.9 to 1.3 mmol/L as the reference group in the multivariate logistic regression models. We conducted sensitivity analyses within different subgroups using forest plots to investigate potential associations. We included product terms between the HDL categories and sex, age, IA size, and IA's location in the models. A Wald test was also used to calculate the multiplicative interaction's P value. As previously mentioned, restricted cubic splines were conducted in males and females separately. In males, the reference group was 0.8 to 1.1 mmol/L of HDL; in females, the reference group was 1.1 to 1.4 mmol/L of HDL. Furthermore, we conducted two data imputations to validate our results' robustness.

All analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.8 (Free Clinical Medical Technology Co., Ltd, Beijing, China), and $p < 0.05$ was considered to indicate significance.

Results

Of the 1368 patients with IA, the mean age was 56.69 years old, 416(30%) patients with ruptured IA, with a higher proportion of female patients than male [936 (68.4%) vs. 432 (31.6%), $p = 0.004$]. IA was more likely to occur at the C7 location, and the ACA was more prone to rupture than other locations [159 (38.2%) vs. 133 (32%)]. Ruptured IA patients consistently had lower levels of triglycerides [(1.24 ± 0.80) vs. (1.53 ± 0.96), $p < 0.001$],

total cholesterol [(4.23 ± 1.06) vs. (4.47 ± 0.93), $p < 0.001$], and low-density lipoprotein cholesterol [(2.42 ± 0.83) vs. (2.60 ± 0.80), $p < 0.01$] than unruptured patients. The proportion of patients with HDL levels < 0.9 mmol/L or ≥ 1.3 mmol/L was higher in the ruptured group compared to the 0.9 to 1.3 mmol/L range (Table 1).

Univariable logistic regression analysis indicated that sex, height, weight, hypertension, current tobacco and alcohol use, size, location, and HDL were all associated with an increased IA rupture risk (Table 2). The restricted cubic splines analysis revealed that the lowest risk of ruptured IA was observed in patients with HDL levels between 0.9 and 1.3 mmol/L (Fig. 2). Therefore, the range of HDL was used as the reference group in the multivariable logistic regression models. Compared to HDL levels in the range of 0.9 ~ 1.3 mmol/L, patients with HDL levels lower than 0.9 mmol/L had a 79% increase in the risk of rupture [OR (95%CI): 1.79 (1.16 ~ 2.78), $p = 0.009$], while an increase of 60% [OR (95%CI): 1.6 (1.19 ~ 2.17), $p = 0.002$] was observed in patients with HDL levels higher than 1.3 mmol/L, after adjusting for confounding variables (Table 3).

Multivariable logistic regression analysis in subgroups showed that sex was a critical modifier when stratified ($p = 0.034$). Our results were robust in subgroups of age, location, and size (Fig. 3). Restricted cubic splines analysis revealed that the lowest risk of ruptured IA was observed in males with HDL levels ranging from 0.8 to 1.1 mmol/L and females with levels ranging from 1.1 to 1.4 mmol/L (Fig. 2 and Table 3). In females, the risk of rupture was higher for those with lower HDL levels (< 1.1 mmol/L), while in males, higher HDL levels (≥ 1.1 mmol/L) increased the risk of rupture. Compared to HDL levels in the range of 0.8 ~ 1.1 mmol/L, males

Table 1 Baseline of study population

Variables	Total ($n = 1368$)	Unruptured ($n = 952$)	Ruptured ($n = 416$)	*p* value
Age (years)	56.69 ± 11.59	56.81 ± 11.40	56.43 ± 12.02	0.583
Sex				**0.004**
Female	936 (68.4)	674 (70.8)	262 (63)	
Male	432 (31.6)	278 (29.2)	154 (37)	
Height(cm)	159.91 ± 7.73	159.49 ± 7.74	160.87 ± 7.63	**0.002**
Weight(kg)	61.16 ± 10.12	60.70 ± 10.15	62.20 ± 9.99	**0.012**
BMI(kg/m^2)	23.87 ± 3.26	23.81 ± 3.26	24.01 ± 3.27	0.31
Comorbidities				
Hypertension	529 (38.7)	347 (36.4)	182 (43.8)	**0.011**
Diabetes Mellitus	96 (7.0)	74 (7.8)	22 (5.3)	0.098
Coronary Artery Disease	40 (2.9)	32 (3.4)	8 (1.9)	0.146
Atrial Fibrillation	11 (0.8)	10 (1.1)	1 (0.2)	0.189
Current Tobacco Use	375 (27.4)	209 (22)	166 (39.9)	**< 0.001**
Current Alcohol Use	410 (30.0)	239 (25.1)	171 (41.1)	**< 0.001**
Size(mm)	7.33 ± 5.22	7.61 ± 5.69	6.68 ± 3.87	**0.002**
Location				**< 0.001**
C7	356 (26.0)	197 (20.7)	159 (38.2)	
ACA	240 (17.5)	107 (11.2)	133 (32)	
MCA	228 (16.7)	144 (15.1)	84 (20.2)	
C4, C5, C6	496 (36.3)	472 (49.6)	24 (5.8)	
VBA	48 (3.5)	32 (3.4)	16 (3.8)	
Triglycerides(mmol/L)	1.45 ± 0.92	1.53 ± 0.96	1.24 ± 0.80	**< 0.001**
Total Cholesterol(mmol/L)	4.40 ± 0.98	4.47 ± 0.93	4.23 ± 1.06	**< 0.001**
HDL (mmol/L)	1.33 ± 0.38	1.33 ± 0.37	1.33 ± 0.40	0.866
HDL (mmol/L)				**0.014**
< 0.9	149 (10.9)	91 (9.6)	58 (13.9)	
0.9 ~ 1.3	526 (38.5)	388 (40.8)	138 (33.2)	
> = 1.3	693 (50.7)	473 (49.7)	220 (52.9)	
LDL (mmol/L)	2.54 ± 0.81	2.60 ± 0.80	2.42 ± 0.83	**< 0.001**

Values are the mean ± SD, n (%)

Abbreviations: HDL hHigh-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *BMI* body massive index, *C7* communicating segment of the internal carotid artery, *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *C4* cavernous segment of the internal carotid artery, *C5* clinoid segment of the internal carotid artery, *C6* ophthalmic segment of the internal carotid artery, *VBA* vertebro-basilar artery

Table 2 Univariable logistic regression between HDL and ruptured intracranial aneurysm

Variable	OR (95%CI)	*P* value
Age(yrs.)	1 (0.99 ~ 1.01)	0.583
Sex (Male vs. Female)	1.43 (1.12 ~ 1.82)	**0.004**
Height(cm)	1.02 (1.01 ~ 1.04)	**0.002**
Weight(kg)	1.01 (1 ~ 1.03)	**0.012**
BMI(kg/m^2)	1.02 (0.98 ~ 1.05)	0.31
Hypertension (Yes vs. No)	1.36 (1.07 ~ 1.71)	**0.011**
Diabetes Mellitus (Yes vs. No)	0.66 (0.41 ~ 1.08)	0.1
Coronary Artery Disease (Yes vs. No)	0.56 (0.26 ~ 1.23)	0.152
Atrial Fibrillation (Yes vs. No)	0.23 (0.03 ~ 1.78)	0.158
Current Tobacco Use (Yes vs. No)	2.36 (1.84 ~ 3.03)	**< 0.001**
Current Alcohol Use (Yes vs. No)	2.08 (1.63 ~ 2.66)	**< 0.001**
Size(mm)	0.96 (0.94 ~ 0.99)	**0.003**
Location (ACA vs. C7)	1.54 (1.11 ~ 2.14)	**0.01**
Location (MCA vs. C7)	0.72 (0.51 ~ 1.02)	0.062
Location (C4, C5, C6 vs. C7)	0.06 (0.04 ~ 0.1)	**< 0.001**
Location (VBA vs. C7)	0.62 (0.33 ~ 1.17)	0.14
HDL (mmol/L)	1.03 (0.76 ~ 1.39)	0.866
HDL (< 0.9 mmol/L vs. 0.9 ~ 1.3 mmol/L)	1.79 (1.22 ~ 2.63)	**0.003**
HDL (≥ 1.3 mmol/L vs. 0.9 ~ 1.3 mmol/L)	1.31 (1.02 ~ 1.68)	**0.037**

Abbreviations: HDL high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *BMI* body massive index, *MCA* middle cerebral artery, *C4* cavernous segment of the internal carotid artery, *C5* clinoid segment of the internal carotid artery, *C6* ophthalmic segment of the internal carotid artery, *VBA* vertebro-basilar artery, *C7* communicating segment of the internal carotid artery

with HDL levels higher than 1.1 mmol/L had an 87% increase in the risk of rupture [OR (95%CI): 1.87 (1.11 ~ 3.12), $p = 0.018$] after adjusting for confounding variables. Similarly, females with HDL levels higher than 1.4 mmol/L had a 63% increase in the risk of rupture [OR (95%CI): 1.63 (1.1 ~ 2.43), $p = 0.015$]. Females with HDL levels lower than 1.1 mmol/L had a 91% increase in the risk of rupture [OR (95%CI): 1.91 (1.2 ~ 3.06), $p = 0.007$] after adjusting for confounding variables (see Table 3).

Discussion

The findings of this cross-sectional study suggest a U-shaped connection between HDL levels and the incidence of IA rupture among both males and females. The study revealed that individuals with HDL levels below 0.9 mmol/L and those with levels above or equal to 1.3 mmol/L had significantly heightened risks of IA rupture compared to those with HDL levels in the range of 0.9 to 1.3 mmol/L. Specifically, the results showed that the risk of aneurysm rupture for individuals with HDL levels below 0.9 mmol/L and above or equal to 1.3 mmol/L increased by 79% and 60%, respectively. Interestingly, males with HDL levels ranging from 0.8 to 1.1 mmol/L and females with levels ranging from 1.1 to 1.4 mmol/L had the lowest risk of IA rupture.

Previous studies have discovered different relationships between HDL levels and health outcomes, with some showing an inverse or linear correlation between HDL and adverse health outcomes like mortality, CAD, and stroke [8–10]. Although HDL has traditionally been considered protective against cardiovascular disease, recent studies have challenged this view. Liu et al. [11] and Trimarco et al. [12] found that both extremely low and high HDL levels may increase cardiovascular risk, while Koch et al. [13] highlighted the heterogeneity of HDL subspecies in influencing stroke risk. Pownall et al. [14] and Feng et al. [15] further emphasized that HDL elevation does not always improve outcomes, with a U-shaped relationship observed between HDL levels and

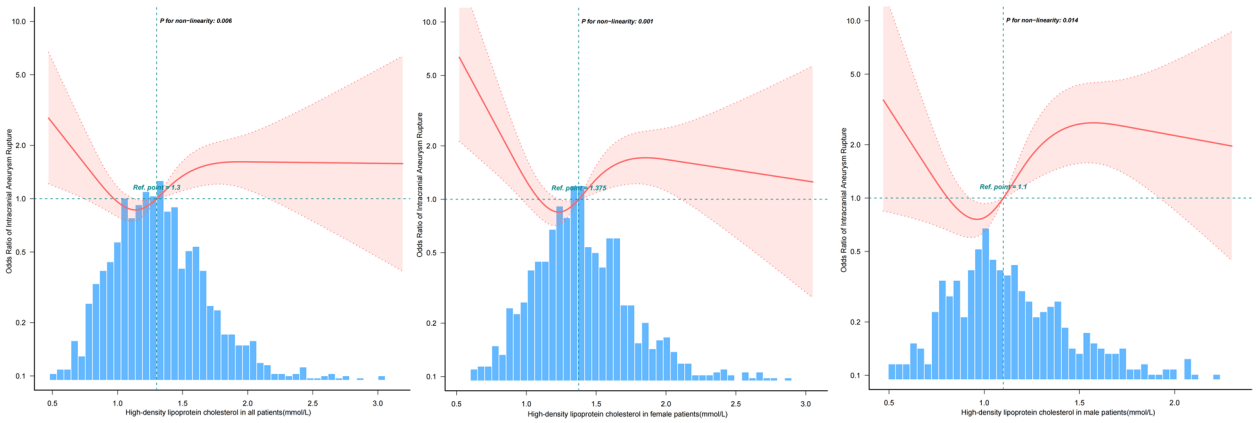

Fig. 2 Restricted cubic spline analysis for the association between HDL (high-density lipoprotein cholesterol) levels and the risk of ruptured intracranial aneurysm. (**A**) A U-shaped relationship between HDL levels and the risk of rupture in the overall patient population. (**B**) The association between HDL levels and rupture risk in female patients, showing specific HDL range intervals associated with increased risk. (**C**) The association between HDL levels and rupture risk in male patients, highlighting different HDL range intervals linked to increased risk

Table 3 Multivariable logistic regression between HDL and ruptured intracranial aneurysm

Variable	No	Ruptured event%	Crude OR (95%CI)	Crude *P* value	Adjusted OR (95%CI)	Adjusted *P* value
HDL for all population(mmol/L) [a]						
0.9 ~ 1.3	526	138 (26.2)	1(Ref)		1(Ref)	
< 0.9	149	58 (38.9)	1.79 (1.22 ~ 2.63)	0.003	1.79 (1.16 ~ 2.78)	**0.009**
> = 1.3	693	220 (31.7)	1.31 (1.02 ~ 1.68)	0.037	1.6 (1.19 ~ 2.17)	**0.002**
P for Trend	1368	416 (30.4)				0.414
HDL for female population(mmol/L) [b]						
1.1 ~ 1.4	316	69 (21.8)	1(Ref)		1(Ref)	
< 1.1	178	63 (35.4)	1.96 (1.31 ~ 2.95)	0.001	1.91 (1.2 ~ 3.06)	**0.007**
> = 1.4	442	130 (29.4)	1.49 (1.07 ~ 2.09)	0.02	1.63 (1.1 ~ 2.43)	**0.015**
P for Trend	936	262 (28)				0.932
HDL for male population(mmol/L) [b]						
0.8 ~ 1.1	165	44 (26.7)	1(Ref)		1(Ref)	
< 0.8	45	17 (37.8)	1.67 (0.83 ~ 3.34)	0.148	1.37 (0.62 ~ 3.02)	0.439
> = 1.1	222	93 (41.9)	1.98 (1.28 ~ 3.07)	0.002	1.87 (1.11 ~ 3.12)	**0.018**
P for Trend	432	154 (35.6)				0.092

Abbreviations: HDL high-density lipoprotein cholesterol, *BMI* body massive index

[a] ajusted for Age + Sex + BMI + Hypertension + Diabetes Mellitus + Coronary Heart Disease + Atrial Fibrillation + Current Tobacco Use + Current Alcohol Use + Size + Location

[b] ajusted for Age + BMI + Hypertension + Diabetes Mellitus + Coronary Heart Disease + Atrial Fibrillation + Current Tobacco Use + Current Alcohol Use + Size + Location

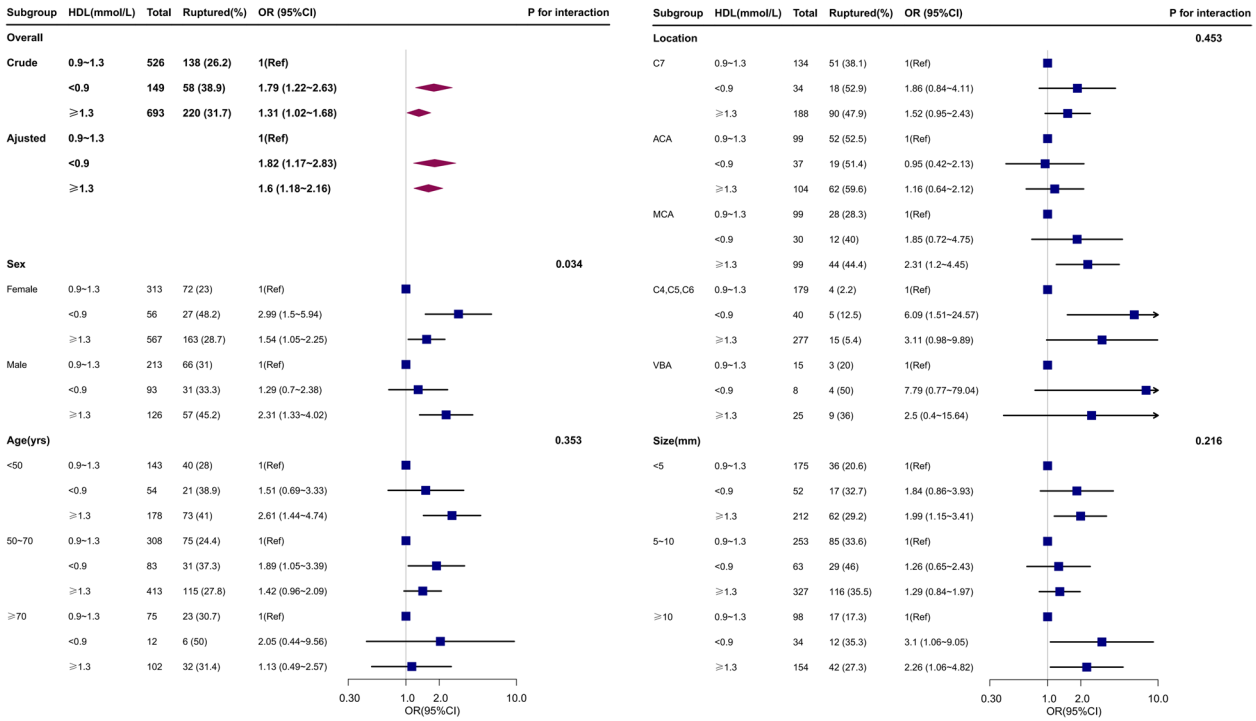

Fig. 3 Association between HDL and risk of intracranial aneurysm rupture. Forest plot of HDL (< 0.9mmol/L) OR (≥ 1.3mmol/L) compared with reference HDL (0.9 ~ 1.3 mmol/L) in different subgroups

cardiovascular disease. These findings suggest that simply raising HDL levels may not be an effective therapeutic strategy. However, most of these studies were conducted among patients with existing cardiovascular disease, making it challenging to generalize the results to other populations. Additionally, individuals with both low and high cumulatively averaged HDL have an increased risk of ischemic and hemorrhagic strokes based on the findings of a prospective cohort study that included individuals without a history of stroke, myocardial infarction, or cancer at baseline [16]. These complex relationships between HDL and clinical outcomes suggest that the term "good cholesterol" requires re-evaluation.

This study found that both low and high HDL levels are associated with an increased risk of IA rupture. For instance, Can et al. [5] identified low HDL levels as an independent risk factor for IA rupture, while Zhang et al. [4] supported this finding, suggesting that low HDL levels may contribute to IA rupture by impairing vascular lipid metabolism and promoting inflammation. Additionally, Gu et al. [10] provided indirect evidence, showing that low HDL levels are associated with an elevated risk of hemorrhagic stroke, including SAH. Conversely, a trial conducted in Finland reported that serum HDL levels of ≥ 0.85 mmol/L reduced the risk of SAH in 85 men [17]. However, other studies have suggested that higher HDL levels may increase the risk of IA rupture. For example, an observational cohort study of 581 patients with IA found that elevated HDL levels exceeding 1.27 mmol/L were associated with an increased risk of IA rupture [7]. These findings suggest a potential bidirectional effect of HDL levels on IA rupture risk, where moderately elevated HDL levels may provide vascular protection, but excessively high levels could have adverse effects. Further research is needed to elucidate the complex role of HDL in IA rupture and SAH. Notably, our study employed strict exclusion criteria, such as excluding patients with MIAs and those with an onset time exceeding 48 h at the time of hospitalization (refer to our exclusion criteria). These measures likely minimized confounding factors, enabling a more precise evaluation of the relationship between HDL levels and IA rupture. Moreover, our research is the first to show a U-shaped association between HDL levels and the risk of IA rupture while adjusting for confounding factors. Furthermore, our findings confirmed a U-shaped curve in both sexes, and we identified the optimal range of HDL for men and women. Men with HDL levels of 0.8 to 1.1 mmol/L and women with 1.1 to 1.4 mmol/L had the lowest risk of IA rupture. Therefore, our research fills the critical void in the current knowledge regarding the IA population. This is because current risk estimation tools consider high HDL levels as a safeguard against IA rupture. However, we discovered that a protective influence may not be valid at high levels and could increase the risk instead. Hence, for patients with IA, it seems reasonable to keep HDL levels within an appropriate range according to sex. The identification of sex-specific HDL thresholds highlights the importance of considering sex-based differences in risk stratification for IA rupture. Future clinical guidelines may need to account for these thresholds to optimize patient outcomes.

Low HDL levels may increase the risk of IA rupture through several biological mechanisms. HDL plays a critical role in maintaining endothelial function, and reduced levels can lead to endothelial dysfunction, weakening the vascular wall and increasing its susceptibility to rupture [11, 14, 16]. Additionally, HDL-C has anti-inflammatory properties, and low levels may fail to suppress inflammatory responses, resulting in increased infiltration of inflammatory cells and structural fragility of the aneurysmal wall [18, 19]. HDL also regulates platelet function, and its deficiency may lead to abnormal platelet activation, exacerbating vascular stress [20]. Genetic factors, such as cholesteryl ester transfer protein (CETP) gene variants, have been linked to low HDL levels and increased cerebrovascular risk [21]. Finally, low HDL levels may impair lipid metabolism in the arterial wall, contributing to maladaptive vascular remodeling and increased fragility [22]. These mechanisms collectively explain the association between low HDL levels and elevated IA rupture risk.

The reasons behind the potential association between high HDL levels and an increased risk of IA rupture are yet to be fully understood. Nevertheless, clinical and basic research and essential research insights can shed light on this matter. Firstly, studies have found that genetic variants that increase HDL levels, such as those found in CETP, have been associated with higher risks of stroke [23]. Secondly, elevated plasma HDL levels resulting from the deletion of Scarb1 in mice have been shown to cause abnormalities in platelets [24], erythrocytes [25], atherosclerosis [26], heart defects [27, 28], and female infertility [29], suggesting a potential correlation with IA rupture. Thirdly, the transfer of free cholesterol (FCh) between macrophages and HDL is reversible, and this means that the reverse process may be involved in the development of increased atherosclerotic cardiovascular disease (ASCVD) in cases of high plasma HDL-FCh concentrations [14]. A U-shaped correlation between ASCVD and plasma HDL concentrations has been observed due to the transfer of FCh from triglyceride-rich lipoproteins to HDL during lipolysis [15], highlighting the relevance of FCh concentrations in plasma and HDL for treatment strategies [14]. Fourthly, the functional role of heterogeneous groups of HDL particles beyond their

levels may be a critical factor, as only apoA1 in HDL that lacked apoC3, apoJ, or apoE has been inversely related to the prevalence of covert stroke [13]. Lastly, HDL's potential contribution to endothelial dysfunction [30] could also play a role in IA formation [31] and rupture [32, 33]. Further research is needed to investigate the mechanisms controlling FCh concentrations, HDL subfractions, and the functionality of HDL apolipoprotein components to better understand the association between high levels of HDL and IA rupture.

The major strength of our study is the high-quality database. Among the patients we excluded are those with arteriovenous brain malformations, dura mater arteriovenous fistulas, fusiform or dissecting aneurysms, pseudoaneurysm, moyamoya disease, non-aneurysmal SAH, coagulation disorders, thrombocytopenia, cerebral hemorrhage in basal ganglia, lobar intracerebral hemorrhage, tumor, and pregnancy. We also excluded patients who had undergone treatment for their IA(s) before their presentation. Additionally, we made sure to specifically exclude patients with MIAs, as these have a higher risk of growth and rupture due to a family predisposition [34–36].

Building on this rigorous selection process, one of the additional strengths of our study is the careful timing of serum lipid measurements. We ensured that serum lipid levels were measured within 48 h after stroke onset, a critical window during which acute-phase effects are minimal and unlikely to significantly alter lipid concentrations. Previous studies have shown that the induction of the acute phase response in humans can result in a reduction of HDL phospholipids without significantly altering HDL levels. This stability is attributed to mechanisms such as the recycling of apoA-I back into the HDL fraction, which reduces apoA-I clearance and helps maintain HDL levels [37, 38]. Furthermore, serum amyloid A (SAA)-containing HDL, while cleared more rapidly, retains ABCA1- and SRBI-dependent cholesterol efflux capacity, which may also contribute to the preservation of plasma HDL levels [39, 40]. Additionally, studies have demonstrated that serum lipid levels measured within 48 h after stroke onset accurately reflect prestroke lipid concentrations, as acute-phase effects are minimal within this short timeframe [41, 42]. Given that serum lipid levels in our study were measured within this critical window, we believe that the inclusion of ruptured IA cases is valid and provides important insights into the relationship between HDL levels and IA rupture risk. This approach ensures that the acute-phase response does not significantly confound our findings, while capturing the specific effects related to ruptured aneurysms.

The study that has been conducted comes with certain limitations that need to be considered. One of the primary limitations is the retrospective design that has been used. Another limitation that may impact the data is the unknown fasting status of HDL levels. However, it is essential to note that studies indicate no significant difference between fasting versus unknown fasting lipid levels within subjects [5]. Another limitation of our study is the potential for different confounding biases associated with higher and lower HDL levels. While we adjusted for known risk factors, residual confounding cannot be completely ruled out, and future studies should further explore these potential biases. Furthermore, the findings obtained from the study may not be applicable or relevant to other populations as only ethnically Chinese adults mainly residing in Sichuan Province were included in the research. In addition, information on lipid-lowering medication use was not consistently available in our dataset, which may have introduced residual confounding in the analysis of serum HDL levels. To confirm the results, the need for additional data from studies like Mendelian randomization, clinical trials, and mechanistic studies cannot be ignored.

Conclusions

According to the results of our research, it has been established that there exists a correlation between both low and high levels of HDL and an elevated risk of IA rupture. In the Chinese population, individuals with HDL levels ranging from 0.9 to 1.3 mmol/L exhibited the least likelihood of experiencing a ruptured IA.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04099-3.

Supplementary Material 1.

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Authors' contributions

Concept and design: Miao, You, XY Wang. Acquisition, analysis, or interpretation of data: XY Wang, Miao, Guo. Drafting of the manuscript: Miao, You. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: XY Wang, Miao. Administrative, technical, or material support: Miao, XY Wang, Guo, You. Supervision: You. 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

This study was approved by the Biomedical Ethics Review Committee of West China Hospital of Sichuan University and was registered with the Chinese Clinical Trials Registry (ChiCTR2300071616). Following national legislation and institutional requirements, informed consent was not necessary for participation in this study. All of our authors confirm that all methods have been carried out in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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