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The value of serum lipoprotein-associated phospholipase A2, ischemia-modified albumin, and cystatin C in predicting coronary heart disease risk: a single center retrospective cohort study

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Abstract. – OBJECTIVE: This study aims to explore the value of serum lipoprotein-associated phospholipase A2 (Lp-PLA2), ischemia-modified albumin (IMA), and cystatin C (Cys-C) in predicting the risk of coronary heart disease (CHD).

PATIENTS AND METHODS: Clinical data from 104 CHD patients admitted to our hospital from January 2020 to December 2022 were analyzed. Of them, 31 patients had stable angina (Group-S), 36 patients were diagnosed with unstable angina (Group-U), and 37 patients had acute myocardial infarction (Group-A). Additionally, clinical data from 35 healthy individuals undergoing physical examination during the same time period were selected as the control group. Levels of blood lipid indicators and serum Lp-PLA2, IMA, and Cys-C levels were compared between the groups.

RESULTS: The rates of diabetes, hypertension, and smoking in Group-S, Group-U, and Group-A were significantly higher than those in the control group ($p<0.05$). Levels of Lp-PLA2, IMA, and Cys-C in Group-S, Group-U, and Group-A were significantly higher than those in the control group ($p<0.05$). Levels of Lp-PLA2, IMA, and Cys-C in Group-U and Group-A were significantly higher than those in Group-S, and Group-A had the highest value of these indexes ($p<0.05$). Multivariate logistic regression analysis showed that Lp-PLA2, Cys-C, and IMA were important risk factors for the onset of CHD ($p<0.05$). Receiver operating characteristic (ROC) curve analysis showed that the area under the curve (AUC) of Lp-PLA2, IMA, and Cys-C predicting the occurrence of CHD was 0.775, 0.835, and 0.735, respectively. The combined prediction of the three factors has an AUC of 0.920, which is higher than the individual prediction.

CONCLUSIONS: Lp-PLA2, IMA, and Cys-C are closely related to the onset and progression of CHD. These indicators, therefore, can be used in clinical practice to predict and evaluate CHD.

Key Words:
Coronary heart disease, Lipoprotein-associated phospholipase A2, Ischemia-modified albumin, Cystatin C.

Introduction

Coronary heart disease (CHD) is a clinically common type of cardiovascular disease that tends to occur in middle-aged and elderly populations and is associated with poor prognosis and high mortality[1]. Risk factors of CHD include diabetes, hyperlipidemia, hypertension, etc., and the disease is difficult to treat or reverse[2,3]. Therefore, accurate prediction and timely evaluation of CHD patients is crucial to ensure good patient outcomes[4,5].

Coronary angiography is the gold standard for the diagnosis of CHD[1,6]. However, while this procedure has high diagnostic value, it is complex and invasive, with a risk of complications[7]. Moreover, the efficiency and safety of the procedure depend on the equipment and the operator's skills, making it difficult to popularize and apply in general practice[6,7]. The detection of serum biochemical indicators, such as lipoprotein-associated phospholipase A2 (Lp-PLA2), ischemia-modified albumin (IMA), and cystatin C (Cys-C), is also an important measure for

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predicting and evaluating CHD, with advantages such as simplicity, high safety, and low cost[6-8]. Lp-PLA2 is an important inflammatory marker with strong vascular specificity that plays a role in the pathogenesis and progression of atherosclerosis and is an important risk factor for cardiovascular disease[9]. IMA is a marker of myocardial ischemia with strong sensitivity and specificity[10]. Cys-C can activate neutrophils and play a role in inflammatory reactions, thereby triggering and exacerbating CHD[11].

This study retrospectively analyzed clinical data of CHD patients admitted to the Affiliated Nanhua Hospital to clarify the expression characteristics and prediction value of serum Lp-PLA2, IMA, and Cys-C in CHD.

Patients and Methods

The study was conducted in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient or legal guardian, and the medical Ethics Committee of our hospital approved this study (No. 2023-KY-153, Date: 2023-04-23).

Patients

Clinical data from 104 CHD patients admitted to the Affiliated Nanhua Hospital from January 2020 to December 2022 were retrospectively collected. Patients were grouped based on the diagnosis: 31 patients with stable angina pectoris were assigned to Group-S; 36 patients with unstable angina pectoris were assigned to Group-U; 37 patients with acute myocardial infarction were assigned to Group-A.

Inclusion Criteria

- Meets the diagnostic criteria for CHD.
- CHD confirmed by coronary angiography and electrocardiogram examination.
- At least 1 coronary artery stenosis ≥50%.
- Complete clinical data.

Exclusion Criteria

- Emorrhagic cerebrovascular disease.
- Blood system diseases.
- Benign and malignant tumors.
- Renal and liver lesions.
- Consumptive diseases and malnutrition.
- Immune system and infectious diseases.

Data Collection

Baseline data of all patients was collected and included gender, age, basic diseases, smoking, body mass index (BMI), blood lipid indicators [low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), total cholesterol (TC)] levels.

Serum from 4 ml of fasting venous blood was used to measure the levels of biochemical indexes using the automatic biochemical analyzer (Canon FX-8). Lp-PLA2 levels were measured by rate method; IMA was detected using albumin cobalt binding assay; Cys-C levels were measured using immune transmission turbidimetry. The above reagent kits were purchased from Shanghai Xinfan Biotechnology Co., Ltd (Shanghai, China).

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). According to the distribution normality evaluated by the Shapiro-Wilk test, continuous variables were reported as mean and standard deviation (SD) or median and interquartile spacing (IQR). Single-factor analysis of variance (ANOVA) of normal distribution data was used to evaluate the statistical significance of continuous variable differences between the four groups. Bonferroni post-test was used for paired comparisons. The categorical variables were reported as frequency and percentage, and the differences between the four groups were evaluated using the Chi-square test or Fisher exact test, as appropriate. Establish a multivariate logistic regression model for the occurrence of CHD. The ability of Lp-PLA2, IMA, and Cys-C indicators to predict the occurrence of CHD was evaluated using the receiver operating characteristic (ROC) curve. A p-value lower than 0.05 was considered statistically significant. All reported p-values were two-sided.

Results

There was no significant difference among the four groups in terms of gender, age, BMI, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and total cholesterol (TC) levels ($p>0.05$). The rates of diabetes, hypertension, and smoking in Group-S, Group-U, and Group-A were significantly higher than those in the control group ($p<0.05$) (Table I).

Table I. Comparison of four baseline data groups.

Baseline information	Control-group (n = 35)	Group-S (n = 31)	Group-U (n = 36)	Group-A (n = 37)
Gender (male/female)	18/17	19/12	21/15	22/15
Age (year)	66.9 ± 8.0	68.9 ± 7.5	66.0 ± 7.8	67.6 ± 7.7
BMI (kg/m^2)	24.0 ± 2.0	23.3 ± 2.4	23.0 ± 2.4	23.6 ± 2.3
LDL-C (mmol/L)	2.70 ± 0.80	2.61 ± 0.90	2.90 ± 0.81	2.86 ± 0.73
HDL-C (mmol/L)	1.82 ± 0.52	1.94 ± 0.69	1.97 ± 0.53	2.03 ± 0.52
TG (mmol/L)	1.62 ± 0.58	1.71 ± 0.58	1.50 ± 0.49	1.56 ± 0.53
TC (mmol/L)	4.71 ± 0.76	4.70 ± 0.65	4.58 ± 0.70	4.86 ± 0.73
Diabetes [n (%)]	9 (25.7)	15 (48.4)[a]	17 (47.2)[a]	18 (48.6)[a]
Hypertension [n (%)]	9 (25.7)	16 (51.6)[a]	18 (50.0)[a]	20 (54.1)[a]
Smoking Status [n (%)]	15 (42.9)	22 (71.0)[a]	23 (63.9)[a]	25 (67.6)[a]

Compared with the Control-group, [a]$p < 0.05$; body mass index (BMI); low-density lipoprotein-cholesterol (LDL-C); high-density lipoprotein cholesterol (HDL-C); triglyceride (TG); total cholesterol (TC).

The levels of Lp-PLA2, IMA, and Cys-C in Group-S, Group-U, and Group-A were significantly higher than those in the control group (p<0.05). The levels of Lp-PLA2, IMA, and Cys-C in Group-U and Group-A were significantly higher than those in Group-S. Levels of Lp-PLA2, IMA, and Cys-C were the highest in Group-A (p<0.05) (Table II).

Multivariate logistic regression analysis showed that Lp-PLA2, IMA, and Cys-C were important risk factors for the onset of CHD (p<0.05) (Table III).

ROC curve analysis showed that the AUCs of Lp-PLA2, IMA, and Cys-C for predicting CHD were 0.775, 0.835, and 0.735, respectively. Using the combined application of ROC theory mode using SPSS software, a joint prediction model for various indicators was constructed. The results showed that the joint prediction AUC was the highest, with a value of 0.920 (Table IV) (Figure 1). The cut-off values during indicator testing were 366.5 ug/L, 53.5 U/ml, and 0.85 mg/L, respectively.

Discussion

The results of this study showed that the rates of diabetes, hypertension, and smoking in CHD patients were higher than those of the con-

Table II. Comparison of biochemical index levels among four groups.

Group	N	Lp-PLA2 (ug/L)	IMA (U/ml)	Cys-C (mg/L)
Control-group	35	319.8 ± 73.6	46.8 ± 7.7	0.82 ± 0.21
Group-S	31	375.0 ± 80.1[a]	52.0 ± 6.9[a]	0.90 ± 0.20[a]
Group-U	36	395.0 ± 90.2[a,b]	61.2 ± 8.8[a,b]	1.03 ± 0.22[a,b]
Group-A	37	467.5 ± 111.3[a,b,c]	66.7 ± 9.2[a,b,c]	1.12 ± 0.22[a,b,c]

Compared with the Control-group, [a]$p < 0.05$; Compared with Group-S, [b]$p < 0.05$; Compared to Group-U, [c]$p < 0.05$; lipoprotein-associated phospholipase A2 (Lp-PLA2); ischemia-modified albumin (IMA); cystatin C (Cys-C).

Table III. Multivariate logistic analysis of CHD incidence.

Covariates	β	S.E.	Wald χ^2	p	OR	95% CI
Lp-PLA2	0.009	0.004	5.642	0.018	1.009	1.002-1.16
IMA	0.164	0.041	15.707	< 0.001	1.179	1.087-1.278
Cys-C	2.896	1.384	4.379	0.036	18.102	1.202-272.706

Lipoprotein-associated phospholipase A2 (Lp-PLA2); ischemia-modified albumin (IMA); cystatin C (Cys-C).

Table IV. The value of Lp-PLA2, IMA, and Cys-C alone and joint prediction to the onset of CHD.

Index	AUC	S.E.	*p*	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
Lp-PLA2	0.775	0.043	< 0.001	0.690-0.860	366.5	63.5	82.9
IMA	0.853	0.035	< 0.001	0.785-0.921	53.5	71.2	85.7
Cys-C	0.735	0.049	< 0.001	0.639-0.831	0.85	75.0	60.0
Joint prediction	0.920	0.024	< 0.001	0.872-0.967		87.5	85.7

Lipoprotein-associated phospholipase A2 (Lp-PLA2); ischemia-modified albumin (IMA); cystatin C (Cys-C).

trol group. Similarly, serum levels of Lp-PLA2, IMA, and Cys-C were higher in the CHD groups compared to the control group. There was a significant difference between the serum levels of Lp-PLA2, IMA and Cys-C in different types of CHD patients. Logistic analysis of the influencing factors also found that Lp-PLA2, IMA, and Cys-C were important risk factors for the onset of CHD (p<0.05), indicating that Lp-PLA2, IMA, and Cys-C may be involved in the pathogenesis and progression of CHD. Previous clinical studies[12-14] have explored the detection value of Lp-PLA2, IMA, and Cys-C in CHD. A study by Ma et al[12] showed that Lp-PLA2 is widely distributed in platelets, smooth muscle cells, and endothelial cells, and abnormal expression of Lp-PLA2 may increase the risk of CHD. Zhang et al[13] showed that there were significant differences in IMA and Lp-PLA2 levels in patients with various subtypes of CHD (acute myocardial infarction, stable angina, and unstable angina) and healthy individuals undergoing physical examination. Our logistic

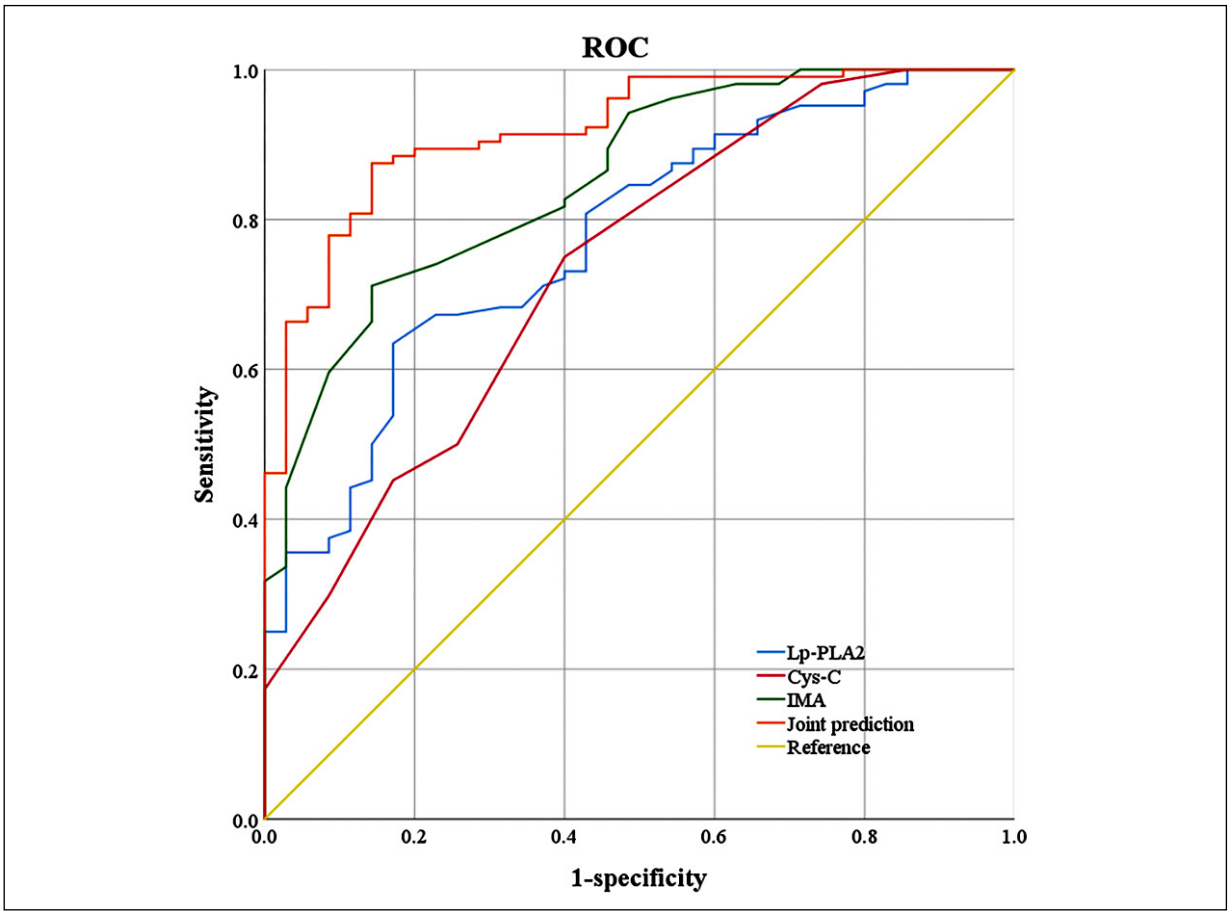

Figure 1. Receiver operating characteristic of Lp-PLA2, IMA, and Cys-C predicting CHD separately and jointly.

regression analysis also confirmed that abnormal levels of IMA and Lp-PLA2 are important risk factors for the degree of myocardial ischemia in CHD. Tian et al[14] investigated the changes and significance of serum MCP-1 and Lp-PLA2 in hypertensive patients with CHD and showed that the levels of Lp-PLA2 and other indicators in hypertensive patients with CHD were higher than those in simply hypertensive patients or healthy individuals. These studies[12-14] suggested that Lp-PLA2 may be involved in the pathogenesis of coronary artery disease, providing an objective reference for the diagnosis and treatment of CHD.

IMA as an important biomarker for clinical diagnosis of myocardial ischemia[15]. Its serum content can sharply increase within minutes after myocardial ischemia, and this increase is maintained for several hours after the improvement of ischemia. Compared to troponin, creatine kinase, etc., IMA has higher sensitivity and application value in auxiliary diagnosis of CHD. It was found that serum IMA levels in CHD patients are higher than those in healthy subjects. The research results of Xiao et al[16] showed that the IMA levels in patients with single, double, and multiple vessel disease in CHD were significantly higher than that of healthy individuals. Moreover, a serum IMA concentration of 72 U/L was associated with a sensitivity of 76.0% and a specificity of 72.3%, which has a certain application value in the diagnosis and evaluation of CHD and is consistent with the results of our study[15,16].

Zhao et al[17] showed that Cys-C is a non-glycosylated alkaline protein product, closely related to the severity of CHD and plaque stability. They found that the levels of Cys-C in hypertensive patients with CHD were higher than those in the control group, and the expression levels showed an increasing trend with the increase of lesion number. Cys-C, therefore, can serve as an independent risk factor for CHD and predict the risk of CHD in hypertensive patients. Tan et al[18] also confirmed that there is a significant correlation between Cys-C levels and cardiac function in CHD patients, which can be used for predicting and evaluating the effectiveness of disease treatment. All these studies have confirmed the application value of Lp-PLA2, IMA, and Cys-C in the diagnosis and evaluation of CHD[15-18]. In addition, the results of our study show that the combined prediction of Lp-PLA2, Cys-C, and IMA for CHD is more valuable than a single indicator and can provide a reference for the onset and progression of CHD.

Limitations

This is a single-center retrospective analysis, with a small sample size and selection bias and only a few observation indicators. Therefore, there may be unadjusted confounding factors. Further observational multi-center and large-scale studies are needed to confirm our results.

Conclusions

Lp-PLA2, IMA, and Cys-C are closely related to the onset and progression of CHD and may be used in clinical practice to predict and evaluate CHD.

Conflict of Interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Authors' Contribution

QL and JL conceived and designed the study. QL collected the data and performed the analysis. QL, JL and LC were involved in the writing of the manuscript and are responsible for the integrity of the study.

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Ethics Approval

Our study was approved by the Ethics Review Board of The Affiliated Nanhua Hospital (Approval No.: 2023-KY-153; Date: April 23th, 2023).

Data Availability

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

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