Association of Elevated Non-HDL-C and LDL-C with Carotid atherosclerosis among Tibetans Living at High Altitudes: A Cross-sectional Study

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Research Article

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Abstract

Background: Hypoxic circumstances impair endothelial function and may contribute to carotid atherosclerosis. In high-altitude areas, there is a scarcity of data on the correlation between lipid particles and carotid atherosclerosis.

Methods: A total of 587 patients who underwent carotid artery ultrasound and met the inclusion and exclusion criteria were enrolled in our cross-sectional study. All participants resided in Luhuo County, Ganzi Tibetan Autonomous Prefecture, Sichuan Province, China (mean altitude: 3,860 meters). We used questionnaires, physical examination, blood sample testing, and ultrasound in our investigation. Spearman correlation analysis and multiple linear regression analysis were performed to explore the association between lipid particles and carotid atherosclerosis. We compared the disparity between lipid particles in predicting atherosclerosis using the receiver operator characteristic curve.

Results: We found a statistically significant association between lipid particles and carotid atherosclerosis. After adjustment for certain variables, including age, gender, mean arterial pressure, and fasting blood glucose, we discovered that non-high-density lipoprotein-cholesterol (non-HDL-C) was a risk factor for carotid intima-media thickness ($\beta = 0.012$, $p = 0.032$) but not for low-density lipoprotein cholesterol (LDL-C) ($p = 0.073$). In terms of lifestyle, non-HDL-C was also found to be a risk factor for atherosclerosis independent of cigarette smoking and vegetarian ($\beta = 0.012$, $p = 0.049$). The area under the curve (AUC) of non-HDL-C was 0.644 (CI: 0.583 – 0.706) while LDL-C was 0.599 (CI: 0.534 - 0.664) in predicting carotid atherosclerosis. The optimal cut-off value of non-HDL-C was 3.625 mmol/L in predicting carotid plaques.

Conclusions: Among Tibetans living in high-altitude areas, non-HDL-C is a better biomarker than LDL-C for carotid artery atherosclerosis independent of conventional risk factors. It is crucial to resolve non-HDL-C dyslipidemia in order to mitigate carotid atherosclerosis in Tibetans living at high-altitude settings.

Background

Globally, atherosclerotic cardiovascular disease (ASCVD) remains a leading cause of premature death (1, 2). According to past reports, carotid intima-media thickness (cIMT) is a measure of atherosclerosis and is associated with future risk of ASCVD(3). In previous studies, hypertension, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, cigarette smoking, and a lack of regular physical exercise were identified as crucial components of incremental ASCVD risk (4–7). Apart from these risk factors, few studies to date have reported ambient hypoxia-induced atheroma formation owing to regulation of intraplaque angiogenesis (8–12). Regarding lipid particles, low density lipoprotein-cholesterol (LDL-C) and non-high-density lipoprotein-cholesterol (non-HDL-C) have been independently linked with an increased relative risk of cardiovascular events (13). These lipid particles are highly correlated but not identical, as non-HDL-C in addition to LDL-C include triglyceride-rich lipoproteins (14). However, which particle is a better predictor of future cardiovascular mortality remains controversial.

More than 140 million people worldwide live at altitudes above 2,400 m. Current evidence indicates that living in a plateau environment has a considerable impact on the cardiovascular system (15). Excessive activation of the sympathetic nervous system is induced after acute hypobaric hypoxia, leading to a remarkable increment in heart rate, blood pressure, cardiac output, and pulmonary vascular pressure (16–18). For people born and permanently dwelling in high-altitude areas, various compensation mechanisms enable them to adapt to chronic hypobaric hypoxia exposure, to a certain extent. However, the prevalence of cardiovascular diseases, such as hypertension, is higher among populations living in high-altitude areas than in populations living at sea level. Moreover, the mean value of cIMT and prevalence of carotid plaques and its relationship to various lipid particles remains largely unknown in these special areas.

The objective of this study was to investigate the association between different lipid particles and carotid atherosclerosis using carotid ultrasonography among a high-altitude population living on the Tibetan Plateau.

Methods

1. Participants

This was a cross-sectional study performed by West China Hospital, which enrolled 618 Tibetan individuals permanently living on the Tibetan Plateau in Luhuo County (3,860 meters above sea level), Ganzi Tibetan Autonomous Prefecture, Sichuan Province from December 2018 to September 2019 (Chart 1). The inclusion criteria were as follows: (i) over 18 years old; (ii) Tibetan born and permanently living on the plateau; and (iii) underwent carotid ultrasound examination. The exclusion criteria were as follows: (i) presence of severe liver, renal or mental disorder; (ii) established acute cardiovascular and cerebrovascular diseases; (iii) undergoing lipid modification therapy; (iv) did not complete the relevant examinations and questionnaire; and (v) individuals with other serious medical conditions whom the investigator considered inappropriate for the study. Finally, 587 participants were enrolled in this study. Of these, a total of 327 participants underwent measurement of percutaneous oxygen saturation (SpO_2). This study was approved by Ethics Committee of Sichuan University and conducted in accordance with the Declaration of Helsinki. All enrolled participants were informed about the purposes of the study and provided their written informed consent.

2. Physical examination and laboratory measurement

All measurements were performed in the morning after at least 8 hours' fasting, with no smoking or caffeine or alcohol consumption permitted. Before testing, all participants rested at least 15 minutes in a quiet room at a temperature of 20°C. Brachial blood pressure and heart rate were measured using an automated sphygmomanometer (HBP-1100, Omron, Japan) with patients in the supine position. Three measurements were taken at 2-minute intervals and the average of the last two measurements was calculated and recorded. SpO_2 was assessed with a pulse oximeter (YX303, Yuwell, China) and weight, height and waist circumference (Waist-c) were also measured. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Fasting blood samples, collected into vacuum tubes by trained nurses, were centrifuged for 15 minutes and transferred to freezing tubes. Samples were stored at − 20°C and transported to West China Hospital on dry ice as soon as possible, and tested in the clinical laboratory.

3. Carotid ultrasonography

Measurement of carotid intima-media thickness (cIMT) was performed by trained clinicians using a color Doppler ultrasound machine (CX-50, Philips) in a quiet examination room. All patients were in a supine position with the head angled 45° to the left side. The scanning area included the common carotid artery, carotid bulb, internal carotid artery, and external carotid artery, and the presence of atherosclerotic plaques in each segment of the carotid artery were carefully identified. The final images were selected in the 1-cm straight segment of the internal and external carotid artery to the bifurcation. Each sampling point was measured twice and the mean value was calculated as the cIMT of one side. The contralateral cIMT was obtained using the same method, and the final cIMT value was the mean value of both sides. Carotid plaque was screened simultaneously using ultrasound.

4. Statistical analysis

We used IBM SPSS 25.0 in all the analyses (IBM Corp., Armonk, NY, USA). All variables in this study were assessed using descriptive statistics prior to the analysis. Continuous variables are expressed as mean and standard deviation for normally distributed variables and median and interquartile range for non-normally distributed variables. Categorical variables are expressed as number and percentage. Spearman correlation was used to analyze the correlation between cIMT and other variables. We used multiple linear regression to analyze the risk factors of cIMT. A receiver operator characteristic (ROC) curve was used to compare the discrepancy between lipid particles in predicting atherosclerosis. Statistical significance was defined as $P < 0.05$.

Results

1. Demographic characteristics

We included a total of 587 participants (38.50% men), with mean age 49.33 ± 13.31 years. All individuals were born and lived permanently in Luhuo County on the Tibetan Plateau. Demographic characteristics of the study participants are shown in Table 1. The mean BMI and Waist-C were 25.96 ± 4.15 kg/m² and 87.75 ± 13.73 cm, respectively. Among the study population, 35.09% were overweight and 29.47% were obese. It is noteworthy that SpO_2 (87.52 ± 4.76) in our study population was lower than that among plain dwellers whereas heart rate (76.43 ± 12.66 beats per minute) was compatible with chronic adaption to high altitudes. The mean systolic blood pressure (SBP) was 128.88 ± 20.66 mmHg, mean diastolic blood pressure (DBP) was 81.54 ± 12.82 mmHg, and mean arterial pressure (MAP) was 97.93 ± 14.87 mmHg among the population in this study. Furthermore, the prevalence of hypertension in this area was 31.35%. Moreover, hematological characteristics were as follows: hemoglobin (153.87 ± 24.72 g/L), estimated glomerular filtration rate (eGFR; 101.36 ± 15.06 ml/min/1.73 m^2), uric acid (UA; 290.86 ± 98.29 **μ**mol/L), fasting blood glucose (FBG; 4.71 ± 1.78 mmol/L), total cholesterol (TC; 5.11 ± 1.03 mmol/L), triglyceride (TG; 1.32 ± 0.80 mmol/L), LDL-C (3.21 ± 0.92 mmol/L), HDL-C (1.46 ± 0.30 mmol/L) and non-HDL-C (3.66 ± 1.01 mmol/L). As for lifestyles, 19.59% of participants were ovo-lacto vegetarian with egg and milk consumption, 4.94% smoked, and 6.98% had consumed alcohol for at least 6 months. In this study, the mean value of cIMT was 0.65 ± 0.15 mm on ultrasound and 13.65% of participants were screened for carotid plaques.

Table 1
Demographic Characteristics of the Study Population (N = 587)

Variables	Total
Age (years)	49.33 ± 13.31
Gender (male)	38.50%
BMI (kg/m²)	25.96 ± 4.15
BMI classification	
BMI < 24	35.43%
24 ≤ BMI < 28	35.09%
28 ≤ BMI	29.47%
Waist-c (cm)	87.75 ± 13.73
SpO_2 (%)	87.52 ± 4.76
SBP (mmHg)	128.88 ± 20.66
DBP (mmHg)	81.54 ± 12.82
MAP (mmHg)	97.93 ± 14.87
Hypertension	31.35%
HR (bpm)	76.43 ± 12.66
Hemoglobin (g/L)	153.87 ± 24.72
eGFR (ml/min/1.73m^2)	101.36 ± 15.06
UA (μmol/L)	290.86 ± 98.29
FBG (mmol/L)	4.71 ± 1.78
TC (mmol/L)	5.11 ± 1.03
TG (mmol/L)	1.32 ± 0.80
LDL-C (mmol/L)	3.21 ± 0.92
HDL-C (mmol/L)	1.46 ± 0.30
Non-HDL-C (mmol/L)	3.66 ± 1.01
Vegetarian	19.59%
Cigarette smoking	4.94%
Alcohol consumption	6.98%
CIMT (mm)	0.65 ± 0.15

Continuous variables expressed as mean ± standard deviation and categorical variables as percentages.

Variables	Total
Carotid plaques	13.63%
Continuous variables expressed as mean ± standard deviation and categorical variables as percentages.	

2. Correlation between cIMT and demographic variables

Among Tibetans living on the plateau in this study, the relationships between cIMT and demographic variables are listed in Table 2. cIMT showed a significant positive correlation with age, gender, waist-c, mean arterial pressure, hemoglobin, uric acids, fasting blood glucose, LDL-C, and non-HDL-C and a negative correlation with heart rate, eGFR and cigarette smoking ($P < 0.05$).

Table 2
Correlation Analysis between cIMT and Demographic Variables (N = 587)

Variables	CIMT	
	r	p
Age (years)	0.554	< 0.001#
Gender	0.265	< 0.001#
Waist-c (cm)	0.294	< 0.001#
SpO2	-0.102	0.066
MAP (mmHg)	0.240	< 0.001#
HR (bpm)	- 0.086	0.038#
Hemoglobin (g/L)	0.219	< 0.001#
eGFR (ml/min/1.73m2)	- 0.453	< 0.001#
UA (μmol/L)	0.251	< 0.001#
FBG (mmol/L)	0.276	< 0.001#
LDL-C (mmol/L)	0.287	< 0.001#
Non-HDL-C (mmol/L)	0.314	< 0.001#
Vegetarian	0.02	0.688
Cigarette smoking	- 0.10	0.025#
# p value < 0.05.		

3. Multiple linear regression analysis

In multiple linear regression analysis, we used three models including various variables. As listed in Table 3, model - 1 and model - 2 showed that non-HDL-C was a

risk factor of cIMT ($\beta = 0.012$, $p = 0.032$) while LDL-C was not ($p = 0.073$), after adjusting for age, gender, mean arterial pressure and fasting blood glucose. Further, model - 3 showed that non-HDL-C was an independent risk factor of CIMT increment ($\beta = 0.012$, $p = 0.049$), after adjusting for age, gender, mean arterial pressure, fasting blood pressure, vegetarian diet, and cigarette smoking.

Table 3
Multiple Linear Regression Analysis of cIMT and Demographic Variable (N = 587)

Variables	Model - 1			Model - 2			Model - 3		
	β	β(Sta)	p	β	β(Sta)	p	β	β(Sta)	p
Age (tertiles - 1)	reference	-	-	reference	-	-	reference	-	-
Age (tertiles - 2)	0.051	0.158	< 0.001#	0.050	0.154	< 0.001#	0.049	0.151	< 0.001#
Age (tertiles - 3)	0.154	0.471	< 0.001#	0.151	0.463	< 0.001#	0.149	0.455	< 0.001#
Gender	0.061	0.192	< 0.001#	0.061	0.192	< 0.001#	0.058	0.183	< 0.001#
MAP (mmHg)	0.001	0.102	0.004#	0.001	0.101	0.005#	0.001	0.092	0.012#
FBG (mmol/L)	0.010	0.112	0.002#	0.009	0.110	0.002#	0.009	0.106	0.003#
LDL-C (mmol/L)	0.011	0.067	0.073	-	-	-	-	-	-
Non-HDL-C (mmol/L)	-	-	-	0.012	0.081	0.032	0.012	0.075	0.049#
Cigarette smoking	-	-	-	-	-	-	0.006	0.008	0.815
Vegetarian	-	-	-	-	-	-	-0.011	-0.029	0.415

p value < 0.05.
tertiles – 1: age≤43 years;

tertiles – 2: 43 years≤age≤54years;

tertiles – 3: 54 years≤age.

4. ROC curve of non-HDL-C

The ROC curve of non-HDL-C and LDL-C are depicted in Chart 2. The area under the curve (AUC) of non-HDL-C was 0.644 (CI: 0.583 – 0.706) while LDL-C was 0.599 (CI: 0.534 - 0.664). Comparing these AUC of non-HDL-C and LDL-C, discrepancy was statistically significant ($p < 0.001$). The optimal cut-off value of non-HDL-C was 3.625 mmol/l; the sensitivity, specificity, and Youden Index were 0.713, 0.548, and 0.261, respectively.

As shown, 3.625 mmol/L is the optimal cut-off value of non-HDL-c, with sensitivity and specificity 0.713 and 0.548, respectively.

Discussion

This study was conducted at high altitude (3,860 meters) to investigate the association between lipid particles and cIMT. We confirmed that elevated non-HDL-C was an independent risk factor with cIMT rather than LDL-C in high-altitude areas, after adjusting for demographic variables. Additionally, we compared the AUC of non-HDL-C and LDL-C in hypobaric hypoxic conditions.

The Tibetan Plateau is one of the harshest environments inhabited by humans in the world because of its extremely high altitude. Hypobaric hypoxia affects vascular construction and function, such as endothelial function (19, 20). On the basis of correlation analysis in our study, however, we found that low SpO_2 was not correlated with elevated cIMT. This was indicated that Tibetans have adapted to hypobaric hypoxia conditions to some extent in accordance with previous research regarding genetic adaption of Tibetans to high altitudes over a period of 30,000 to 40,000 years (21–24).

CIMT is a surrogate marker of ASCVD. There are few epidemiological surveys regarding carotid atherosclerosis among people living in plateau regions. We found that the mean value of cIMT was 0.65 mm and the prevalence of carotid plaques was 13.63% among indigenous Tibetans on the plateau. In correlation analysis, we found that cIMT was related to age, gender, waist-c, mean arterial pressure, heart rate, hemoglobin, uric acids, fasting blood glucose, lipids, and cigarette smoking. This conclusion is similar to the results of past studies (6, 25). Regarding lipid particles, findings differ among different populations. In participants treated with LDL-lowing therapy, lipoprotein(a) was predictive of a progressive atherosclerosis burden (26). Among individuals with type 2 diabetes, it has been suggested that reducing LDL-C results in regression of cIMT (27). In contrast, some new biomarkers, such as non-HDL-C, oxidized LDL, small dense LDL-C and the ratio of varying lipid particle combinations, are deemed to be better predictors (28–33). In multiple linear regression analysis, we performed three models included different variables and lipid particles. In a comparison of these models, we determined that the concentration of non-HDL-C was a better biomarker than LDL-C for cIMT among Tibetans. Some last research indicated that non-HDL-C was one of the modifiable risk factors of cIMT and the risk of developing high cIMT could be normalized when non-HDL-C dyslipidemia resolved(34, 35). There were a few studies conducted in China aimed to investigate the relationship between non-HDL-C and carotid atherosclerosis and drew a conclusion similar with our study(36–38). It is a little different between previous researches and our study that the altitude of participants living. Our results have been partly confirmed by other researchers (39, 40) who established that non-HDL-C was more stable than LDL-C and showed significantly higher predictive value.

In our study, We found that non-HDL-C was better that LDL-C in predicting carotid atherosclerosis and the optimal cut-off value was 3.625 mmol/L among Tibetans. In Japan, a study aimed to identify the threshold level for non-HDL-C in a general population of 8,132 individuals. The optimal cut-off value was found to be 3.62 mmol/L (140 mg/dl) (41). Among Japanese patients with type 2 diabetes, the threshold of non-HDL-C was 3.89 mmol/L (31).

Several limitations of this study should be mentioned. First, this was a cross-sectional study and the results cannot demonstrate causality. Hence, our findings should be verified in further cohort studies. Second, We did not include other conventional lipid particles, such as apolipoprotein B. Lastly, it is hard to obtain detail information of carotid atherosclerosis. Most of the equipment used in this study was brought from Chengdu (at sea level) to the Qinghai-Tibet Plateau because of limited medical resources in local villages.

Conclusions

Among Tibetans living in high-altitude areas, the concentration of non-HDL-C was found to be a better biomarker than LDL-C for cIMT. The cut-off value of non-HDL-C is 3.625 mmol/L in predicting atherosclerosis. It is crucial to resolve non-HDL-C dyslipidemia in order to mitigate carotid atherosclerosis in Tibetans living in high-altitude settings.

Abbreviations

ASCVD: Atherosclerotic cardiovascular disease; AUC: Area under the curve; BMI: Body mass index; CIMT: Carotid intima-media thickness; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; HR: Heart rate; LDL-C: Low-density lipoprotein cholesterol; MAP: Mean arterial pressure; Non-HDL-C: Non-high-density lipoprotein cholesterol; ROC: Receiver operator characteristic; SBP: Systolic blood pressure; SpO_{2}: Percutaneous oxygen saturation; TC: Total cholesterol; TG: Triglyceride; UA: Uric acid; Waist-c: Waist circumference.

Declarations

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Authors’ Contributions

XJH wrote the manuscript and performed all data analysis. XJH, XZ and QLG contributed to carotid color doppler ultrasonography. XJH, ZPZ, and XRL collected demographic information and performed medical examinations. RYY and ZPZ collected blood and urine samples. XPC designed and coordinated this cross-sectional study and edited the manuscript, as the corresponding author. All authors have given their consent for the submission of this manuscript for publication.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used in the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by Ethics Committee of Sichuan University and conducted in accordance with the Declaration of Helsinki. All enrolled participants were informed about the purposes of the study and provided their written informed consent.

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Figures

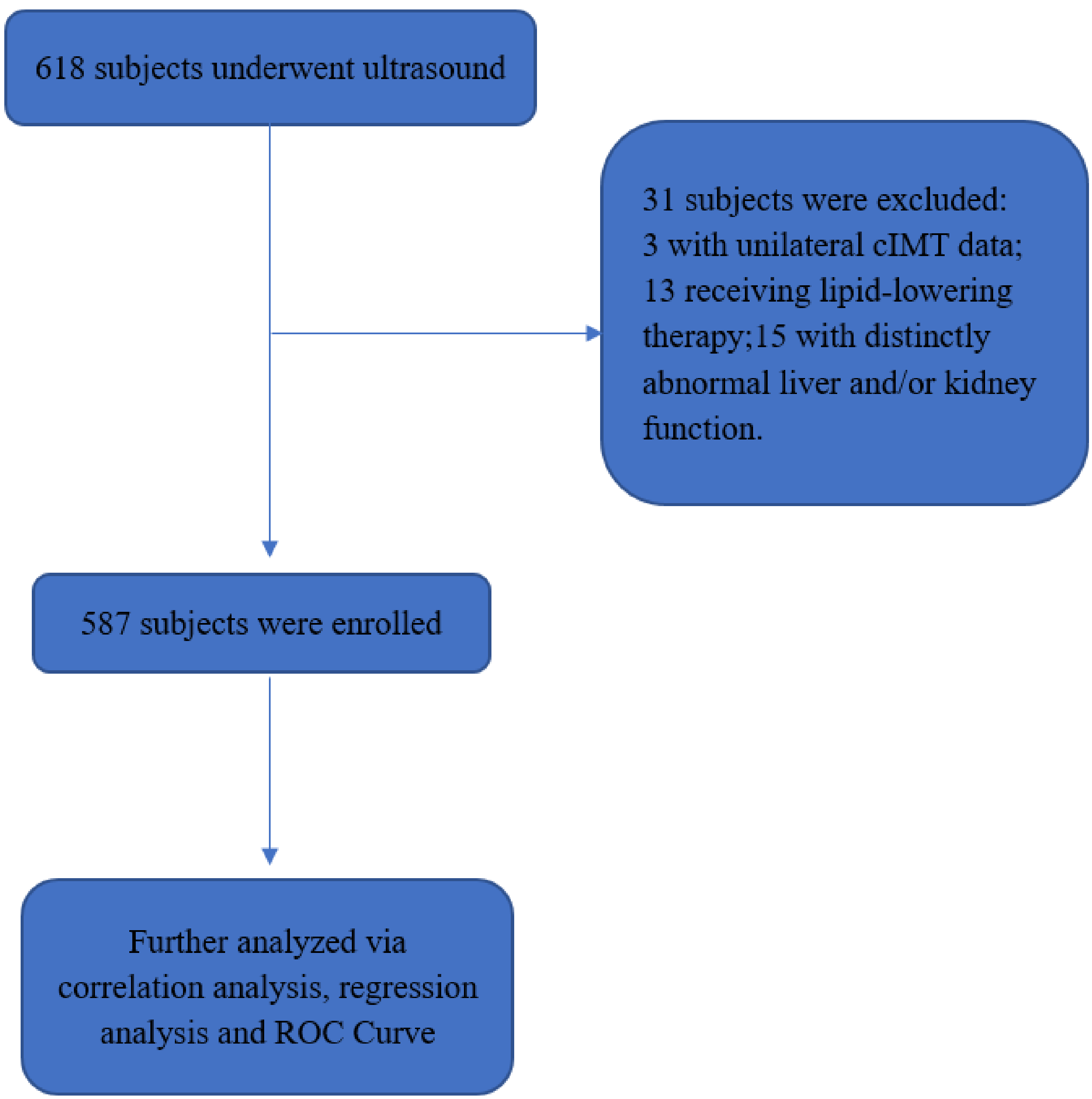

Figure 1

Flow Diagram

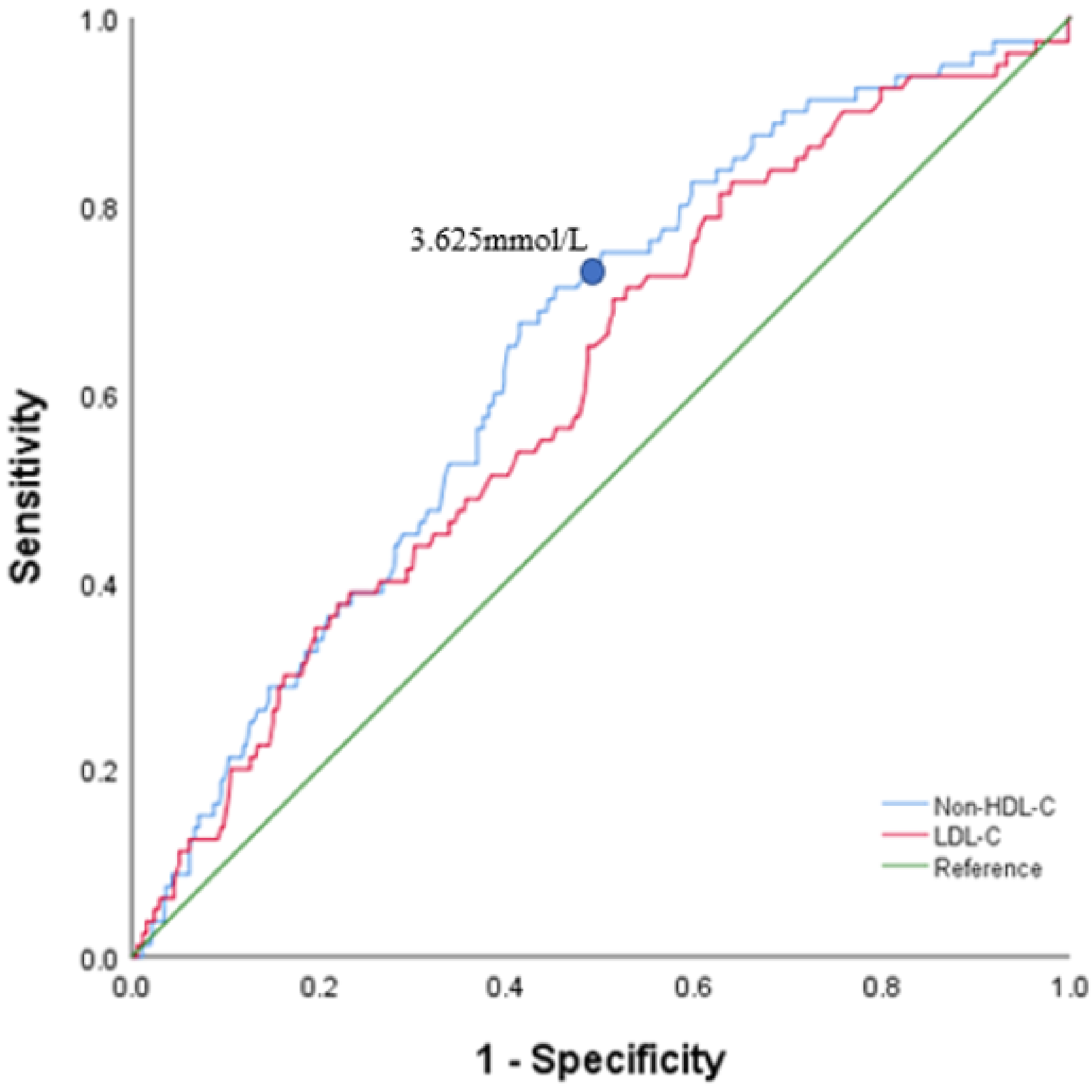

Figure 2

ROC Curve of non-HDL-C and LDL-C

As shown, 3.625 mmol/L is the optimal cut-off value of non-HDL-c, with sensitivity and specificity 0.713 and 0.548, respectively.