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Original Article

Significance of lipoprotein a and high-sensitivity CRP combined assay in diagnosing coronary heart disease and their relationship with coronary lesion severity

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Abstract: Objective: To evaluate the diagnostic performance of lipoprotein A (LP(a)) and high-sensitivity C-reactive protein (hs-CRP) combined assay for coronary heart disease (CHD) and their association with the severity of coronary lesions. Methods: This retrospective study included 106 patients who underwent coronary angiography (CAG) due to thoracic distress at Xi'an International Medical Center Hospital from June 2020 to October 2021. The patients were categorized into two groups: the CHD group (n=67) and the non-CHD group (n=39). Subgroup analysis was performed within the CHD group based on the Gensini score. Serum levels of LP(a) and hs-CRP were compared between the groups and subgroups, and their correlations with the Gensini score were analyzed. The diagnostic performance of LP(a), hs-CRP, and their combined assay for detecting CHD was evaluated using receiver operating characteristic (ROC) curve analysis. Results: Serum levels of LP(a) and hs-CRP were significantly higher in the CHD group than those in the non-CHD group (P<0.001). Within the CHD subgroups, both LP(a) and hs-CRP levels were significantly elevated in the moderate and high Gensini score groups compared to the low Gensini score group (P<0.001). There was a positive correlation between LP(a) and hs-CRP levels with the Gensini score (r=0.288, P=0.003; r=0.276, P=0.004). The area under the ROC curve (AUC) for the combination of LP(a) and hs-CRP (0.924, 95% CI: 0.865-0.983) was significantly greater than that for LP(a) (0.858, 95% CI: 0.783-0.933) or hs-CRP (0.854, 95% CI: 0.772-0.936) alone (P<0.05). Conclusion: Elevated serum levels of LP(a) and hs-CRP are associated with CHD and correlate with the severity of coronary lesions. The LP(a) and hs-CRP combined assay improves the diagnostic performance for CHD, suggesting potential clinical value.

Keywords: Coronary heart disease, lipoprotein a, high-sensitivity CRP, coronary lesion extent, combined assay

Introduction

Coronary heart disease (CHD) remains one of the leading causes of morbidity and mortality worldwide, posing a substantial burden on healthcare systems [1, 2]. Timely diagnosis and intervention are crucial for reducing the risk of CHD and improving patient outcomes [3, 4]. Traditional diagnostic methods, such as evaluating clinical symptoms and using electrocardiography, often lack specificity, while coronary angiography (CAG), the gold standard for CHD diagnosis, is both invasive and costly [5-7]. Therefore, there is a pressing need for simple and reliable laboratory markers to aid in the early diagnosis of CHD.

Both abnormal lipid metabolism and inflammation play pivotal roles in the pathogenesis of CHD [8, 9]. Lipoprotein A (LP(a)), a low-density lipoprotein (LDL)-like particle, has been recognized as an independent risk factor for CHD [10, 11]. Elevated LP(a) levels contribute to atherosclerosis by enhancing the expression of adhesion molecules and reducing nitric oxide bioavailability [12, 13]. Similarly, high-sensitivity C-reactive protein (hs-CRP), an indicator of systemic inflammation, has been associated with the initiation and progression of atherosclerosis [14, 15]. Although previous studies have established LP(a) and hs-CRP as independent risk factors for CHD [16, 17]; the potential diagnostic value of combining these two markers for CHD has not been fully elucidated.

This retrospective study aimed to evaluate the diagnostic performance of LP(a) and hs-CRP combined assay for CHD and to explore their

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association with the extent of coronary lesions, thereby providing further insights into the potential clinical application of these markers.

Materials and methods

Study population

Participants and grouping: This retrospective study included 106 patients who underwent CAG due to thoracic distress at Xi'an International Medical Center Hospital between June 2020 and October 2021. Patients were divided into the CHD group (n=67) and the non-CHD group (n=39) based on CAG results. The study was approved by the Ethics Committee of Xi'an International Medical Center Hospital.

Inclusion and exclusion criteria: The inclusion criteria were as follows: (1) patients who underwent CAG due to thoracic distress at Xi'an International Medical Center Hospital between June 2020 and October 2021; (2) patients with complete medical records that included baseline characteristics, laboratory parameters, and CAG results; (3) for the CHD group, patients with CAG findings showing ≥50% stenosis in any major coronary artery (the left main, left anterior descending, left circumflex, or right coronary artery); for the non-CHD group, patients with CAG findings showing <50% stenosis or normal coronary arteries [18].

The exclusion criteria were as follows: (1) patients with incomplete medical records; (2) patients with a prior history of percutaneous coronary intervention or coronary artery bypass grafting; (3) patients exhibiting liver or kidney dysfunction (hepatitis, cirrhosis, nephrotic syndrome, chronic nephritis, CKD stage 3-5); (4) patients with immune-related diseases (arteritis systemic lupus erythematosus); (5) patients suffering from severe trauma or infectious diseases (pelvic fracture, lung infection); (6) patients with cerebrovascular diseases (cerebral infarction, cerebral hemorrhage); (7) patients currently using statins or other lipid-lowering drugs; (8) patients exhibiting moderate to severe anemia; (9) patients with hemorrhagic diseases (leukemia, disseminated intravascular coagulation); (10) patients with chronic wasting diseases (malignancy, tuberculosis); and (11) patients with concurrent heart valve disease, cardiomyopathy, or congenital heart disease.

Data collection and laboratory measurements

Baseline characteristics were collected, including age, gender, height, weight, body mass index (BMI), duration of diabetes mellitus, |presence of hypertension, smoking history, and alcohol consumption. Blood samples were obtained within 48 hours of hospital admission, and the following laboratory parameters were measured: fasting blood glucose (FBG), glycated hemoglobin (HbA1c), serum creatinine (Scr), uric acid (Uric), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), homocysteine (HCY), LP(a), and hs-CRP.

Serum levels of LP(a) and hs-CRP were determined by immunoturbidimetry using a Roche HITACHI-7060 automatic biochemical analyzer. The reference ranges were 0-300 mg/L for LP(a) and 0.00-3.00 mg/L for hs-CRP.

Coronary lesion extent assessment

The Gensini scoring system was used to evaluate the severity of coronary lesions based on CAG results [19]. Coronary arteries were divided into 14 segments, with stenosis severity assigned a score as follows: ≤25%, 1 point; 26-50%, 2 points; 51-75%, 4 points; 76-90%, 8 points; 91-99%, 16 points; and 100%, 32 points. Each segment was assigned a weighting factor: left main artery ×5; left anterior descending artery segments 1-3 (×2.5, ×1.5, ×1, respectively); circumflex 1 ×2.5 (ostial ×3.5); circumflex 2, obtuse marginal artery, right coronary artery, posterior descending artery, and diagonal branch 1 (×1 each); diagonal branch 2 and posterior lateral branch (×0.5 each). The total Gensini score for each patient was calculated by summing the scores for all segments.

Outcomes

The primary outcome was the diagnostic performance of LP(a), hs-CRP, and their combination for CHD, assessed by receiver operating characteristic (ROC) curve analysis. Secondary outcomes included the differences in LP(a) and hs-CRP levels between the CHD and non-CHD groups and the correlation between these markers and the Gensini score.

Table 1. Comparison of baseline characteristics between healthy population and CHD patients (Mean ± SD)

Data	CHD group (n=67)	Non-CHD group (n=39)	Statistical values	*P* value
Age (years)	56.30±8.80	54.87±8.10	0.830	0.408
BMI (kg/m^2)	23.74±3.12	24.19±3.51	0.684	0.496
Female [n (%)]	8 (11.94)	6 (15.38)	0.255	0.613
Smoking history [n (%)]	37 (55.22)	13 (33.33)	4.740	0.029
History of alcohol consumption [n (%)]	5 (7.46)	3 (7.69)	0.002	0.966
History of hypertension [n (%)]	37 (55.22)	20 (51.28)	0.154	0.695
History of diabetes mellitus [n (%)]	19 (28.36)	4 (10.26)	4.754	0.029
FBG (mmol/L)	6.52±1.23	5.61±0.97	3.956	<0.001
HbA1c (%)	5.92±0.63	5.43±0.31	4.541	<0.001
Scr (μmol/L)	82.60±9.24	80.13±11.22	1.225	0.223
Uric (μmol/L)	403.58±87.16	393.24±78.49	0.610	0.543
TC (mmol/L)	4.58±1.02	4.62±1.04	0.193	0.847
TG (mmol/L)	1.42±0.63	1.46±0.59	0.323	0.748
LDL-C (mmol/L)	3.10±0.89	3.06±0.92	0.220	0.826
HDL-C (mmol/L)	1.42±0.50	1.12±0.24	3.514	0.001
HCY (μmol/L)	8.24±2.12	7.98±2.06	0.615	0.540

Note: CHD, Coronary Heart Disease; BMI, Body Mass Index; FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin; Scr, Serum Creatinine; Uric, Uric Acid; TC, Total Cholesterol; TG, Triglycerides; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; HCY, Homocysteine.

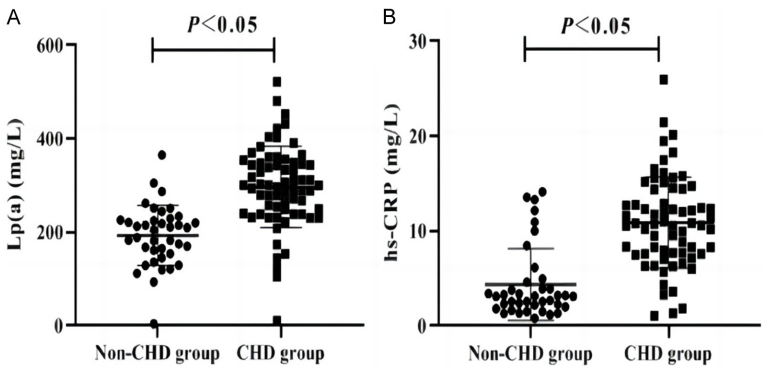

Figure 1. Serum LP(a) and hs-CRP levels in CHD and non-CHD groups. A. Serum LP(a) levels were significantly higher in the CHD group than those in the non-CHD group (P<0.05). B. Serum hs-CRP levels were significantly higher in the CHD group than those in the non-CHD group (P<0.05). Note: LP(a), Lipoprotein(a); hs-CRP, High-sensitivity C-reactive Protein; CHD, Coronary Heart Disease.

Statistical analysis

Data were analyzed using SPSS 20.0 software. Categorical variables were expressed as n (%) and compared using the chi-square test. Continuous variables were presented as mean ± standard deviation and compared using the independent samples t-test or one-way analysis of variance (ANOVA). The relationship between LP(a), hs-CRP, and the Gensini score was assessed using Spearman correlation analysis. Multivariate logistic regression analysis was performed to identify independent risk factors for CHD. ROC curve analysis was conducted to evaluate the diagnostic performance of LP(a), hs-CRP, and their combination for CHD. The optimal cut-off values were determined by maximizing the Youden index. The DeLong test was used to compare the areas under the ROC curves (AUCs). A *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics

The CHD group consisted of 67 patients (63.21%), with a mean age of 56.30±8.80 years, 11.94% females, 55.22% with hypertension, and 28.36% with diabetes. The non-CHD group included 39 patients (36.79%), with a mean age of 54.87±8.10 years, 15.38%

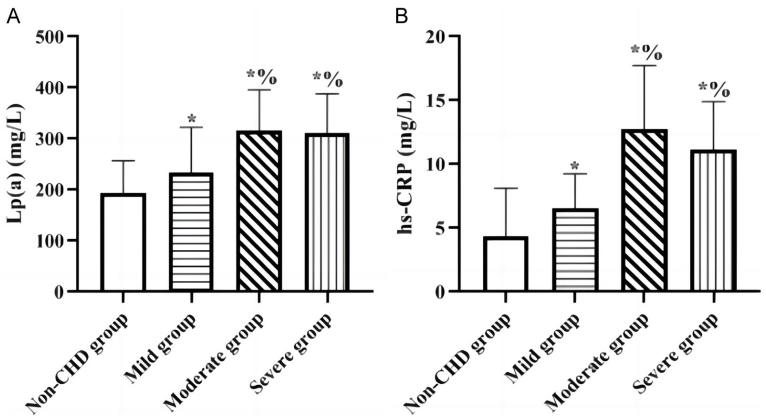

Figure 2. Serum LP(a) and hs-CRP levels among CHD subgroups. A. Serum LP(a) levels were significantly higher in the moderate and high Gensini score groups compared to those in the low Gensini score group (P<0.001). B. Serum hs-CRP levels were significantly higher in the moderate and high Gensini score groups compared to those in the low Gensini score group (P<0.001). No significant differences were observed between the moderate and high Gensini score groups (P>0.05). Note: Compared with non-CHD, *P<0.05; compared with mild group, %P<0.05. Note: LP(a), Lipoprotein(a); hs-CRP, High-sensitivity C-reactive Protein; CHD, Coronary Heart Disease.

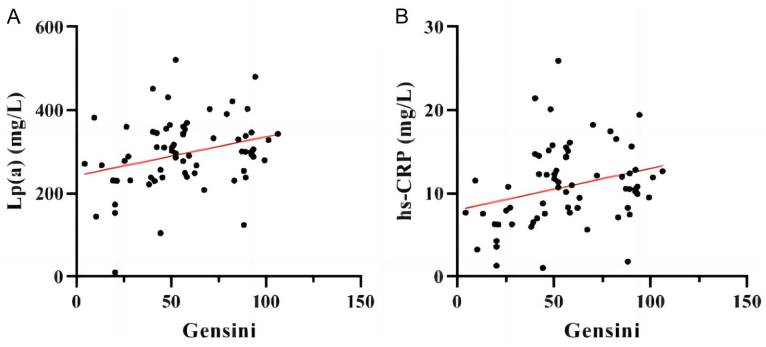

Figure 3. Scatter plots of the correlations between LP(a), hs-CRP, and the Gensini score. A. LP(a) positively correlated with the Gensini score (r=0.288, P=0.003). B. Hs-CRP positively correlated with the Gensini score (r=0.276, P=0.004). Note: LP(a), Lipoprotein(a); hs-CRP, High-sensitivity C-reactive Protein.

females, 51.28% with hypertension, and 10.26% with diabetes. The proportions of patients with diabetes and smoking history were significantly higher in the CHD group than in the non-CHD group (P=0.029 and P=0.029, respectively). No significant differences were observed between the two groups in terms of age, gender, alcohol consumption history, BMI, or hypertension history (P>0.05). Regarding laboratory parameters, FBG, HbA1c, and HDL-C levels were significantly higher in the CHD group (P<0.001, P<0.001, and P=0.001, respectively), while no significant differences were found in Scr, Uric, TC, TG, LDL-C, or HCY levels (P>0.05) (**Table 1**).

Comparison of LP(a) and hs-CRP levels between CHD and non-CHD groups

Serum LP(a) and hs-CRP levels were significantly higher in the CHD group than in the non-CHD group (P<0.001 for both) (**Figure 1**).

Comparison of LP(a) and hs-CRP levels among CHD subgroups

CHD patients were divided into low, moderate, and high Gensini score groups based on tertiles. Both LP(a) and hs-CRP levels were significantly higher in the moderate and high Gensini score groups compared to the low Gensini score group (P<0.001 for both). However, no significant differences were observed between the moderate and high Gensini score groups (P>0.05) (**Figure 2**).

Correlation between LP(a), hs-CRP, and the Gensini score

There was a positive correlation between LP(a) and hs-CRP levels with the Gensini score (r=0.288, P=0.003 and r=0.276, P=0.004, respectively) (**Figure 3**).

Logistic regression analysis

Smoking history (OR=2.401, 95% CI: 1.898-3.038], diabetes history (OR=2.782, 95% CI: 1.509-5.127), HDL-C (OR=2.125, 95% CI: 1.720-2.627), LP(a) (OR=1.483, 95% CI: 1.191-1.847), and hs-CRP (OR=1.614, 95% CI: 1.319-1.976) were identified as independent risk factors for CHD (P<0.05) (**Table 2**).

The logistic regression model for the combined LP(a) and hs-CRP assay was as follows: Logit(P) = -3.142 + 1.483 × LP(a) + 1.614 × hs-CRP, where P is the probability of CHD, and LP(a) and hs-CRP are the serum levels of these markers.

Table 2. Logistic regression analysis of the correlation between serum Lp(a), hs-CRP and CHD

Variables	β	*SE*	Wald x^2	*P*	*OR (95 CI%)*
Smoking history	0.876	0.120	38.874	<0.001	2.401 (1.898-3.038)
History of diabetes	1.023	0.312	32.563	<0.001	2.782 (1.509-5.127)
FBG	0.563	0.409	0.876	0.435	1.756 (0.788-3.914)
HbA1c	0.342	0.187	1.346	0.121	1.408 (0.976-2.031)
HDL-C	0.754	0.108	33.587	<0.001	2.125 (1.720-2.627)
Lp(a)	0.394	0.112	7.120	0.008	1.483 (1.191-1.847)
hs-CRP	0.479	0.103	19.423	<0.001	1.614 (1.319-1.976)

Note: Lp(a), Lipoprotein(a); hs-CRP, High-sensitivity C-reactive Protein; CHD, Coronary Heart Disease; FBG, Fasting Blood Glucose; HbA1c, Glycated Hemoglobin; HDL-C, High-Density Lipoprotein Cholesterol.

Table 3. Diagnostic value of serum Lp(a), hs-CRP and their combination for diagnosing coronary artery disease

Indicator	AUC	Cut-off	Sensitivity	Specificity	95 CI%
Lp(a)	0.858	0.676	79.50	88.10	0.783-0.933
hs-CRP	0.854	0.705	79.50	91.00	0.772-0.936
Combination of two indicators	0.924	0.833	92.30	91.00	0.865-0.983

Note: Lp(a), Lipoprotein(a); hs-CRP, High-sensitivity C-reactive Protein; AUC, Area Under the Curve.

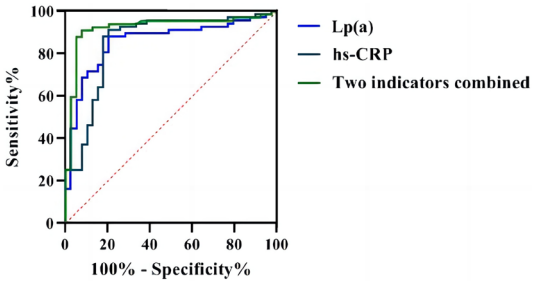

Figure 4. Serum Lp(a), hs-CRP, and their combined use in the diagnosis of coronary artery disease. Note: LP(a), Lipoprotein(a); hs-CRP, High-sensitivity C-reactive Protein.

Diagnostic performance of LP(a), hs-CRP, and their combination for CHD

The AUCs for LP(a), hs-CRP, and their combination in predicting CHD were 0.858 (95% CI: 0.783-0.933), 0.854 (95% CI: 0.772-0.936), and 0.924 (95% CI: 0.865-0.983), respectively. The optimal cut-off values were 0.676 for LP(a) (sensitivity: 79.50%, specificity: 88.10%) and 0.705 for hs-CRP (sensitivity: 79.50%, specificity: 91.00%). The combination of LP(a) and hs-CRP yielded a sensitivity of 92.30% and a specificity of 91.00% for CHD diagnosis. The DeLong test revealed that the AUC for the combination of LP(a) and hs-CRP was significantly greater than that for LP(a) or hs-CRP alone (P<0.05) (**Table 3**; **Figure 4**).

Discussion

This retrospective study investigated LP(a) and hs-CRP combined assay in diagnosing CHD and their association with the extent of coronary lesions. The main findings were as follows: (1) Serum levels of LP(a) and hs-CRP were significantly higher in patients with CHD compared to those without CHD; (2) Both LP(a) and hs-CRP levels showed a positive correlation with the severity of coronary lesions, as indicated by the Gensini score; (3) The combination of LP(a) and hs-CRP demonstrated superior diagnostic performance for CHD over either marker alone.

LP(a) and hs-CRP are implicated in the pathogenesis of atherosclerosis and CHD [10, 11, 14, 15]. Elevated LP(a) levels contribute to the development of atherosclerotic lesions by enhancing the expression of adhesion molecules and reducing nitric oxide bioavailability [12, 13]. Similarly, Hs-CRP, a marker indicative of systemic inflammation, has been identified in early atherosclerotic lesions and is associated with both the initiation and progression of atherosclerosis [14, 15]. Our findings support the role of LP(a) and hs-CRP in CHD pathogenesis, as evidenced by their significantly elevated levels in CHD patients and their positive correlation with the severity of coronary lesions.

Previous studies have identified LP(a) and hs-CRP as independent risk factors for CHD [16, 17]. In our study, multivariate logistic regression analysis further corroborated these markers as independent risk factors for CHD, in addition to a history of smoking, a history of diabetes, and HDL-C levels. However, the diagnostic value of LP(a) and hs-CRP combined assay for CHD has not been thoroughly investigated. Our study demonstrated that the combination of these markers provides enhanced diagnostic performance for CHD when compared to the use of each marker independently, as evidenced by the significantly elevated AUC and improved sensitivity and specificity.

This study has several limitations. First, the retrospective design and single-center nature may affect the generalizability of the results. Second, the relatively small sample size necessitates further validation through larger, prospective studies. Third, the prognostic value of LP(a) and hs-CRP for CHD was not evaluated in this study, which warrants further investigation.

In conclusion, serum levels of LP(a) and hs-CRP are elevated in CHD patients and correlate with the severity of coronary lesions. The LP(a) and hs-CRP combined assay offers superior diagnostic performance for CHD compared to either marker alone, suggesting its potential clinical value in the early detection and management of CHD. Further large-scale, prospective studies are needed to confirm these findings and to explore the prognostic significance of these markers in CHD.

Disclosure of conflict of interest

None.

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