RESEARCH ARTICLE

The diagnostic efficacy and predictive value of combined lipoprotein laboratory indexes for atherosclerosis

Wei Xiao,[1] Yi Yang,[2] Jiao Shi,[3] Jia Xu,[4] Jianguang Zhu,[5] Zhinong Wu[6]

Abstract

Objective: To investigate the diagnostic efficacy and predictive value of combined lipoprotein laboratory indexes for atherosclerosis.

Methods: Clinical data of 250 patients with atherosclerosis admitted to Xianning central hospital, China from January 2015 to December 2018 and 80 healthy subjects on physical examination in the same period were analyzed retrospectively. Serological laboratory indices related to lipid metabolism were measured, and their diagnostic efficacy and predictive value for atherosclerosis were evaluated by univariate and multivariate statistical methods.

Results: The levels of lipoprotein-associated phospholipase A2 (Lp-PLA2), small dense low density lipoprotein (sd-LDL), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG) and high-sensitivity C-reactive protein (hs-CRP) of the atherosclerosis group were significantly higher than those of the healthy group ($P<0.05$). Logistic regression analysis showed that the levels of LP-PLA2, sd-LDL and hs-CRP were independent factors influencing the occurrence of atherosclerosis ($P<0.05$). Lp-PLA2 combined with sd-LDL had the largest area under ROC curve, and their diagnostic efficiency was higher than that of single serological laboratory indices. There was no significant difference in the levels of Lp-PLA2 and sd-LDL among different types of atherosclerotic diseases ($P<0.05$). The levels of LP-PLA2 and sd-LDL in triple-vessel or left main coronary artery disease were significantly higher than those of single- or double-vessel disease ($P<0.05$). The levels of LP-PLA2 and sd-LDL in double-vessel disease were significantly higher than those of single-vessel disease ($P<0.05$). The level of serum sd-LDL of atherosclerotic patients with alcohol history were significantly higher than those without alcohol history ($P<0.05$).

Conclusion: When being used to detect atherosclerosis, Lp-PLA2 combined with sd-LDL has better diagnostic efficacy than separate tests. Meanwhile, there is a correlation between their levels and the severity of disease, which can be used to predict the occurrence of atherosclerosis independently of other risk factors.

Keywords: Lipoprotein, Laboratory, Atherosclerosis, Diagnostic efficacy, Predictive. (JPMA 70:115[Special Issue]; 2020)

Introduction

At present, ischaemic cardiovascular and cerebrovascular diseases have become one of major disease types threatening life safety of middle-aged and elderly people. As a chronic inflammatory lesion, atherosclerosis has been proven to play a critical role in the process of cardiovascular and cerebrovascular disease occurrence and progression.[1] Atherosclerosis diagnosis mainly depends on imaging means, biomarkers clinical examination, and the diagnostic effect of conventional serum biomarker.[2] sd-LDL belongs to one of subgroups of LDL, and its level is closely related to the occurrence and development of cardiovascular disease. Besides, it is more sensitive to coronary heart disease diagnosis than LDL. LP-PLA2 is a new blood vessel inflammatory biomarker, and its level increase will aggravate atherosclerosis.[3,4] However, there is still no clear conclusion in the medical circle about the correlation of sd-LDL and LP-PLA2 with atherosclerosis and the improvement of atherosclerosis diagnostic effect by the combination of the two. This retrospective study was conducted to explore the diagnosis and prediction value of lipoprotein-related laboratory indices in atherosclerosis compared to a control group.

Patients and Methods

A total of 250 atherosclerosis patients treated in Xianning central hospital from January 2015 to December 2018 were selected as the study subjects whereas 80 healthy individuals underwent physical examination and were taken as controls. Exclusion criteria were cardiomyopathy, hypertensive heart disease, congenital heart disease, pulmonary heart disease, acute or chronic infection or inflammation, liver and kidney dysfunction, gestation, connective tissue disease, presence of a malignant tumour, rheumatic disease, intake of lipid lowering drugs,

[1,3-6]Department of Clinical Laboratory, Xianning Central Hospital, The First Affiliated Hospital of Hubei University of Science and Technology, Xianning, [2]Department of Clinical Laboratory, The Third Clinical Medical College of the Three Gorges University, Gezhouba Central Hospital of Sinopharm, Yichang, China.

Correspondence: Zhinong Wu. Email: 343463657@qq.com

drug addiction, and incomplete clinical data. The research programme was approved by the ethics committee of the hospital. All patients and their family members signed the informed consent form.

The clinical data of both groups were retrospectively analyzed. Diagnosis of atherosclerosis was made by CTA or MRA. The healthy persons had no obvious vascular shadows.

Laboratory index detection method: All of the laboratory indices were tested by the central laboratory of our hospital, collected and analyzed by specially-assigned staff. The tests of LDL-C, TC, TG, hs-CRP, LP-PLA2 and sd-LDL were done with Beckman Coulter AU5800 Clinical Chemistry Analyzer. Three ml of fasting venous blood was drawn and centrifuged at the rate of 8000g for 5 minutes to extract the serum. Among them, sd-LDL was tested by peroxidase method, LP-PLA2 by rate method, hs-CRP by immunity transmission turbidity, LDL-C by surfactant removal method, TC by CHOD-POD method and TG by GPO-PAP method.

Statistical method: SPSS 20.0 was used to process the data. The measurement data were compared with LSD-t test and variance analysis, expressed with (x±s). The enumeration data were compared with χ^2 test, expressed with %. Logistic regression model was employed for multiple-factor analysis. Spearman method was used for correlation analysis. ROC was drawn and AUC was calculated to analyze the diagnosis effect. Test level α=0.05.

Results

The differences in age and gender of both groups were not significant (P>0.05). In the atherosclerosis group, the levels of LP-PLA2, sd-LDL, LDL-C, TC, TG and hs-CRP were significantly higher than those of the control group (P<0.05), as shown in Table-1.

Correlation analysis verified that, TC and LDL-C are significantly correlated (r=0.84, P=0.00). To eliminate significantly correlated indices, the independent variables included the indices with statistical significance (except TC), gender and age. The dependent variable was atherosclerosis. Logistic regression model analysis showed that, the levels of LP-PLA2, sd-LDL and hs-CRP are independent factors influencing the occurrence of atherosclerosis (P<0.05), as shown in Table-2.

AUC of ROC of LP-PLA2 and sd-LDL detection was maximum. The diagnosis effect was higher than that of

Table-1: Analysis of demographic data and laboratory indexes.

Index	Atherosclerosis group (n=250)	Healthy group (n=80)	Z	P
Age (year)	63.41±5.52	62.27±5.10	0.55	0.82
Proportion of men [n,%]	120 (48.00)	43 (53.75)	0.40	0.91
LP-PLA2 (iu/l)	667.22±130.72	572.90±105.19	5.38	0.00
sd-LDL (mg/dl)	148.84±25.83	39.23±8.85	6.76	0.00
LDL-C (mg/dl)	214.91±54.31	90.25±17.21	6.15	0.00
TC (mg/dl)	260.25±71.15	163.96±46.79	5.89	0.00
TG (mg/dl)	240.84±82.35	103.59±31.87	5.27	0.00
hs-CRP (mg/l)	4.72±1.12	2.95±0.72	3.80	0.00

*Compared with the first cycle, P <0.05.
LP-PLA2: lipoprotein-associated phospholipaseA2. sd-LDL: Small dense low density lipoprotein. LDL-C: low-density lipoprotein cholesterol. TC: Total Cholesterol. TG: Triglycerides.
hs-CRP: high-sensitivity C-reactive protein.

Table-2: Multiple-factor analysis of atherosclerosis morbidity.

Index	β	SE	Wald χ^2	OR	95%CI	p
LP-PLA2	0.01	0.00	9.04	1.17	1.02~1.26	0.00
sd-LDL	2.32	0.83	6.56	8.50	1.72~40.64	0.01
LDL-C	0.85	0.52	3.49	2.62	0.93~5.80	0.08
Gender	-0.44	0.56	0.96	0.82	0.37~1.49	0.35
Age	0.02	0.03	0.71	1.24	0.95~1.07	0.41
TG	0.64	0.37	3.88	2.09	0.95-3.40	0.06
hs-CRP	0.17	0.08	6.14	1.77	1.10~1.99	0.00

Lipoprotein-associated phospholipase A2 (Lp-PLA2), small dense low density lipoprotein (sd-LDL), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG) and high-sensitivity C-reactive protein (hs-CRP): high-sensitivity C-reactive protein.

Table-3: Auxiliary diagnosis value of LP-PLA2 combined with sd-LDL in atherosclerosis.

Index	Cut-off value	Sensitivity (%)	Specificity (%)	ROC-AUC	Youden index
LDL-C	2.63	85.66	67.31	0.78	0.53
TC	4.89	83.26	69.16	0.78	0.52
TG	1.55	76.82	74.59	0.76	0.51
hs-CRP	5.16	80.00	52.76	0.63	0.33
LP-PLA2	642.10	57.69	89.11	0.75	0.47
sd-LDL	0.97	73.68	78.24	0.81	0.62
LP-PLA2+sd-LDL	0.75	72.86	89.14	0.85	0.62

Lipoprotein-associated phospholipase A2 (Lp-PLA2), small dense low density lipoprotein (sd-LDL), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG) and high-sensitivity C-reactive protein (hs-CRP): high-sensitivity C-reactive protein.

Table-4: Comparison of LP-PLA2 and sd-LDL level of atherosclerosis at different lesion position.

Lesion degree	No.	LP-PLA2 (iu/l)	sd-LDL (mg/dl)
Coronary artery	94	669.13±143.29	159.62±27.24
Brain artery	88	662.04±150.16	147.36±22.35
Aorta	16	702.23±89.80	151.76±23.82
Carotid artery	22	614.11±161.87	140.33±22.15
Multiple arteries involved	30	653.87±97.92	131.56±19025
Z		8.33	5.81
P		0.13	0.25

Table-5: Comparison of LP-PLA2 and sd-LDL level of coronary artery at different lesion degree.

Lesion degree	No.	LP-PLA2 (iu/l)	sd-LDL (mg/dl)
Single branch lesion	50	571.68±175.09	146.37±25.64
Double branch lesion	24	665.72±156.12	158.29±28.22
Three-branch or left main Coronary artery	30	713.76±245.94	171.56±36.44
Z		7.83	10.34
P		0.03	0.02

single use of other serum laboratory indices, as shown in Table-3.

The comparison difference of LP-PLA2 and sd-LDL level of atherosclerosis at different lesion position had no significance (P>0.05), as shown in Table-4.

LP-PLA2 and sd-LDL level of three-branch or left main coronary artery were higher than those of single branch lesion and double branch lesion (P<0.05). LP-PLA2 and sd-LDL level of double branch lesion were higher than those of single branch lesion (P<0.05), as shown in Table-5.

The serum sd-LDL level of atherosclerosis patients with history of alcohol intake was significantly higher than that of atherosclerosis patients not taking alcohol (P<0.05). The comparison difference of LP-PLA2 and sd-LDL level in other indexes had no significance (P>0.05), as shown in Table-6.

Discussion

Multiple basic and clinical studies have verified that,[5,6] vascular abnormal oxidative stress and chronic inflammatory injury are the key initiating factors for the

Table-6: Comparison between LP-PLA2 and sd-LDL level of dangerous factors of atherosclerosis.

Index		No.	LP-PLA2 (iu/l)	Z	P	sd-LDL (mg/dl)	Z	P
Gender	Male	120	670.72±85.28	0.42	0.71	161.53±34.62	0.98	0.37
	Female	130	651.47±103.26			153.45±31.57		
Age	?60	110	664.76±120.61	0.78	0.49	163.81±35.16	0.04	0.95
	>60	140	675.23±139.28			167.58±35.92		
Smoking history	Yes	56	676.62±91.88	0.63	0.55	165.21±34.22	0.92	0.35
	No	194	665.51±140.68			152.74±31.18		
Alcohol history	Yes	40	673.69±102.37	1.10	0.25	170.22±37.35	2.17	0.04
	No	210	661.53±132.62			146.54±29.62		
Primary hypertension	Yes	178	671.02±94.32	0.10	0.94	152.37±31.21	0.42	0.75
	No	72	662.49±110.67			148.26±28.64		
Type 2 diabetes	Yes	48	622.83±103.62	1.42	0.21	146.39±27.85	0.88	0.40
	No	202	658.53±112.42			149.22±30.26		

occurrence and development of atherosclerosis and secondary cardiovascular and cerebrovascular diseases. The inflammatory cytokines represented by CRP and hs-CRP are closely related to atherosclerosis, clinical classification and long-term adverse events. A study has verified that,[7] lipid metabolism disorder such as LDLD increase is the most important pathophysiological basis of atherosclerosis occurrence. But in the practical clinical diagnosis process, the above conventional laboratory indices cannot accurately reflect the occurrence of atherosclerosis in the early stage.[8] Identifying laboratory indices for achieving early diagnosis and treatment of atherosclerosis has become a focused issue of in medical practice.

In accordance with particle density and diameter of LDL micromolecule, LDL can be divided into different subgroups. sd-LDL is the main component of LDL3-7 subgroup. An overseas study indicates that,[9] sd-LDL level abnormity is more closely related to the occurrence and severity of atherosclerosis. The expression level of LP-PLA2 obviously rises in atherosclerosis patients. It is reported that,[10] mPLA2 detection can reflect instability of atherosclerotic plaque and the severity of coronary heart disease.

Abnormal CRP and hs-CRP level lead to chronic vascular inflammation, which is considered to be one of main mechanisms of atherosclerosis. It has been verified that LDL-C, TC and TG disorder could reflect lipidosis of arteries, indirectly indicating the possibility of atherosclerotic plaque formation.[11] Currently, LDL-C, TC, TG and hs-CRP are monitored for the suspected atherosclerosis patients, and they can be used for auxiliary diagnosis and therapeutic effect evaluation. In this study, the levels of LP-PLA2, sd-LDL, LDL-C, TC, TG and hs-CRP in atherosclerosis group were significantly higher than those of healthy group ($P<0.05$), indicating that the abnormality of the above indices can predict atherosclerosis, which conforms to previous reports.[12] Logistic regression model analysis showed that, the levels of LP-PLA2, sd-LDL and hs-CRP are independent factors influencing the occurrence of atherosclerosis ($P<0.05$). LDL-C, TC and TG are not independent risk factors of atherosclerosis prediction, with low diagnostic specificity. Although hs-CRP is verified to be an independent risk factor for the prediction of atherosclerosis, ROC verifies that its diagnostic specificity is only 52.76, AUC=0.63, indicating that the diagnosis effect of single use is poor. Compared with hs-CRP, LP-PLA2 and sd-LDL have higher diagnostic specificity. Meanwhile, AUC of ROC of LP-PLA2 and sd-LDL detection was maximum. The diagnosis effect was higher than that of single use of other serum laboratory indexes. This further indicates LP-PLA2 combined with sd-LDL has a higher diagnostic index on detecting atherosclerosis and contributes to lowering clinical defection omission and excess diagnosis risk.

Endarterium lipidosis and vascular oxidative stress play a critical role in the attack process of atherosclerosis. LP-PLA2 and sd-LDL level are correlated with inflammation of atherosclerotic plaque area and oxidative stress response degree.[13] But, the correlation of LP-PLA2 and sd-LDL with lesion parts of atherosclerosis is still unclear. In this study, the comparison difference of LP-PLA2 and sd-LDL level of atherosclerosis at different lesion position had no significant difference ($P>0.05$), indicating that LP-PLA2 and sd-LDL level have no correlation with the lesion position. In the meantime, LP-PLA2 and sd-LDL level of three-branch or left main coronary artery were higher than those of single branch lesion and double branch lesion ($P<0.05$). LP-PLA2 and sd-LDL level of double branch lesion were higher than those of single branch lesion ($P<0.05$), which is consistent with the previous reports.[14] In other words, LP-PLA2 and sd-LDL rise with the increase in the lesion degree of coronary heart disease. In the author's opinion, the rise of serum LP-PLA2 and sd-LDL level can be used to predict the occurrence of atherosclerosis and reflect lesion severity. Thus, this study can provide certain reference for follow-up clinical treatment.

A scholars' research verifies that,[15] age, smoking and alcohol history, primary hypertension and type 2 diabetes are important risk factors of atherosclerosis. However, there are few reports about the correlation of LP-PLA2 and sd-LDL with risk factors of atherosclerosis.[16,17] The results of this study verify that LP-PLA2 and sd-LDL are independent risk factors of atherosclerosis.[16] But, it is essential to keep under observation that the serum sd-LDL level of atherosclerosis patients with alcohol intake history was significantly higher than that of atherosclerosis patients without alcohol history ($P<0.05$),[18,19] indicating that ethyl alcohol may affect serum sd-LDL level of atherosclerosis patients. Overseas studies exhibit that,[20] the animals with alcohol-induced hypertension have obvious vascular abnormal oxidative stress response, and the formation proportion of atherosclerotic plaque is high, indirectly verifying that alcohol can participate in sd-LDL mediated atherosclerotic plaque formation process.

This study also has certain limitations: (1) small sample size, monocentric and non-foresight design may lead to result bias; (2) the detection kit manufacturers are relatively single; (3) the grouping of research objects is only based on clinical examination results, and the

morbidity and severity of disease fail to be overall assessed; (4) there are many factors influencing atherosclerosis, and the indexes included in this study are relatively limited.

Conclusion

In conclusion, the diagnostic effect of LP-PLA2 combined with sd-LDL in atherosclerosis is better than that of single detection. Besides, LP-PLA2 and sd-LDL are related to the lesion degree, and they can be used to predict the occurrence of atherosclerosis, independent of other dangerous factors.

Limitation

The study patients could not be matched with a similar number of controls which could give a bias to the results.

Disclaimer: The manuscript has not been published or submitted for publication elsewhere.

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