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Clinical Diagnostic Significance of Combined Measurement of Lipoprotein(a) and Neck Circumference in Patients with Coronary Heart Disease

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Objective: The study aimed to explore the clinical diagnostic significance of lipoprotein(a) [Lp(a)] and neck circumference (NC) in patients with coronary heart disease (CHD).

Methods: This cross-sectional study was conducted at Chengde Central Hospital from September 2021 to June 2023, enrolling 791 patients with suspected CHD who underwent selective coronary angiography (CAG). Patients were categorized into CHD and non-CHD groups based on the severity of arterial narrowing. Subsequently, the diagnostic value of Lp(a) combined with NC in patients with CHD was assessed using receiver operating characteristic (ROC) curves. Based on the results of multivariate logistic regression, a nomogram was constructed, and its clinical applicability was validated using decision curve analysis (DCA) and clinical impact curve (CIC).

Results: Multivariate logistic regression proved that high Lp(a) and high NC are risk factors for CHD, with OR of 1.836 (95% CI: 1.282–2.630) and 1.383 (1.0.978–1.955), respectively. Patients in the high NC or Lp(a) group exhibited a higher prevalence of multi-vessel disease. The area under the ROC curve (AUC) of the predictive model combining high Lp(a) and high NC was 0.710 (95% CI: 0.670–0.751) and also demonstrated good calibration (Hosmer-Lemeshow goodness-of-fit test *P* value=0.494). The DCA and CIC confirmed the clinical utility of the nomogram developed to predict CHD based on the combination of high Lp(a) and high NC.

Conclusion: The levels of Lp(a) and NC exhibit a significant correlation with the presence of CHD, and their combined assessment holds specific clinical value in the diagnosis of CHD.

Keywords: coronary heart disease, lipoprotein(a), neck circumference, sensitivity, specificity

Introduction

CHD is characterized by the buildup of lipids and other substances in the coronary arteries, leading to blockages that impair blood flow to the heart muscle, causing ischemia and potentially resulting in myocardial infarction. It is one of the major diseases that seriously endanger human life and health. A recent survey indicated that there are currently 11.39 million patients with CHD in China.[1] Factors such as advanced age, male, smoking, hypertension, and lipid metabolism disorders have been proven to be closely related to CHD, with dyslipidemia being pivotal among multiple risk factors and playing a leading role in the generation and development of CHD.[2] Lp(a), as a member of the lipid family, and its levels are not significantly affected by common lipid-lowering medications in clinical. Neck

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circumference (NC) is an important anthropometric measure associated with lipid metabolism, offering the advantages of easy accessibility, independence from dietary factors, and low cost in clinical practice. Given the aforementioned advantages of Lp(a) and NC, and considering that previous studies mainly focus on evaluating their individual predictive values for CHD, our objective is to investigate the combined predictive value of Lp(a) and NC in relation to CHD.

Lp(a), shares structural similarities with low-density lipoprotein and primarily consists of a cholesterol-rich core and apolipoprotein(a). Lp(a) can accumulate in the inner lesions and promote inflammation by binding with vascular endothelial matrix and other components, mediating endothelial cell dysfunction, stimulating chemotactic activation of monocytes or macrophages, stimulating smooth muscle cell proliferation and so on.[3] Furthermore, lipoprotein(a) enhances thrombin activation by upregulating the monocyte tissue factor expression, which results in the deposition of endometrial fibrin and subsequent thrombosis formation.[4] Lp(a) has been implicated in promoting atherosclerosis, exacerbating inflammation and thrombosis, and significantly contributing to all stages of coronary atherosclerosis.[5,6] It is a critical risk factor for the development of CHD and provides a reference for the early prediction of CHD.[7–9] Therefore, the Chinese expert consensus on non-traditional lipid indicators and ASCVD risk management, the Consensus of the European Atherosclerosis Association, and the Scientific Statement of the National Lipid Association of the United States all recommend that lipoprotein a be included in the global risk assessment.[10–12]

NC serves as a critical body surface index related to lipid metabolism and the distribution of subcutaneous adipose in the upper-body. It undergoes changes when lipid metabolism is abnormal. Subcutaneous fat in upper-body, considered an independent fat depot, constitutes a significant source of free fatty acids in circulation. Elevated levels of free fatty acid released from upper-body subcutaneous fat are commonly detected in obese individuals, contributing to the development of dyslipidemia.[13] Recent studies have pointed out that NC is associated with cardiovascular risk factors and insulin resistance, highlighting its potential as an external physical indicator for predicting CHD. Unlike other anthropometric indices such as body mass index (BMI), waist circumference, and waist-hip ratio, NC remains uninfluenced by eating, posture, or breathing. This characteristic confers distinct advantages, including ease of measurement, cost-effectiveness, and excellent reproducibility, rendering it a valuable tool in clinical and research settings.[14,15]

However, there are few reports about the relationship between Lp(a), NC, and the number of stenotic coronary arteries in patients with CHD, as well as their combined diagnostic utility for CHD. Therefore, our study aimed to investigate the correlation between Lp(a) and NC levels with the number of coronary artery lesions and the clinical significance of measuring Lp(a) in conjunction with NC for diagnosing CHD.

Materials and Methods

Study Population

A total of 791 patients aged 18 to 80 years with suspected CHD who received coronary angiography (CAG) at Chengde Central Hospital from September 2021 to June 2023 were enrolled in this study. Exclusion criteria: 1) Patients with a definite history of cardiovascular heart disease or previous coronary revascularization, such as percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG), as well as those with other cardiac conditions such as cardiomyopathies or valvular heart disease; 2) Patients with severe renal diseases or allergy to contrast agents; 3) Patients with comorbidities affecting lipid metabolism such as liver cirrhosis, severe hepatitis, abnormal thyroid function (hyperthyroidism and hypothyroidism), and nephrotic syndrome; 4) Individuals who had been taking medications known to influence lipid levels, such as hormonal medications or chemotherapy in the previous three months, or lipid-lowering medications within the past month. The flowchart of this study is shown in Figure 1. The Ethics Committee of Chengde Central Hospital approved the research protocols, and all patients signed informed consent. This trial is registered at http://www.chictr.org.cn, and the Chinese clinical registration number is ChiCTR2000041499.

Clinical Data

The study recorded general data of enrolled patients, including sex, age, medical diseases (such as diabetes, hypertension, and hyperlipidemia), smoking, and family history of CHD. Baseline data on electrocardiogram (ECG), height, weight, and blood pressure at admission were meticulously collected, and BMI was calculated from these measurements.

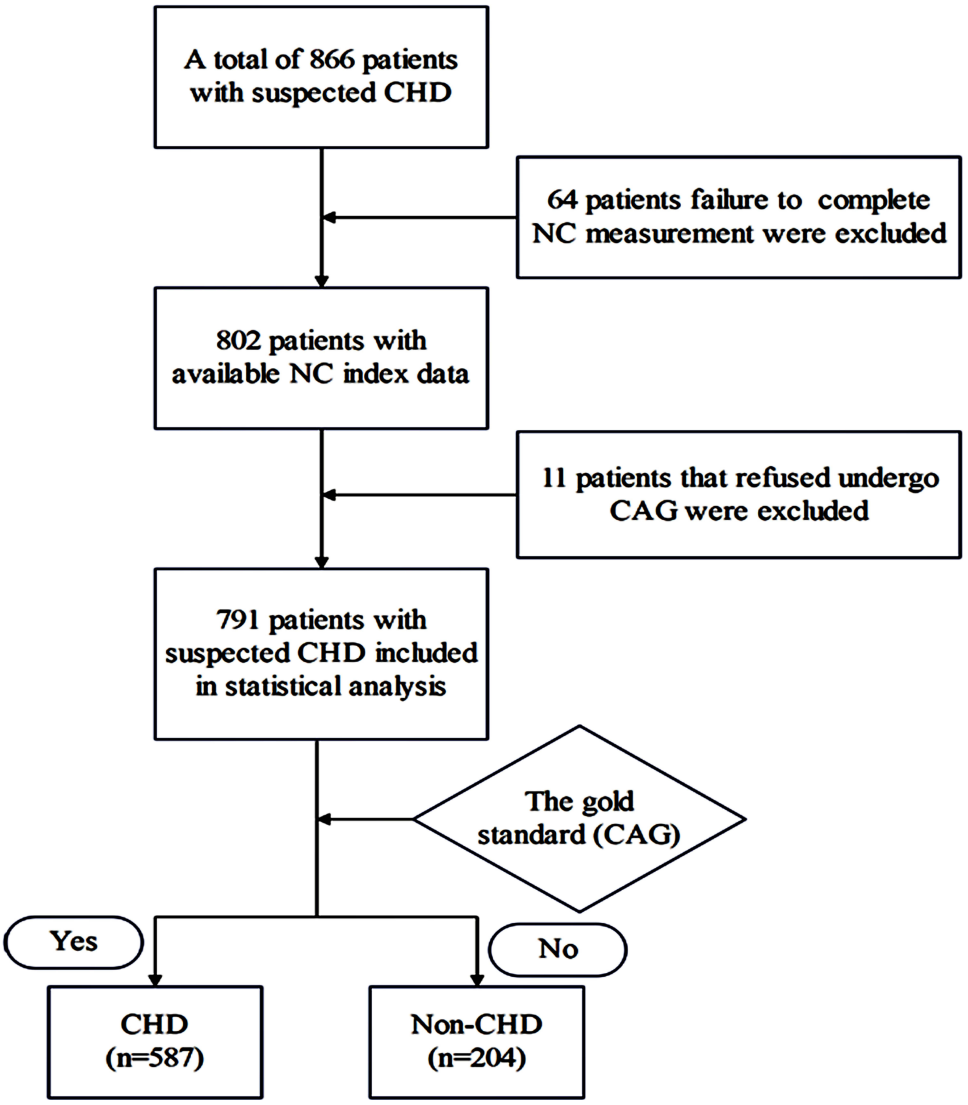

Figure 1 Flowchart for the selection of study patients.
Abbreviations: CHD, Coronary heart disease; NC, Neck circumference; CAG, Coronary angiography.

Laboratory Examinations

All patients involved in the study underwent a fasting period of over 12 hours before extracting 5 mL of blood from the cubital vein the following morning. The serum was separated by centrifugation at 3500 rpm/min for 10 minutes. Biochemical indicators of the patients were determined using a fully automatic biochemical analyzer (HITACHI 7600, Japan). Parameters included Lp(a), creatinine (CR), fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and cystatin C (Cys-C). Additionally, serum myocardial necrosis markers and high-sensitivity troponin-I (hsTNI) were evaluated.

Neck Circumference Measurement Method

NC was measured to the nearest 0.1cm using a soft ruler and rolled horizontally from the area below the laryngeal node to the upper border of the seventh cervical vertebra. The patient maintained an upright posture with a neutral gaze and relaxed upper limbs, breathing calmly to ensure neck muscle relaxation.

Coronary Angiography

Skilled interventional physicians performed a selective multiposition CAG in a catheterization room following the Judkins method through the femoral or radial artery access. At least two experienced interventional cardiologists assessed the angiographic results. Discrepancies were resolved through consensus with a third physician. CHD was diagnosed when at least one epicardial coronary artery or its major branches showed a diameter stenosis of ≥50% based on the CAG results.

Grouping of the Included Patients

The included subjects (n=791) were divided based on CAG findings into two groups: the CHD group (n=587) and the non-CHD group (n=204). CHD patients were categorized into two subgroups according to their medical history, clinical findings, ECG, and hsTNI: angina pectoris and myocardial infarction (MI). Additionally, CHD patients were classified according to the extent of coronary artery involvement into several categories: non-vessel disease (patients diagnosed with MI but without detectable stenosis on CAG), single-vessel disease, double-vessel disease, and triple-vessel disease groups. Furthermore, participants were stratified into groups based on high or low Lp(a) and NC using predetermined cut-off values, with optimal cut-off value determination using Youden's index.

Sample Size and Statistical Analysis

Considering our study's binary outcome, we conducted sample size calculations using the "pmsampsize" function from the R package developed by Riley et al.[16] This function was applied with the parameters [pmsampsize (type="b", csrsquared=0.14, parameters=6, prevalence=0.102)], resulting in a calculated maximum sample size of 355.[1] Thus, a minimum sample size of 355 is necessary for developing the predictive model. This study used SPSS26.0 statistical software and R software (version 4.4.0) for data analysis. The Kolmogorov–Smirnov test was applied to assess the normal distribution. Normally distributed quantitative data were described as mean ± standard deviation and analyzed using the *t*-test for inter-group comparisons. Non-normally distributed data were expressed as M (*P*25, *P*75), and then the Mann–Whitney *U*-test was used to compare different groups. One-way analysis of variance (ANOVA) or the Kruskal–Wallis Test was employed for comparisons among multiple groups. Categorical variables were presented as n (%), and group comparisons were conducted using the chi-square test ($\chi 2$) or Fisher's exact test. The cut-off values corresponding to the maximum Youden's index of NC were ascertained based on gender variations, and accordingly, the NC was categorized into low and high NC groups. We used univariate and multivariate logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association of high Lp(a), high NC with CHD. Based on multivariate logistic regression, we developed a nomogram to assess the risk of CHD. The model's discrimination ability was assessed via the area under the receiver operating characteristic (ROC) curve (AUC). Calibration curves were employed to measure the agreement between predicted probabilities and observed outcomes. Decision curve analysis (DCA) and clinical impact curve (CIC) were utilized to evaluate the model's clinical validity. A two-side $P<0.05$ was considered statistically significant.

Results

Baseline Clinical Characteristics

A comparison of baseline clinical characteristics between the groups revealed that patients in the CHD group were older than those in the non-CHD group. They also exhibited a higher prevalence of hypertension, diabetes, males, and smoking. Moreover, levels of Lp(a), CR, FBG, Cys-C, and NC were significantly elevated in the CHD group compared to the non-CHD group ($P<0.05$). Conversely, HDL-C levels were significantly lower in the CHD group than in the non-CHD group ($P<0.05$). There were no significant differences between the groups in the family history of CHD, systolic BP, diastolic BP, BMI, TC, TG, and LDL-C ($P>0.05$) (Table 1).

Baseline Characteristics of the Different Levels of Lp(a) and NC

Table 2 and Table 3 illustrate the baseline characteristics of all participants stratified by the optimal cut-off values of Lp(a) and NC levels. The final analysis obtained a Youden index of 0.123, identifying an optimal Lp(a) threshold of

Table 1 Comparison of Baseline Characteristics Between the Two Groups

Characteristics	CHD (n=587)	Non-CHD (n=204)	$t/\chi^2/Z$	*P* value
Male, n (%)	373(63.54)	88(43.14)	25.927	<0.001
Smoking history, n (%)	298(50.77)	68(33.33)	18.507	<0.001
Hypertension, n (%)	386(65.76)	115(56.37)	5.743	0.017
Diabetes mellitus, n (%)	178(30.32)	33(16.18)	15.491	<0.001
Family history of CHD, n (%)	51(8.69)	16(7.84)	0.139	0.709
Hyperlipidemia, n (%)	240(40.89)	88(43.14)	0.297	0.586
Age (years)	60.75 ± 9.23	58.59 ± 9.15	−2.937	0.003
BMI (kg/m^2)	25.56 ± 3.40	25.35 ± 3.31	−0.789	0.430
Systolic BP (mmHg)	137.74 ± 20.06	134.04 ± 19.46	−1.714	0.087
Diastolic BP (mmHg)	82.24 ± 12.60	86.71 ± 69.15	1.486	0.138
Heart rate (beats/minute)	75.90 ± 13.06	76.40 ± 12.10	0.494	0.622
Lp(a) (mg/dL)	20.80(10.75, 35.20)	16.60(8.05, 28.27)	−2.847	0.004
NC (cm)	38.10 ± 3.24	37.08 ± 3.31	−3.915	<0.001
CR(ummol/L)	67.00(57.00, 77.00)	62.00(52.00, 70.00)	−4.251	<0.001
FBG (mmol/L)	5.50(4.90, 6.80)	5.25(4.90, 6.00)	−2.697	0.007
TC (mmol/L)	4.18 ± 1.07	4.38 ± 2.42	1.613	0.107
TG (mmol/L)	1.50(1.09, 2.12)	1.43(1.07, 1.95)	−1.174	0.240
HDL-C (mmol/L)	1.06(0.92, 1.23)	1.17(1.00, 1.39)	−4.712	<0.001
LDL-C (mmol/L)	2.24(1.71, 2.81)	2.19(1.67, 2.76)	−0.746	0.450
Cys-C (mg/L)	1.00(0.88, 1.13)	0.96(0.84, 1.06)	−2.815	0.005

Abbreviations: CHD, Coronary heart disease; BMI, Body mass index; Systolic BP, Systolic blood pressure; Diastolic BP, Diastolic blood pressure; Lp(a), Lipoprotein(a); NC, Neck circumference; CR, Creatinine; FBG, Fasting blood glucose; TC, Total cholesterol; TG, triglycerides; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; Cys-C, Cystatin C.

Table 2 Baseline Characteristics of the Different Levels of Lp(a)

Characteristics	Low Lp(a) group (n = 486)	High Lp(a) group (n = 305)	$t/\chi^2/Z$	*P* value
CHD, n (%)	342(70.37)	245(80.33)	9.708	0.002
Non-CHD, n (%)	144(29.63)	60(19.67)		
Number of diseased			2.456	0.482
Non- vessel disease, n (%)	7(1.44)	4(1.31)		
Single-vessel disease, n (%)	139(28.60)	88(28.86)		
Double-vessel disease, n (%)	85(17.49)	74(24.26)		
Triple-vessel disease, n (%)	111(22.84)	79(25.90)		
Male, n (%)	279(57.40)	182(59.70)	0.395	0.530
Smoking history, n (%)	223 (45.90)	143 (46.90)	0.075	0.784
Hypertension, n (%)	309 (63.60)	192 (63.00)	0.032	0.858
Diabetes mellitus, n (%)	131 (27.00)	80 (26.20)	0.050	0.822
Family history of CHD, n (%)	40 (8.20)	27 (8.90)	0.094	0.760
Hyperlipidemia, n (%)	202(41.60)	126(41.30)	0.009	0.925
Age (years)	60.36 ± 9.06	59.84 ± 9.54	0.770	0.441
BMI (kg/m^2)	25.64 ± 3.40	25.28 ± 3.33	1.466	0.143
Systolic BP (mmHg)	136.75 ± 20.45	134.86 ± 19.03	1.298	0.195
Diastolic BP (mmHg)	84.78 ± 46.98	81.35 ± 12.21	1.246	0.213
Heart rate (beats/minute)	75.82 ± 12.64	76.38 ± 13.07	−0.592	0.554
NC (cm)	37.83 ± 3.31	37.81 ± 3.27	−0.101	0.920

(*Continued*)

Table 2 (Continued).

Characteristics	Low Lp(a) group (n = 486)	High Lp(a) group (n = 305)	t/χ^2/Z	*P* value
CR (ummol/L)	65.00(56.00, 77.00)	64.00 (56.00, 74.00)	−0.579	0.562
FBG (mmol/L)	5.40(4.90, 6.60)	5.40 (4.90, 6.58)	−0.157	0.875
TC (mmol/L)	4.12 ± 1.03	4.43 ± 2.13	−2.721	0.007
TG (mmol/L)	1.49(1.10, 2.12)	1.45(1.05, 2.07)	−0.704	0.481
HDL-C (mmol/L)	1.08 (0.94, 1.25)	1.10 (0.92, 1.31)	−0.467	0.641
LDL-C (mmol/L)	2.14(1.64, 2.68)	2.44(1.83, 3.03)	−4.260	<0.001
Cys-C (mg/L)	0.99 (0.87, 1.13)	0.98 (0.87, 1.10)	−1.313	0.189

Abbreviations: CHD, Coronary heart disease; BMI, Body mass index; Systolic BP, Systolic blood pressure; Diastolic BP, Diastolic blood pressure; Lp(a), Lipoprotein(a); NC, Neck circumference; CR, Creatinine; FBG, Fasting blood glucose; TC, Total cholesterol; TG, Triglycerides; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; Cys-C, Cystatin C.

Table 3 Baseline Characteristics of the Different Levels of NC

Characteristics	Low NC group (n=337)	High NC group (n=454)	t/ χ^2/Z	*P* value
CHD, n (%)	231(68.50)	356(78.40)	9.842	0.002
Non-CHD, n (%)	106(31.50)	98(21.60)		
Number of diseased			6.470	0.091
Non- vessel disease, n (%)	5(1.40)	6(1.30)		
Single-vessel disease, n (%)	100(29.70)	127(28.00)		
Double-vessel disease, n (%)	50(14.80)	109(24.00)		
Triple-vessel disease, n (%)	76(22.60)	114(25.10)		
Male, n (%)	173(51.30)	288(63.40)	11.649	0.001
Smoking history, n (%)	130 (38.60)	236 (52.00)	13.984	<0.001
Hypertension, n (%)	179 (53.10)	322(70.90)	26.419	<0.001
Diabetes mellitus, n (%)	67 (19.90)	144 (31.70)	13.855	<0.001
Family history of CHD, n (%)	31 (9.20)	36(7.90)	0.402	0.526
Hyperlipidemia, n (%)	123(36.50)	205(45.30)	6.101	0.014
Age (years)	60.73 ± 8.69	59.73 ± 9.63	1.504	0.133
BMI (kg/m^2)	23.45 ± 2.84	27.03 ± 2.90	−17.283	<0.001
Systolic BP (mmHg)	133.79 ± 190.40	137.68 ± 20.17	−2.727	0.007
Diastolic BP (mmHg)	80.63 ± 11.26	85.56 ± 48.61	−1.824	0.069
Heart rate (beats/minute)	75.12 ± 13.06	76.72 ± 12.58	−1.740	0.082
Lp(a) (mg/dL)	20.50(10.90, 36.70)	18.650(9.60, 30.20)	−1.504	0.133
CR (ummol/L)	62.00(54.00, 71.00)	67.12 (57.00, 78.00)	−4.718	<0.001
FBG (mmol/L)	5.20(4.80, 6.00)	5.70 (5.00, 7.10)	−5.122	<0.001
TC (mmol/L)	4.23 ± 1.07	4.24 ± 1.84	−0.200	0.841
TG (mmol/L)	1.28(0.96, 1.84)	1.62(1.19, 2.28)	−5.697	<0.001
HDL-C (mmol/L)	1.18 (1.01, 1.39)	1.03(0.89, 1.18)	−7.549	<0.001
LDL-C (mmol/L)	2.21(1.67, 2.75)	2.24(1.71, 2.83)	−0.924	0.356
Cys-C (mg/L)	0.96(0.85, 1.08)	1.00 (0.88, 1.13)	−2.437	0.015

Abbreviations: CHD, Coronary heart disease; BMI, Body mass index; Systolic BP, Systolic blood pressure; Diastolic BP, Diastolic blood pressure; Lp(a), Lipoprotein(a); CR, Creatinine; FBG, Fasting blood glucose; TC, Total cholesterol; TG, triglycerides; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; Cys-C, Cystatin C; NC, Neck circumference.

26.15 mg/dL, a Youden index of 0.151 for females and 0.055 for males, identifying an optimal NC threshold of 35.25 and 38.25cm for female and male respectively. As shown, those in the high Lp(a) group (Lp(a) > 26.15mg/dL) tended to have higher levels of TC and LDL-C and were more likely to be CHD and had a higher prevalence of the multi-vessel disease. In addition, those in the high NC group (NC > 35.25cm for females and NC > 38.25cm for males) exhibited higher BMI,

systolic BP, CR, TG, FBG, and Cys-C, and were more likely to be male, increased smoking prevalence, and a higher incidence of CHD, including a greater prevalence of multi-vessel disease.

Analysis of Factors Affecting the Occurrence of CHD

Univariate logistic regression revealed significant associations between CHD and male, age, diabetes mellitus, hypertension, high NC, and high Lp(a) ($P<0.05$). No significant correlations were observed with BMI, FBG, TG, TC, and LDL-C ($P>0.05$). Subsequently, variables with statistical significance in univariate logistic regression analysis were further analyzed through multivariate logistic regression analysis. This analysis identified male ($P<0.001$), age ($P=0.001$), diabetes mellitus ($P<0.001$), and high Lp(a) ($P=0.001$) as significant independent risk factors for CHD. The ORs for high NC and hypertension were 1.383 and 1.384, respectively; however, the corresponding P values were greater than 0.05 (Table 4 and Table 5). Furthermore, after adjusting for confounding factors of age, sex, BMI, LDL-C, TC, the ORs associated with high NC and high Lp(a) concentrations were found to be 1.520 and 1.757, respectively, with both demonstrating statistical significance ($P<0.05$) (Supplemental Table 1S).

Comparison of Lp(a) and NC in the CHD Subgroups

Patients with CHD were further subdivided into the angina pectoris group (n=404) and MI group (n=183) according to their symptoms and the results of ECG and hsTNI. Plasma Lp(a) levels were markedly higher in the MI group compared to both non-CHD groups [23.30(12.25, 41.50) mg/dL vs 16.60(8.05, 28.27) mg/dL, $P=0.003$] and angina pectoris group

Table 4 Univariate Logistic Regression Analysis of Risk Factors for CHD

Variable	β	χ^2	*P* value	OR	95% CI
Male	0.832	25.312	<0.001	2.298	1.662–3.177
Age	0.023	6.643	0.010	1.023	1.005–1.040
Hypertension	0.396	5.710	0.017	1.486	1.074–2.057
Diabetes mellitus	0.813	14.958	<0.001	2.255	1.493–3.405
High Lp(a)	0.542	9.592	0.002	1.719	1.220–2.423
High NC	0.511	9.751	0.002	1.667	1.210–2.297
BMI	0.024	1.025	0.311	1.025	0.977–1.075
FBG	0.007	0.236	0.627	1.007	0.980–1.035
TG	0.104	2.178	0.140	1.109	0.967–1.273
TC	−0.078	2.030	0.154	0.925	0.831–1.030
LDL-C	0.099	0.971	0.324	1.104	0.907–1.343

Abbreviations: CHD, Coronary heart disease; BMI, Body mass index; Lp(a), Lipoprotein(a); NC, Neck circumference; FBG, Fasting blood glucose; TC, Total cholesterol; TG, Triglycerides; LDL-C, Low density lipoprotein cholesterol; OR, Odds ratio; CI, Confidence interval.

Table 5 Multivariate Logistic Regression Analysis of Risk Factors for CHD

Variable	β	χ^2	*P* value	OR	95% CI
Male	1.102	35.998	<0.001	3.009	2.100–4.313
Age	0.033	11.716	0.001	1.034	1.014–1.054
Hypertension	0.325	3.160	0.075	1.384	0.967–1.980
Diabetes mellitus	0.856	14.786	<0.001	2.353	1.521–3.641
High Lp(a)	0.608	10.972	0.001	1.836	1.282–2.630
High NC	0.324	3.374	0.066	1.383	0.978–1.955

Abbreviations: Lp(a), Lipoprotein(a); NC, Neck circumference; OR, Odds ratio; CI, Confidence interval.

[23.30(12.25, 41.50) mg/dL vs 19.85(9.90, 34.70) mg/dL, *P*=0.290]. Moreover, the angina pectoris group also showed higher Lp(a) levels relative to the non-CHD group [19.85(9.90, 34.70) mg/dL vs 16.60(8.05, 28.27) mg/dL, *P*=0.093]. However, statistical significance was not achieved in the latter comparison (Figure 2A). On the other hand, NC measurements were higher in the MI group compared to both the non-CHD group (38.56±3.07cm vs 37.02±3.32cm, *P*<0.001) and the angina pectoris group (38.56±3.07cm vs 37.89±3.29cm, *P*=0.021). The levels in those with angina pectoris were higher than in non-CHD groups (37.89±3.29cm vs 37.02±3.32cm, *P*=0.002) (Figure 2B).

Diagnostic Value of Lp(a) Combined with NC in CHD

Figure 3 shows the performance of the high Lp(a), high NC, and ensemble models for CHD assessment. The AUC for screening high Lp(a) and high NC was 0.562 and 0.563, respectively, whereas model 3 achieved an AUC of 0.595, surpassing the individual AUCs of high Lp(a) and high NC. Model 4 incorporating conventional risk factors yieded an AUC of 0.689. The ensemble model (model 5) achieved an AUC of 0.710 (95% CI: 0.670–0.751), with a specificity of 0.819 and sensitivity of 0.528. We further assessed the ensemble model containing high Lp(a), high NC, and conventional risk factors for CHD. We found that the AUC value of model 5, after incorporating high Lp(a) and high NC, was higher than that of model 4, with a Z value of 2.257 and *P*-value of 0.024, indicating a statistically significant difference. As shown in Table 6, incorporating high Lp(a) and high NC into the model improved risk reclassification for CHD, with a net reclassification improvement (NRI) of 1.053% (*P*<0.001) and an integrated discrimination improvement (IDI) of 0.146% (*P*<0.001).

A nomogram was developed incorporating six predictive variables derived from multivariate logistic regression (Figure 4). Each variable was allocated a specific score on a rating scale. The cumulative scores of all variables were calculated, and a vertical line was dropped at the total score position to estimate the predicted probability of CHD. Higher total scores indicated a higher probability of CHD. The VIF test revealed VIF values < 2 for all variables, indicating no multicollinearity. Figure 5A illustrates the calibration curve for nomogram, where the x-axis represents the predicted probability of CHD risk, and the y-axis indicates the observed probability of CHD. The Hosmer-Lemeshow goodness of fit test showed a *P* value of 0.494, indicating excellent model fit. DCA (Figure 5B) and CIC (Figure 5C) were conducted to evaluate the clinical applicability of the nomogram. The DCA demonstrated that the nomogram provides greater net benefits for predicting CHD within a high-risk threshold probability range of 17–62%. Additionally, the CIC analysis, based on a sample size of 1000, indicated that the number of identified cases of CHD closely aligned with the actual number when the threshold probability exceeded 0.6, with a cost-to-benefit ratio of 1.67.

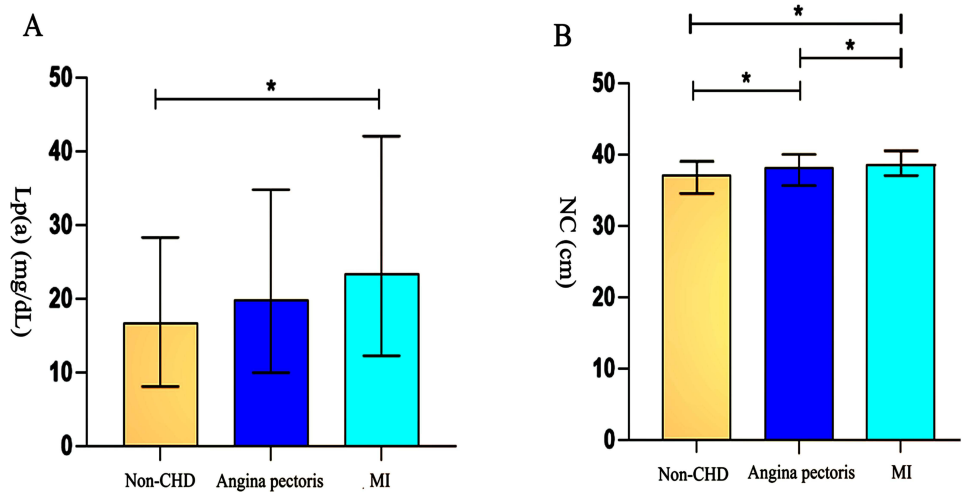

Figure 2 (**A**) Comparison of Lp(a)in the CHD subgroups; (**B**) Comparison of NC in the CHD subgroups.
Note: *represents *P*<0.05.
Abbreviations: CHD, Coronary heart disease; Lp(a), Lipoprotein(a); NC, Neck circumference; MI, Myocardial infarction.

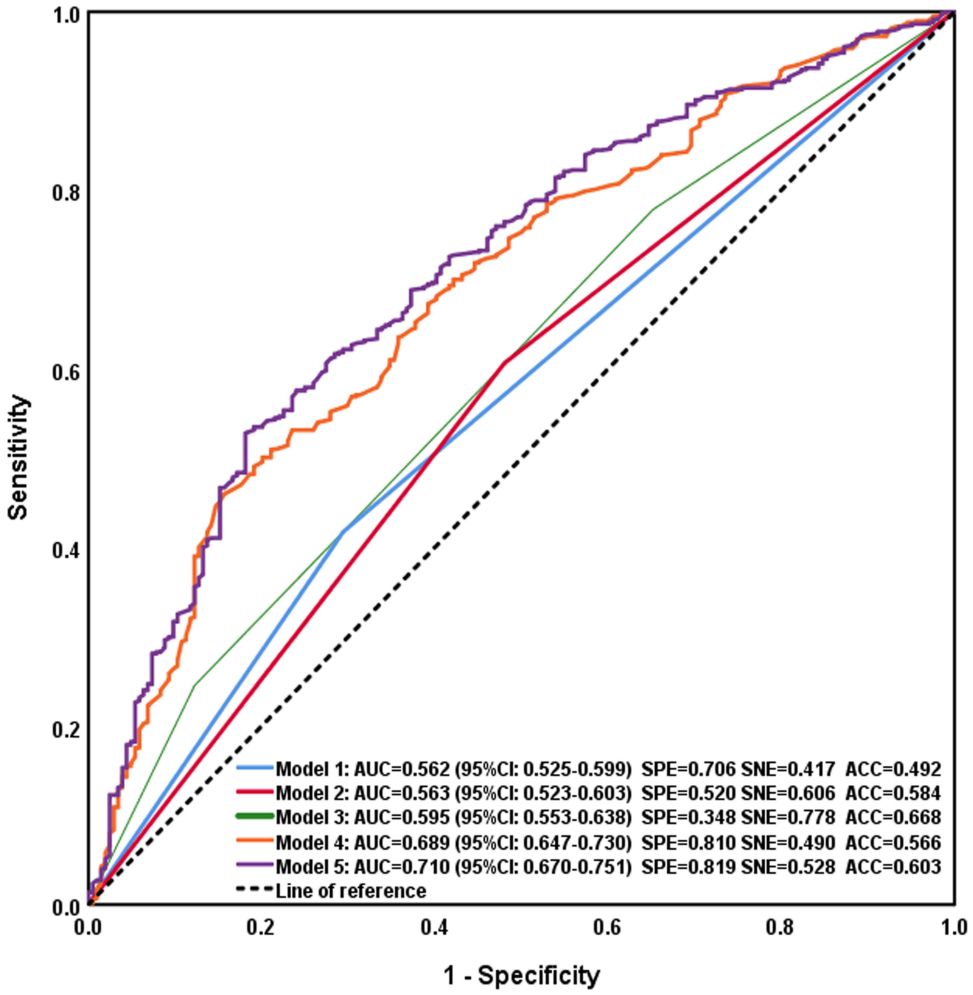

Figure 3 ROC curves of model 1–5.
Abbreviations: AUC, Area under the ROC curve; SPE, Specificity; SNE, Sensitivity; ACC, Accuracy.

Discussion

Presently, CHD is still one of the cardiovascular diseases that seriously endanger human health and life. Dyslipidemia is widely recognized as a significant contributor to the initiation and progression of CHD, serving as an independent and modifiable risk factor. Lp(a), a distinct type of lipoprotein particle similar to low-density lipoprotein, is synthesized in the liver and is not synthesized from very-low-density lipoprotein nor convertible into other lipoproteins.[8] The Lp(a) has been recommended for assessing and stratifying CHD risk according to the latest guidelines.[17,18]

Our findings indicated a positive association between Lp(a) levels and the number of coronary artery lesions in patients with CHD. Previous investigations have similarly explored the relationship between Lp(a) and vascular lesions

Table 6 Reclassification and Discrimination Statistics for CHD by High Lp(a), High NC, and Conventional Risk Factors

	NRI		IDI	
	Estimate (95% CI)	***P* value**	**Estimate (95% CI)**	***P* value**
Model 4	Reference	–	Reference	–
Model 5	1.053(0.932–1.174)	<0.001	0.146(0.131–0.160)	<0.001

Abbreviations: NRI, Net reclassification improvement; IDI, Integrated discrimination improvement.

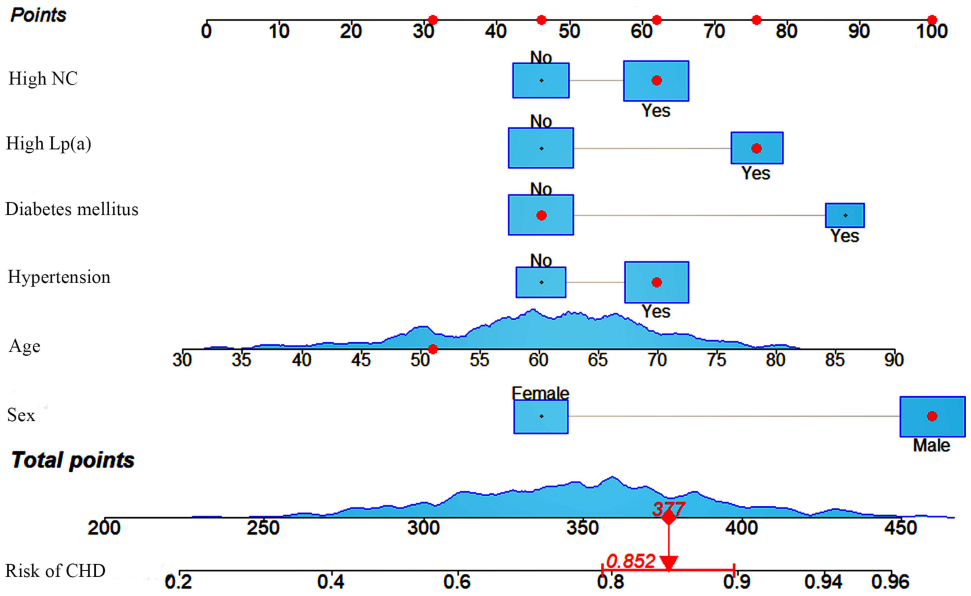

Figure 4 Nomogram of model 5.
Abbreviations: CHD, Coronary heart disease; Lp(a), Lipoprotein(a); NC, Neck circumference.

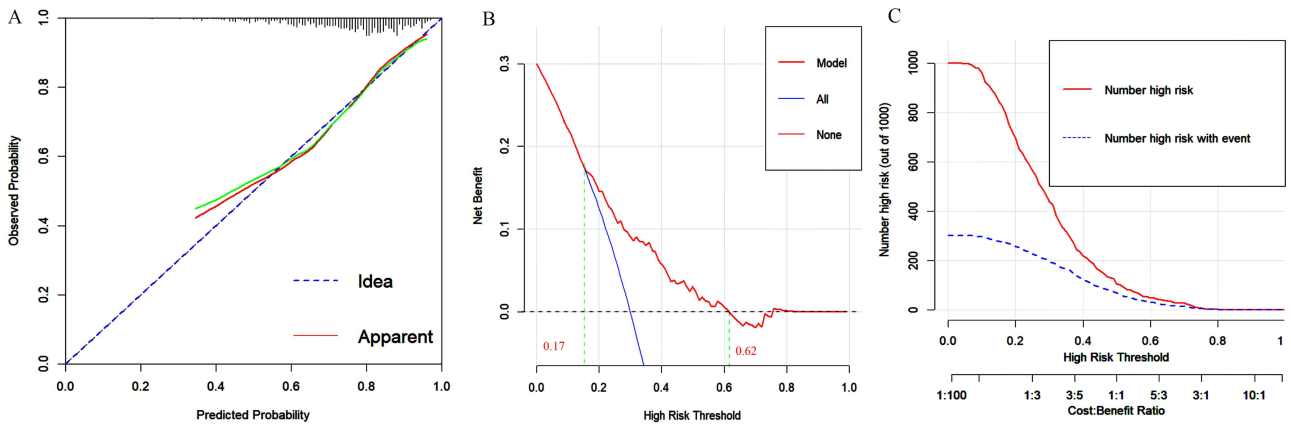

Figure 5 The performance of the nomogram for identifying CHD. (**A**) Calibration plot for the nomogram. (**B**) Decision curve analysis of the nomogram. (**C**) Clinical impact curve of the nomogram.

in patients with CHD, emphasizing a positive correlation between Lp(a) levels and the number of coronary diseases (r=0.25, P<0.01).[19] A cohort study and meta-analysis have substantiated the significance of Lp(a) levels as a significant independent predictor for increased CHD risk. Each 3.5-fold increase in Lp(a) concentration was associated with a 13% increased risk of CHD, suggesting that Lp(a) detection may enhance the precision of CHD prediction.[20,21] Furthermore, research on a multi-ethnic Asian population revealed a significant predictive effect on CHD (OR=1.12, P<0.001). Elevated plasma levels of Lp(a) in CHD patients were also associated with an increased risk of acute myocardial infarction (AMI) (OR=1.02 per 10nmol/L increment, P=0.024).[22] Through multivariate logistic regression analysis, we found high Lp(a) levels are an independent risk factor for CHD (OR=1.836, 95% CI: 1.282–2.630, P=0.001), consistent with previous studies. The Kruskal–Wallis Test proved that serum Lp(a) levels are higher in MI than in non-CHD patients, suggesting a potential for Lp(a) to predict MI occurrence. Kral et al[23] reported that heightened Lp(a) levels correlate with the development of coronary atherosclerotic plaques and are closely linked with increased coronary artery stenosis. Higher Lp(a) levels have also been associated with the number of involved coronary vessels.[24] Gilliland et al[25] analyzed the relationship between Lp(a)and CAG results in patients with CHD. Their analysis revealed a positive

correlation between Lp(a) levels and the presence of multi-vessel lesions; with every doubling increase in Lp(a), there was a 1.10 odds ratio (95% CI: 1.03–1.18, P=0.006) for an increase in multi-vessel disease. The experiment conducted by Ornek et al[26] demonstrated a higher prevalence of elevated Lp(a) levels among individuals with triple-vessel lesions compared to those with double-vessel disease and single-vessel disease (P=0.020, 0.010, respectively). A study involving 1213 AMI patients found a higher incidence of multi-vessel lesions in patients with high serum Lp(a) levels than those with low Lp(a), with the OR value highest in the multi-vessel lesions groups.[24] Our study similarly observed a higher incidence of multi-vessel disease in patients with elevated serum Lp(a) compared to those with lower levels.

NC is a critical indicator of upper body subcutaneous fat, proving more clinically relevant than visceral fat.[10] A cross-sectional study conducted abroad found NC to be a simple and effective tool for predicting CHD.[27] In addition, a prior study had shown that NC is an independent risk factor for CHD, demonstrating its superiority over BMI and waist circumference even after adjusting for age and other cardiovascular risk factors.[10,28] Zen et al[29] revealed that excess fat buildup in the neck of obese patients leads to an increase in NC, which is significantly correlated with the severity of CHD. The findings of a prospective cohort investigation indicated that the incidence of non-fatal cardiovascular disease events was 14.08, 16.65, and 25.21% in the low-NC, medium-NC, and high-NC cohorts, respectively (P<0.001). These data signify a strong correlation between NC levels and the risk of cardiovascular pathology, thereby suggesting the potential utility of NC as a novel predictive biomarker for cardiovascular incidents.[30] NC was considered a robust predictor of CHD risk, surpassing traditional markers risk like BMI.[31] This finding aligns with the current literature, and multivariate regression analysis revealed that NC was a risk factor for CHD (OR=1.383). Although P=0.066 in multivariate regression analysis, high NC was included in the model due to its clinical practicality, accessibility, and cost-effectiveness. We speculated that NC might be associated with the development of CHD and could serve as an early indicator for predicting CHD. Additionally, subgroup analysis within CHD patients revealed a higher prevalence of multi-vessel disease among those with elevated NC compared to their counterparts with lower NC levels.

Lp(a) levels are not significantly affected by common lipid-lowering medications in clinical practice; and NC is readily obtainable, unaffected by diet, and low in cost. Given these advantages, the combined measurement of Lp(a) and NC represents a simple and effective tool for predicting CHD. Moreover, previous studies have suggested that other essential clinical variables, such as age and gender, also provide good performance for predicting CHD.[32] So, we developed an ensemble model that includes high Lp(a), high NC, and conventional risk factors, the AUC for the ensemble model was escalated to 0.710, surpassing the other models and emphasizing the diagnostic potential of a comprehensive approach in CHD assessment.

In the ensemble model, each patient was assigned a personalized score derived from the nomogram, enabling precise categorization into low and high-risk groups. When the nomogram indicates a high probability of CHD, it is advisable to pursue further CAG to detect patients with underlying CHD, as the advantages of prompt revascularization are well established. This advancement has the potential not only to assist physicians in screening for CHD and formulating treatment strategies but also to enhance patient care by minimizing unnecessary invasive procedures and facilitating the initiation of appropriate treatment.

There are a few limitations to the current study. Firstly, the data were derived from a single center and the sample size was limited, which may not account for geographical variations. In future studies, we will conduct a multi-center trial to increase the sample size and validate the clinical applicability of this method. Secondly, the study was a cross-sectional study without follow-up on patients and was inherently limited in its ability to establish causation, future research should include long-term follow-up data for a more comprehensive analysis. Thirdly, although the measurement of NC is conducted by personnel who received specialized training, potential measuring errors may occur due to factors such as the precision of measuring instruments, proficiency in operating techniques, and the applied force during the measurement process. Finally, our study included only subjects who underwent CAG rather than all patients with suspected CHD, which may introduce information bias. Therefore, in the future, the model should be re-evaluated in all patients with suspected CHD for validation and generalization.

Conclusion

This study highlights Lp(a) and NC as significant risk factors for CHD. The research showed a notable increase in Lp(a) and NC levels in hospitalized CHD patients compared to non-CHD patients. The simultaneous assessment of Lp(a) and NC demonstrates potential diagnostic value for CHD and could serve as a novel noninvasive diagnostic approach.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the Chengde Central Hospital /Second Clinical College of Chengde Medical University.

Abbreviations

CHD, Coronary heart disease; BMI, Body mass index; Systolic BP, Systolic blood pressure; Diastolic BP, Diastolic blood pressure; Lp(a), Lipoprotein(a); CR, Creatinine; FBG, Fasting blood glucose; TC, Total cholesterol; TG, Triglycerides; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; Cys-C, Cystatin C; NC, Neck circumference; OR, Odds ratio; CI, Confidence interval.

Data Sharing Statement

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

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Disclosure

The authors report no conflicts of interest in this work.

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