LDL-C/HDL-C is Associated With Ischaemic Stroke in Patients With Non-Valvular Atrial Fibrillation: A Case-Control Study

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Research

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Abstract

Background

This study explored relationships between low-/high-density lipoprotein cholesterol ratio (LDL-C/HDL-C) and other clinical indicators and ischaemic stroke (IS) in non-valvular atrial fibrillation (NVAF) patients in Xinjiang, which could provide a theoretical and therapeutic basis for patients with NVAF.

Methods

NVAF patients who were admitted to 10 medical centres across Xinjiang were divided into the stroke (798 patients) and control (2671 patients) groups according to whether acute IS occurred. Univariate and multivariate logistic regression analysis was used to examine the independent risk factors for IS in NVAF patients. We used factor analysis and principal component regression analysis to analyse the main influencing factors of IS. Receiver operating characteristic (ROC) curve analysis was used to evaluate the optimal cut-off value of LDL-C/HDL-C in predicting IS.

Results

Multivariate logistic regression showed that the risk of IS in the highest quartile of LDL-C/HDL-C (≥ 2.73) was 16.23-fold that in the lowest quartile (< 1.22); IS risk was 2.27-fold higher in obese patients (BMI ≥ 28 kg/m^2) than in normal-weight subjects; IS risk was 3.15-fold higher in smoking than in non-smoking patients. The area under the ROC curve of LDL-C/HDL-C was 0.76, optimal critical value was 2.33, sensitivity was 63.53%, and specificity was 76.34%. Principal component regression analysis showed that LDL-C/HDL-C, age, smoking, drinking, LDL-C and hypertension were risk factors for IS in NVAF patients.

Conclusions

LDL-C/HDL-C > 1.22, smoking and BMI ≥ 24 kg/m^2 were independent risk factors for IS in NVAF patients, of which LDL-C/HDL-C was the main risk factor.

1. Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice and confers a four- to five-fold increase in risk of stroke compared with people without AF. In addition, ischaemic stroke (IS) caused by AF is particularly characterized by a mortality rate of 20% and a disability rate of 60% [1]. With or without anticoagulant therapy, Asian patients with AF were more likely to have IS than non-Asian patients; meanwhile, the risk of haemorrhagic stroke was also higher. The population of Asia is ageing

rapidly. In 2050, it is estimated that there are approximately 72 million patients with AF, of which 2.9 million may have AF-related stroke [2]. The management costs of AF are high—approximately 10100–14200 dollars per person in the United States and 450–3000 dollars per person in Europe [3]. Therefore, the prevention of IS caused by AF is an important part of the treatment strategy of AF.

- $CHADS_2$ and CHA_2DS_2-VASc scores are currently widely used to assess the risk stratification of thromboembolism and stroke in patients with AF. Warfarin or non-vitamin K antagonist oral anticoagulants (NOACs) are recommended for patients at high risk of stroke. However, the above-mentioned two scoring systems do not take into account other potential risk factors, such as renal function impairment, rheumatoid arthritis, obesity or smoking, as well as clinically accessible laboratory indicators, imaging values and other parameters [4, 5]. Friberg *et al.* [6] have shown that clinically diagnosed heart failure is not an independent risk factor for stroke in AF patients. Previous studies have shown that left atrial enlargement and low-density lipoprotein cholesterol (LDL-C) are clinically easy-to-obtain indicators for risk stratification of thromboembolism events in patients with AF [7–9]. High-density lipoprotein (HDL-C) was negatively correlated with the risk or severity of IS [10–11]. An earlier study suggested that the LDL-C/HDL-C ratio was a risk indicator in cardiovascular disease with greater predictive value compared with the isolated parameters used independently, particularly LDL-C [12]. However, data on the association between LDL-C/HDL-C and IS in patients with AF are limited, and the aetiology of IS is complex. Therefore, the present study intends to explore the relationships between LDL-C/HDL-C and other clinical indicators and IS in non-valvular atrial fibrillation (NVAF) patients in Xinjiang to provide a basis for prevention, treatment and the comprehensive management of patients with AF.

2. Methods

2.1 Study design and participants

- This study was approved by the ethics committee of First Affiliated Hospital of Xinjiang Medical University (Ethics Approval Number: 20140925-04). All participants signed written informed consent.
- We enrolled all patients with NVAF who were admitted with their first IS stroke at 10 comprehensive large hospitals in different regions of Xinjiang between 1 January 2017 and 1 January 2019. Patients with NVAF who were admitted to the same hospital at the same time for any reason other than acute IS were selected as controls. The inclusion criteria were as follows: (1) patients with NVAF ≥ 18 years old and (2) acute IS confirmed by head computed tomography (CT) or magnetic resonance imaging (MRI). The exclusion criteria were as follows: (1) congenital heart valve disease, rheumatic heart valve disease, heart valve replacement, senile heart valve disease and other heart valve diseases; (2) malignant tumour, chronic kidney or liver diseases, and thyroid diseases; (3) ischaemic hypoxic encephalopathy, dementia and other intracranial lesions; (4) aetiology involving systemic inflammatory reaction, acute myocardial infarction and other reversible factors; and (5) AF diagnosis after IS. Finally, a total of 798 cases and 2671 controls were included.

2.2 AF and IS assessments

- The diagnosis of AF was obtained from 12-lead electrocardiographs (ECG) or 24-Holter ECG monitor recordings [13] or a history of AF diagnosed by a cardiologist. IS was diagnosed by the diagnostic criteria established by the American Heart Association and the American Stroke Association: an episode of acute onset, focal neurological deficit caused by focal cerebral, spinal, or retinal infarction, responsible ischaemic brain lesions recorded by CT or MRI, and no evidence of frank blood on CT or MRI of the brain [14].

2.3 Data collection and lipid profile analyses

- We recorded the following baseline data: gender, age, smoking status, comorbidities (hypertension, diabetes mellitus, heart failure, and vascular disease) and medication history. The CHA_2DS_2-VASc score (one point each for heart failure, hypertension, 65–74 years old, diabetes mellitus, vascular disease and female; two points each for age over 75 years and previous stroke/transient ischaemic attack (TIA)/thromboembolism) was used to assess the risk of IS in AF patients. Fasting venous blood samples were obtained from all subjects on the second day of hospitalization. The levels of triglycerides (TG), total cholesterol (TC), LDL-C, HDL-C levels, fasting plasma glucose, blood urea nitrogen, creatinine and uric acid were directly measured on an automatic blood cell analyser. Non-HDL cholesterol = TC-HDL-C.

2.4 Statistical analysis

- Statistical analyses were performed using IBM SPSS Statistics, SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA) and MedCalc (MedCalc Software, Mariakerke, Belgium). Continuous variables with a normal distribution are presented as the mean ± standard deviation (SD), and comparisons between groups were conducted by two independent samples Student's t tests; non-normal variables are reported as the median and inter-quartile range (IQR). The Mann-Whitney U test was used for inter-group comparison. The categorical variables are expressed by numbers and percentages and compared using the chi-square test. Univariate and multivariate logistic regression analysis was used to examine the independent risk factors for IS in NVAF patients. We used factor analysis and principal component regression analysis to analyse the main influencing factors of IS. Receiver operating characteristic (ROC) curve analysis was used to evaluate the optimal cut-off value of LDL-C/HDL-C in predicting IS and the ability of LDL-C/HDL-C to predict IS in patients with AF. The pairwise comparison of ROC curves (using the De Long method) was performed using Z statistics. A value of $P < 0.05$ was considered significant.

3. Results

3.1 Baseline characteristics

- Age, BMI, CHA_2DS_2-VASc score, LDL-C level and LDL-C/HDL-C in the stroke group were higher than those in the control group (all $P < 0.05$). The level of HDL-C in the stroke group was lower than that in the control group ($P < 0.01$). The proportions of males, smoking, hypertension, vascular disease and anti-hypertensive drug history in the stroke group were higher than those in the control group (all $P < 0.05$) (Table 1).

Table 1
Baseline characteristics of non-valvular atrial fibrillation patients with and without ischaemic stroke.

Demographic characteristics	Stroke		$t/\chi^2/Z$	*P*
	Yes (n = 798)	No (n = 2671)		
Gender				
Women, n (%)	305 (38.22)	825 (30.89)	15.04	< 0.01
Men, n (%)	493 (61.78)	1846 (69.11)		
Age, year	71.64 ± 9.96	67.30 ± 12.01	-10.28	< 0.01
Body mass index, kg/m^2	25.20 ± 3.26	24.75 ± 3.35	-3.35	< 0.01
Hypertension, n (%)	352 (44.11)	907 (33.96)	27.39	< 0.01
Diabetes mellitus ,n (%)	171 (21.43)	531 (19.88)	0.91	0.34
Heart failure, n (%)	424 (53.13)	1510 (56.53)	2.88	0.09
Vascular disease, n (%)	121 (15.16)	263 (9.85)	17.64	< 0.01
CHA_2DS_2-VASc score, mean	4.96 ± 1.37	2.47 ± 1.40	-44.45	< 0.01
Smoking, n (%)	269 (33.71)	660 (24.71)	25.38	< 0.01
Drinking, n (%)	124 (15.54)	371 (13.89)	1.37	0.24
TG, mmol/L	1.11 ± 0.67	1.14 ± 0.89	1.08	0.28
TC, mmol/L	3.57 ± 1.29	3.48 ± 1.47	-1.55	0.12
non-HDL-C, mmol/L	2.65 ± 1.25	2.48 ± 1.42	-3.10	< 0.01
LDL-C, mmol/L	2.58 ± 1.02	1.69 ± 0.86	-22.18	< 0.01
HDL-C, mmol/L	0.92 ± 0.39	1.00 ± 0.34	5.47	< 0.01
LDL-C/HDL-C	2.83 (1.83, 4.09)	1.55 (1.10, 2.27)	-22.17	< 0.01
Uric acid, umol/L	278.54 ± 147.06	295.71 ± 145.64	2.92	< 0.01
Creatinine, mmol/L	75.44 ± 37.23	76.00 ± 59.92	0.32	0.75
Blood urea nitrogen, mmol/L	5.97 ± 2.68	6.05 ± 2.77	0.67	0.50
Fasting plasma glucose, mmol/L	5.93 ± 2.44	5.75 ± 2.29	-1.92	0.06
Previous Medications				
Anti-hypertensive drugs, n (%)	287 (35.96)	754 (28.23)	17.51	< 0.01

Note: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = Non-HDL-C cholesterol; TC = total cholesterol; TG = triglycerides.

Demographic characteristics	Stroke		$t/\chi^2/Z$	*P*
	Yes (n = 798)	No (n = 2671)		
Anti-diabetic agents, n (%)	141 (17.67)	420 (15.72)	1.71	0.19
Statins, n (%)	85 (10.65)	345 (12.92)	2.90	0.09
anti-platelet drugs, n (%)	150 (18.80)	583 (21.83)	3.39	0.07
anticoagulant drugs, n (%)	189 (23.68)	656 (24.56)	0.26	0.61

Note: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = Non-HDL-C cholesterol; TC = total cholesterol; TG = triglycerides.

3.2 Univariate logistic regression analysis of IS

- Univariate logistic regression showed that the highest quartile (fourth quartile, ≥ 2.73) of LDL-C/HDL-C had an OR of 13.26 (95% CI: 9.84–17.86, P < 0.01) compared with the bottom quartile (first quartile, < 1.22) (Table 2). LDL-C levels (OR: 5.57, 95% CI: 3.53–8.80, P < 0.01) were also found to be a risk factor for IS in patients with NVAF. HDL-C (OR: 0.81, 95% CI: 0.70–0.95, P = 0.01) was a protective factor for IS in patients with NVAF. Other significant correlates of IS were age, female sex, hypertension, vascular disease, CHA_2DS_2-VASc score, smoking and BMI (all p < 0.05).

Table 2
Univariate logistic regression analysis for risk factors of ischaemic stroke.

Characteristic	β	SE	Waldχ^2	OR	95% CI	*P*
Age (years)						
< 65	Reference					
65 to 74	0.57	0.11	27.74	1.77	1.43, 2.20	< 0.01
≥ 75	0.89	0.11	72.50	2.44	1.99, 3.00	< 0.01
Women	0.33	0.08	14.98	1.38	1.17, 1.63	< 0.01
Hypertension	0.43	0.08	27.19	1.54	1.31, 1.80	< 0.01
Diabetes mellitus	0.10	0.10	0.91	1.10	0.91, 1.33	0.34
Vascular disease	0.49	0.12	17.38	1.64	1.30, 2.06	< 0.01
CHA_2DS_2-VASc score	1.27	0.05	724.32	3.55	3.24, 3.90	< 0.01
Smoking	0.44	0.09	25.16	1.55	1.31, 1.84	< 0.01
Drinking	0.13	0.11	1.36	1.14	0.92, 1.42	0.24
Heart failure	-0.14	0.08	2.88	0.87	0.74, 1.02	0.09
TG (mmol/L)						
≤ 2.26	Reference					
> 2.26	-0.19	0.21	0.77	0.83	0.55, 1.26	0.38
TC (mmol/L)						
≤ 6.22	Reference					
> 6.22	0.16	0.31	0.26	1.18	0.64, 2.17	0.61
non-HDL-C (mmol/L)	0.09	0.03	9.03	1.09	1.03, 1.16	< 0.01
LDL-C (mmol/L)						
≤ 4.14	Reference					
> 4.14	1.72	0.23	54.25	5.57	3.53, 8.80	< 0.01
HDL-C (mmol/L)						
≥ 1.04	-2.05	0.08	6.47	0.81	0.70, 0.95	0.01

Note: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = Non-HDL-C cholesterol; TC = total cholesterol; TG = triglycerides; 95% CI = 95% confidence interval; OR = odds ratio; SE = standard error.

Characteristic	β	SE	Waldχ^2	OR	95% CI	*P*
< 1.04	Reference					
LDL-C/HDL-C						
First quartile (< 1.22)	Reference					
Second quartile [1.22, 1.71)	0.69	0.17	16.48	2.00	1.43, 2.79	< 0.01
Third quartile [1.71, 2.73)	1.48	0.16	88.09	4.39	3.22, 5.79	< 0.01
Fourth quartile (≥ 2.73)	2.58	0.15	289.19	13.26	9.84, 17.86	< 0.01
Body mass index (kg/m^2)						
< 24	Reference					
[24, 28)	0.43	0.09	23.18	1.54	1.29, 1.83	< 0.01
≥ 28	0.34	0.12	7.77	1.41	1.11, 1.79	< 0.01
Uric acid (umol/L)	-0.001	0.00	8.46	1.00	0.999, 1.000	< 0.01
Creatinine (mmol/L)	0.00	0.001	0.06	1.00	0.998, 1.001	0.80
Blood urea nitrogen (mmol/L)	-0.01	0.02	0.45	0.99	0.96, 1.02	0.50
Fasting plasma glucose (mmol/L)						
< 7	Reference					
≥ 7	0.13	0.10	1.62	1.13	0.94, 1.38	0.20

Note: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = Non-HDL-C cholesterol; TC = total cholesterol; TG = triglycerides; 95% CI = 95% confidence interval; OR = odds ratio; SE = standard error.

3.3 Multivariate logistic regression analysis of IS

- Multivariate logistic regression showed that the risk of IS in the highest quartile of LDL-C/HDL-C (≥ 2.73) was 16.23-fold higher than that in the lowest quartile (< 1.22) (Table 3). The risk of IS was 2.27-fold higher in obese patients (BMI ≥ 28 kg/m^2) than in normal-weight subjects. LDL-C/HDL-C, BMI and smoking were independent risk factors for IS in NVAF patients. Since LDL-C/HDL-C comprehensively reflects blood lipid information, we further conducted multivariate calibration. The results showed that the multivariable-adjusted ORs of IS in different regression models increased linearly (P < 0.01) (Table 4).

Table 3
Multivariate logistic regression analysis for risk factors of ischaemic stroke.

Characteristic	β	SE	Waldχ^2	OR	95% CI	*P*
CHA_2DS_2-VASc score	1.41	0.06	635.68	4.08	3.66, 4.56	< 0.01
Smoking	1.15	0.14	69.59	3.15	2.41, 4.13	< 0.01
LDL-C/HDL-C						
First quartile (< 1.22)	Reference					
Second quartile [1.22, 1.71)	0.80	0.21	14.50	2.22	1.47, 3.36	< 0.01
Third quartile [1.71, 2.73)	1.65	0.20	68.16	5.21	3.52, 7.72	< 0.01
Fourth quartile (≥ 2.73)	2.79	0.20	194.65	16.23	10.97, 24.01	< 0.01
Body mass index, kg/m^2						
< 24	Reference					
[24, 28)	0.71	0.14	27.40	2.03	1.56, 2.65	< 0.01
≥ 28	0.82	0.19	18.80	2.27	1.57, 3.29	< 0.01

Note: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; 95% CI = 95% confidence interval; OR = odds ratio; SE = standard error.

Table 4
Multivariable adjusted odds ratios of LDL-C/HDL-C quartile in relation to risk factor of ischaemic stroke.

Variables	LDL-C/HDL-C quartile				*P*
	Q1 (n = 865)	Q2 (n = 869)	Q3 (n = 868)	Q4 (n = 867)	
ischaemic stroke case, n (%)	58 (7.27)	109 (13.66)	208 (26.07)	423 (53.00)	< 0.01
Range of LDL-C/HDL-C quartile	< 1.22	[1.22, 1.71)	[1.71, 2.73)	≥ 2.73	
Model1	1.00	2.14 (1.53, 2.99)	5.11 (3.73, 6.99)	16.00 (11.79, 21.71)	< 0.01
Model2	1.00	2.37 (1.60, 3.53)	6.05 (4.13, 8.84)	17.34 (11.87, 25.32)	< 0.01
Model3	1.00	2.56 (1.82, 3.62)	6.19 (4.46, 8.60)	24.45 (17.18, 34.79)	< 0.01

Note: Model1 adjusted for age and gender; Model2 adjusted for CHA_2DS_2-VASc score; Model3 adjusted for blood urea nitrogen, BMI, creatinine, drinking, fasting plasma glucose, non-high-density lipoprotein cholesterol, smoking, triglyceride, total cholesterol, and uric acid. Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

3.4 Prediction of IS by LDL-C/HDL-C

- The area under the ROC curve (AUC) of LDL-C/HDL-C was 0.76, the optimal critical value was 2.33, the sensitivity was 63.53%, and the specificity was 76.34% (Table 5). The AUC of the CHA_2DS_2-VASc score was 0.89, the sensitivity was 85.09%, and the specificity was 75.78%. Meanwhile, the AUC of the CHA_2DS_2-VASc score plus LDL-C/HDL-C was significantly higher than that of the CHA_2DS_2-VASc score alone (0.91 vs. 0.89, $Z = 3.26$, $P < 0.01$). These results suggested that the predictive power of the CHA_2DS_2-VASc score for the risk of IS in patients with NVAF was improved after the addition of LDL-C/HDL-C (Fig. 1).

Table 5
Areas under the receiver operating characteristic curve (AUC) of LDL-C/HDL-C, CHA_2DS_2-VASc and LDL-C/HDL-C + CHA_2DS_2-VASc.

Variables	Sensitivity	Specificity	Cut-off value	AUC	SE	95% CI	*P*
LDL-C/HDL-C	63.53	76.34	2.33	0.76	0.01	0.74, 0.77	< 0.01
CHA_2DS_2-VASc	85.09	75.78	3.00	0.89	0.01	0.88, 0.90	< 0.01
LDL-C/HDL-C + CHA_2DS_2-VASc	79.95	87.98	6.26	0.91	0.01	0.90, 0.92	< 0.01

Note: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; 95% CI = 95% confidence interval; SE = standard error.

3.5 Factor analysis and influencing factor analysis of IS

- Factor analysis was performed on ten clinical indexes. The Kaiser-Meyer-Olkin (KMO) test value was 0.53, and the Bartlett test showed that $\chi^2 = 557.85$, $P < 0.01$. The results of the two tests showed that there was a strong correlation between the indicators, and the data were suitable for factor analysis. As seen in Table 6, the variable correlation matrix has the five largest eigenvalues, namely, 1.73, 1.43, 1.30, 1.25, and 1.08, and the cumulative contribution rate of variance is 67.85%, which shows that the first five principal components provide most of the information contained in the original data. Principal component 1 (PC1) mainly represents LDL-C/HDL-C and HDL-C, PC2 mainly represents smoking and drinking, PC3 mainly represents TC and TG, PC4 mainly represents LDL-C and age, and PC5 mainly represents hypertension. The following shows the factor naming: PC1 is the blood lipid ratio factor, PC2 is the bad living habits factor, PC3 is the blood lipid-related factor, PC4 is the age-related factor, and PC5 is the blood pressure-related factor. Multivariate unconditional logistic regression analysis was performed with the five common factors (PC1-PC5) as covariates and with the absence or presence of IS as the dependent variable. The results showed that, with the exception of PC3, the other factors were risk factors for IS in patients with AF (Table 7). The standardized principal regression equation is as follows: Zy = 0.53 (PC1) + 0.11 (PC2) + 0.99 (PC4) + 0.23 (PC5) -1.45.

Table 6
Factor analysis: loadings of related variables of ischaemic stroke in atrial fibrillation patients .

Variables	PC1	PC2	PC3	PC4	PC5
HDL-C	-0.91	-0.01	0.10	0.21	0.05
LDL-C/HDL-C	0.89	-0.03	0.05	0.27	-0.01
Drinking	-0.02	0.84	0.06	-0.05	0.08
Smoking	0.00	0.83	-0.09	-0.02	-0.06
TG	0.08	0.00	0.79	-0.06	-0.11
TC	-0.22	-0.08	0.66	0.26	0.28
LDL-C	0.03	-0.01	0.21	0.86	-0.16
Age	0.02	-0.11	-0.38	0.56	0.33
Hypertension	0.18	-0.05	0.17	-0.12	0.82
Diabetes mellitus	0.16	-0.05	0.08	-0.06	-0.42
Eigenvalue	1.73	1.43	1.30	1.25	1.08
Explained variance (%)	17.27	14.25	13.04	12.49	10.78
Cumulative variance (%)	17.27	31.52	44.57	57.06	67.85

Note: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PC = principal component; TC = total cholesterol; TG = triglycerides.

Table 7
Principal component regression analysis.

	β	S E	Waldχ^2	OR	95% CI	*P*
PC1	0.53	0.05	107.44	1.70	1.54, 1.88	< 0.01
PC2	0.11	0.04	7.46	1.12	1.03, 1.22	< 0.01
PC3	0.04	0.04	0.86	1.04	0.96, 1.12	0.35
PC4	0.99	0.05	390.52	2.69	2.44, 2.96	< 0.01
PC5	0.23	0.05	21.83	1.26	1.15, 1.39	< 0.01
Constant	-1.45	0.05	882.44	0.24		< 0.01

Note: PC = principal component; 95% CI = 95% confidence interval; OR = odds ratio; SE = standard error.

4. Discussion

- The most common complication of AF is thromboembolism, especially IS. AF-related IS has the characteristics of a high mortality rate and a high disability rate. Because of the combination of high morbidity with a low diagnosis rate of cardiogenic stroke, it is of great significance to accurately identify high-risk patients and give corresponding treatment in time to prevent the occurrence of IS for patients with AF. Currently, there is no risk model that can accurately predict IS in patients with AF. Even the widely used CHA_2DS_2-VASc score has only moderate predictive value [15]. Therefore, the present study explored the risk factors for IS in patients with NVAF in Xinjiang and provided the basis for further clinical treatment. First, multivariate logistic regression analysis showed that LDL-C/HDL-C > 1.22, smoking and BMI ≥ 24 kg/m^2 were independent risk factors for IS in patients with NVAF. Second, principal component regression analysis showed that LDL-C/HDL-C, age, smoking, drinking, LDL-C and hypertension were risk factors for IS in NVAF patients.
- In our study, we found that high LDL-C/HDL-C was an independent risk factor for IS after adjusting for age and other related factors, indicating that high LDL-C/HDL-C may influence the progression of IS through particular pathways. The potential mechanism of the positive correlation between LDL-C/HDL-C and IS in NVAF patients remains unclear, however, there are several possible mechanisms to explain this phenomenon. First, LDL-C/HDL-C indicates the proportion of atherosclerosic and anti-atherosclerotic lipoproteins, which has better predictive power for the development of atherosclerosis. High LDL-C/HDL-C may indicate vulnerability of atherosclerotic plaques, which are prone to plaque rupture and thrombosis and eventually lead to IS. Okuzumi A *et al.* [16] indicated that LDL-C/HDL-C was significantly correlated with aortic plaques and that a ratio of 2.23 might reflect an increase in the amount of mobile and ulcerative aortic plaques in patients with IS. Second, LDL-C/HDL-C may be closely related to inflammation because HDL-C has anti-inflammatory and antioxidant properties [17], and LDL-C may be correlated with inflammation [18]. The high LDL-C/HDL-C ratio may be due to an increase in inflammatory components and a decrease in the anti-inflammatory and antioxidative components reflected in the denominator or both. Pinto A *et al.* [19] identified that inflammatory markers, including TNF-α, IL-6 and von Willebrand factor (vWF), were predictors of new-onset IS in patients with chronic NVAF. Inflammation has been confirmed to be associated with left atrial thrombosis in AF patients [20]. Previous studies have found that inflammatory biomarkers were significantly associated with left atrium or left atrial appendage thrombus outcomes in AF patients [21]. In conclusion, LDL-C/HDL-C may cause IS in NVAF patients by promoting atherosclerosis and left atrial or left atrial appendage thrombosis.
- Nicotine and oxygen free radicals in tobacco cause or aggravate vascular endothelial dysfunction, atherosclerosis and hypercoagulability through a variety of mechanisms. These factors can promote thrombosis. Previous studies have shown that smoking increases the risk of thromboembolism or death in AF patients [22–23]. A recent meta-analysis showed that smoking increased the risk of all-cause and cardiovascular death in AF patients but not stroke or thromboembolism events [24]. A multicentre study identified that smoking was associated with atherosclerosis or thromboembolism in elderly patients with NVAF who did not quit smoking [25]. Incorporating smoking as a risk factor for IS in $CHADS_2$ and CHA_2DS_2-VASc scores could better predict the risk of IS in male patients [26].

The present study found that an increase in BMI is an important risk factor for IS in NVAF patients. Previous studies have shown that BMI is negatively correlated with IS in AF patients [27], which is contrary to the results of the present study. At present, the relationship between obesity and IS remains controversial [27–28]. Large-scale and prospective studies are needed to further explore the impact of BMI on adverse event outcomes in AF patients. We believe that the blood viscosity of obese patients is high and that blood viscosity leads to a decrease in blood flow velocity, which is one of the risk factors for thrombosis.

- Age is an important component of the CHA_2DS_2-VASc score and is one of the risk factors for IS in AF patients. Previous studies have shown that AF is an ageing disease, and with increasing age, the incidence of AF and stroke increases [29–30]. Alcohol intake is a risk factor for thromboembolism. Studies have found that long-term drinking can cause vascular haemodynamic changes, altered blood viscosity, and enhanced platelet aggregation, which subsequently promote the occurrence of IS [31]. Atherosclerosis Risk in Communities (ARIC) studies found that alcohol consumption was not associated with the composite endpoint of IS or cardiovascular death in AF patients [32]. The Stroke Prevention in Atrial Fibrillation (SPAF) I-III trials found that the incidence of IS in patients with AF who regularly drank a small amount of alcohol was lower than that in patients who did not drink alcohol [33]. In contrast, heavy drinking was associated with a higher risk of IS [34]. Hypertension is closely related to stroke, and active and effective control of blood pressure is an important basis for reducing the incidence of IS [35]. Anti-hypertensive treatment could reduce the incidence of stroke in hypertension patients [36]. In terms of mechanisms, hypertension can cause vascular haemodynamic changes, lead to atherosclerosis, further lead to stenosis of the lumen, and affect the blood supply of brain tissue. At the same time, hypertension can promote the remodelling of left atrial structure and function and eventually lead to atrial fibrosis and electrical activity changes. These changes, together with local or systemic inflammatory reactions, lead to local thrombosis or atherosclerotic thrombosis in the left atrium [37].
- The results showed that the contribution rate of PC1 was the highest (17.27%), and the loads of LDL-C/HDL-C and HDL-C were the highest. HDL-C was negatively correlated with IS, and LDL-C/HDL-C was positively correlated with IS. The contribution rate of PC2 was 14.25%, and the factor load of smoking and drinking was the highest, suggesting that bad living habits are one of the risk factors for IS in AF patients. The PC4 contribution rate was 12.49%. The LDL-C and age factor load were the highest, and they were positively correlated with IS. The contribution rate of PC5 was the lowest (10.78%), and the load of the hypertension factor was the highest, suggesting that blood pressure is the influencing factor of IS in AF patients. These results suggest that in clinical practice, in addition to the classic CHA_2DS_2-VASc score to assess the risk of AF stroke, we should also pay attention to blood lipid-related parameters, poor living habits and other factors. The blood lipid-related parameters include LDL-C/HDL-C, which comprehensively considers the impact of LDL-C and HDL-C parameters on stroke and is a better indicator than either measure alone.
- In conclusion, we found that LDL-C/HDL-C, smoking, BMI, age, alcohol consumption, LDL-C and hypertension were risk factors for IS in NVAF patients. LDL-C/HDL-C is the most important risk factor,

which indicates that LDL-C/HDL-C may help identify AF individuals who are at high risk of IS and who may benefit from intensive LDL-lowering therapy. In clinical practice, AF patients often have various diseases, such as hypertension, diabetes, coronary atherosclerotic heart disease, etc., which create challenges for the overall management of AF for medical staff. In addition to focusing on the CHA_2DS_2-VASc score, we should also pay attention to factors such as blood lipid levels, smoking and drinking in AF patients, carry out comprehensive health education, strengthen interventions for unhealthy lifestyles and formulate comprehensive management measures to reduce the incidence rate and harm of IS.

5. Limitations

- Our study was a multicentre case-control study, and the design was retrospective. We will consider conducting a multicentre, prospective study to further explore the relationship between LDL-C/HDL-C and IS in NVAF patients and to further study the relationships between LDL-C/HDL-C and measures in other related disciplines, such as proteomics and genomics.

6. Conclusion

LDL-C/HDL-C, smoking and BMI were independent risk factors for IS in patients with NVAF. LDL-C/HDL-C is the main risk factor, which will also be an important direction of our attention in the future.

Abbreviations

LDL-C/HDL-C: Low-/high-density lipoprotein cholesterol ratio

IS: Ischaemic stroke

NVAF: Non-valvular atrial fibrillation

AF:Atrial fibrillation

NOACs: Non-vitamin K antagonist oral anticoagulants

CT: Computed tomography

MRI: Magnetic resonance imaging

ECG: Electrocardiographs

TIA: Transient ischaemic attack

TG: Triglycerides

TC: Total cholesterol

non-HDL-C:Non-high-density-lipoprotein cholesterol

PC: Principal component

vWF: Von Willebrand factor

Declarations

Ethics declarations

Ethics approval and consent to participate

All participants signed written informed consent. The study conforms to the ethical guidelines of the Declaration of Helsinki. The study was approved by the ethics committee of First Affiliated Hospital of Xinjiang Medical University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflict of interest.

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Authors' contributions

Xian-Hui Zhou and Tao-Peng Tang: Conceptualization, Methodology. **Yao-Dong Li, Jiang-Hua Zhang and Qiang Xing:** Data curation, Software, Visualization. **Ling ZhangandZu Kela Tu-Erhong:** Investigation, Resources. **Lu-Xiang Shang and Yan-Mei Lu:** Project administration, Supervision, Validation.**Xiao-XueZhang:**Formal analysis, Writing-original draft. **Meng Wei :** Writing-review &editing.All authors read and approved the final manuscript.

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Figures

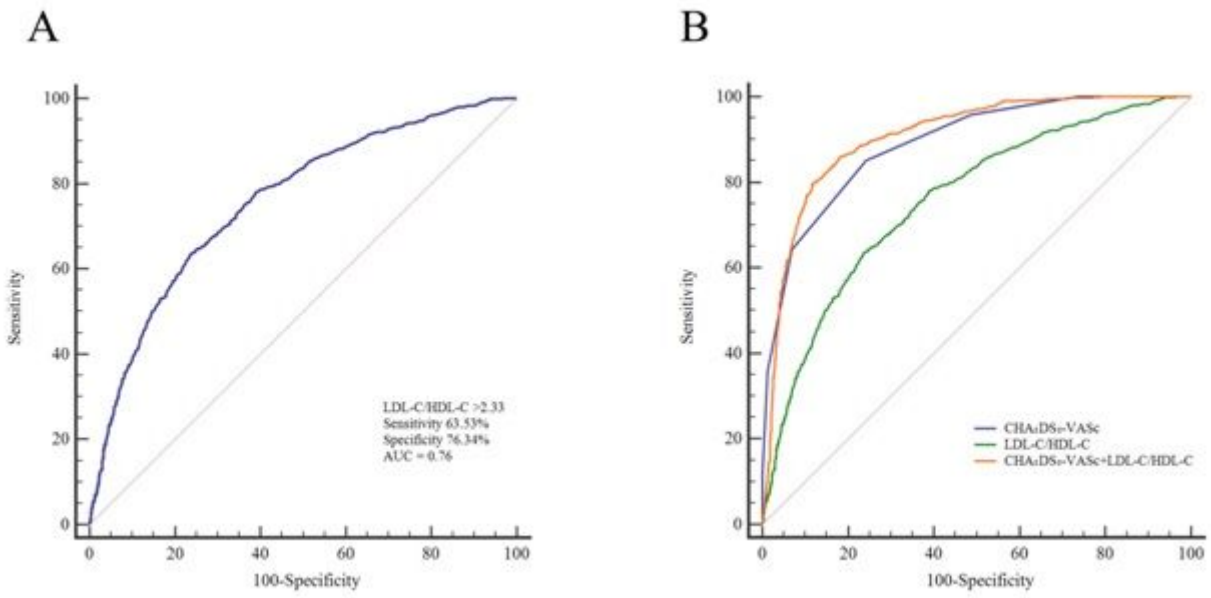

Figure 1

A The ROC curve of LDL-C/HDL-C to predict ischaemic stroke in patients non-valvular atrial fibrillation ; Fig.1B The ROC curves for the CHA2DS2-VASc score and the combination of CHA2DS2-VASc score and LDL-C/HDL-C.Abbreviations:HDL-C =high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.