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ORIGINAL ARTICLE

Predictive Value of Serum Lipoprotein-Associated Phospholipase A2 for Type 2 Diabetes Mellitus Complicated with Metabolic Syndrome in Elderly Patients

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SUMMARY

Background: **The aim was to investigate the predictive value of serum lipoprotein-associated phospholipase A2 (Lp-PLA2) for type 2 diabetes mellitus (T2DM) complicated with metabolic syndrome (MS) in elderly patients.**
Methods: **A total of 296 patients with T2DM admitted from January 2019 to January 2021 were enrolled and assigned to MS group (n = 181) and non-MS group (n = 115). Their clinical data and laboratory test results were compared. Logistic regression analysis was employed to identify independent risk factors for MS in T2DM patients. Spearman's analysis was utilized to explore the correlations between serum Lp-PLA2 level and detection indicators. The predictive value of Lp-PLA2 for MS was analyzed by plotting receiver operating characteristic (ROC) curve, and Cox regression model was applied to explore the correlation of serum Lp-PLA2 level with MS. The results of data subjected to multivariate analysis were used to construct prediction models.**
Results: **The incidence rate of MS was 61.15% in T2DM patients. MS group had a significantly higher serum level of Lp-PLA2 than non-MS group ($p < 0.05$). Serum Lp-PLA2 was significantly positively correlated to FBG, glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), FINS, and HOMA-IR, but significantly negatively associated with LDL-C ($p < 0.05$). The area under the ROC curve of Lp-PLA2 for predicting MS in T2DM patients was 0.724 (95% CI: 0.625 - 0.826, $p < 0.05$). The sensitivity, specificity, positive predictive value, and negative predictive value of Lp-PLA2 with an optimal cutoff value of 82.96 ng/mL were 73.7%, 85.4%, 77.56%, and 93.24%, respectively. TC, TG, HDL-C, HbA1c, and Lp-PLA2 were independent risk factors for MS ($p < 0.05$). The area under the ROC curve of the risk prediction model established based on these indicators was 0.823, and the cutoff value, Youden index, sensitivity, and specificity were 0.219, 0.656, 78.87%, and 87.66%, respectively, indicating higher predictive value.**
Conclusions: **Increased serum Lp-PLA2 level is an independent risk factor for MS in T2DM patients. Lp-PLA2 (82.87 ng/mL) has high predictive value for MS.**
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KEY WORDS

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INTRODUCTION

Metabolic syndrome (MS) is a clinical syndrome characterized by metabolic disorder involving central obesity, impaired glucose tolerance, hypertension, and dyslipidemia, with insulin resistance as the core component [1,2]. MS often occurs in patients who suffer from type 2 diabetes mellitus (T2DM), and the older the age, the higher the risk [3]. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is considered to be a novel inflammatory marker. As reported by numerous clinical studies, Lp-PLA2 is correlated with the complications of T2DM, such as atherosclerotic plaque formation [4] and lower extremity arterial disease [5]. However, the research on the correlation between the serum Lp-PLA2 level and MS in diabetic patients is relatively rare. This study, therefore, aimed to investigate the predictive value of the serum Lp-PLA2 level for MS in T2DM patients, thus providing theoretical references for effective clinical prevention of MS in T2DM patients.

MATERIALS AND METHODS

Subjects

A total of 296 patients with T2DM admitted to the Department of Endocrinology of our hospital from January 2019 to January 2021 were selected. The group included 157 males and 139 females aged 41 - 67 years old with an average of 52.36 ± 11.25 years old. The inclusion criteria were as follows: a) patients who met the diagnostic criteria for DM [6], b) those with complete medical records. The exclusion criteria included: a) patients with acute diabetic complications, b) those with other endocrine diseases or immune disorders, c) those with malignancies, or d) those with hepatic or renal insufficiency. This study was reviewed and approved by the Ethics Review Committee of our hospital. Informed consent was obtained from all participants.

Diagnostic criteria for MS

In accordance with the Standards of medical care for type 2 diabetes in China 2019 [7], the individuals who met three of the following four criteria were diagnosed with MS: a) central obesity, b) hyperglycemia, c) hypertension, and d) fasting triglycerides (TG) ≥ 1.7 mmol/L, and fasting high-density lipoprotein cholesterol (HDL-C) < 1.04 mmol/L.

Grouping method

Patients were assigned to MS group (n = 181) and non-MS group (n = 115) according to the presence or absence of MS.

Collection of baseline data

General clinical data, such as gender, age, and course of disease, were gathered and recorded through review of patients' medical records.

Examination of body indices

Patients' height, body mass, waist circumference, and blood pressure were measured by trained medical staff using standard measurement methods. The height, body mass, and waist circumference were measured in the fasting state, while the blood pressure was tested in the quiet state on the day of admission. Body mass index (BMI) = body mass/height^2.

Detection of laboratory indicators

After fasting for 8 - 10 hours, 5 mL of venous blood was extracted from each subject in the morning. After centrifugation at 4,000 rpm for 10 minutes, the serum samples were collected. The levels of fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum uric acid (UA) were detected using an automatic biochemistry analyzer (Modular DP, Roche, Switzerland). Ion chromatography was adopted to determine the level of glycosylated hemoglobin (HbA1c). Chemiluminescence assay was utilized to test the level of fasting insulin (FINS). The Lp-PLA2 level was detected *via* enzyme-linked immunosorbent assay kits (CSB-E08319h, CUSABIO, USA). Besides, the C-reactive protein (CRP) level was measured using a protein analyzer (IMMAGE 800, Beckman Coulter, USA). The level of insulin resistance was evaluated *via* homeostasis model assessment of insulin resistance (HOMA-IR) index: HOMA-IR = (FBG x FINS)/22.5.

Statistical analysis

SPSS 23.0 software was used for statistical analysis. The measurement data conforming to normal distribution were expressed by mean ± standard deviation ($\bar{x}$ ± s), and independent-samples (two-sample) *t*-test was employed for comparison between two groups. The data not conforming to normal distribution were expressed as median [M (Q1, Q3)], and Mann-Whitney U test was used for comparison between two groups. Numerical data were expressed as percentage [n (%)] and compared using chi-squared test. Spearman's correlation analysis was utilized. Logistic regression analysis was employed to identify independent risk factors for MS in T2DM patients. Receiver operating characteristic (ROC) curve was plotted to evaluate the predictive value of Lp-PLA2 for MS. $p < 0.05$ was considered statistically significant.

RESULTS

Clinical data of T2DM patients

MS occurred in 181 out of the 296 patients with T2DM, with an incidence rate of 61.15%. The MS group had higher BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, HbA1c, TC, TG, HDL-C, CRP, UA, FINS, HOMA-IR, and Lp-PLA2 levels and larger waist circumference than non-MS group (p <

Table 1. General clinical data and laboratory test indicators of patients.

Indicator	MS group (n = 181)	Non-MS group (n = 115)	$\chi^2/Z/t$	p
Male [n (%)]	95 (52.49)	62 (53.91)	0.735	0.396
Age (y)	52.31 ± 11.06	51.09 ± 10.81	0.306 [a]	0.762
Course of disease (y)	7.37 ± 6.36	8.90 ± 7.54	0.601 [a]	0.553
BMI (kg/m^2)	26.84 ± 2.76	23.25 ± 2.64	3.640 [a]	0.001
Waist circumference (cm)	93.37 ± 8.72	84.22 ± 8.36	2.911 [a]	0.007
SBP (mmHg)	138.45 ± 12.22	124.25 ± 11.24	3.312 [a]	0.002
DBP (mmHg)	86.39 ± 7.28	76.58 ± 8.05	3.501 [a]	0.002
FBG (mmol/L)	9.58 ± 0.85	8.75 ± 0.84	2.690 [a]	0.012
HbA1c (%)	8.92 ± 0.53	8.44 ± 0.47	2.624 [a]	0.014
TC (mmol/L)	5.33 (4.54, 5.91)	4.52 (4.09, 4.75)	3.571 [b]	0.020
TG (mmol/L)	3.28 (2.65, 3.79)	1.38 (0.71, 1.65)	39.02 [b]	0.000
LDL-C (mmol/L)	2.87 ± 0.32	3.16 ± 0.55	1.765 [a]	0.088
HDL-C (mmol/L)	1.07 (0.62, 1.41)	1.25 (0.83, 1.76)	12.15 [b]	0.006
CRP (mg/L)	4.93 (3.79, 6.96)	4.34 (3.22, 5.79)	8.95 [b]	0.026
UA (μmol/L)	334.62 ± 85.47	271.52 ± 81.65	2.068 [a]	0.048
FINS (Um/mL)	19.65 ± 3.97	14.06 ± 3.68	3.999 [a]	0.000
HOMA-IR	4.85 (3.84, 6.55)	4.02 (2.96, 5.08)	53.26 [b]	0.000
Lp-PLA2 (ng/mL)	178.18 ± 48.86	112.35 ± 29.48	6.354[a]	0.000

[a]: *t*-value; [b]: *Z* value; others: χ^2 value.

Table 2. Multivariate logistic regression analysis results of MS in T2DM patients.

Parameter	Regression coefficient	Standard error	Wald χ2	p	OR	95% confidence interval (CI)
BMI (kg/m2)	0.150	0.340	0.193	0.660	1.161	0.596 ~ 2.263
Waist circumference (cm)	0.033	0.038	0.725	0.395	1.033	0.959 ~ 1.113
SBP (mmHg)	0.018	0.042	0.166	0.648	1.017	0.935 ~ 1.108
DBP (mmHg)	0.014	0.018	0.646	0.419	1.014	0.981 ~ 1.052
FBG (mmol/L)	0.000	0.003	0.028	0.872	1.000	0.980 ~ 1.050
HbA1c (%)	0.438	0.196	3.569	0.031	1.451	1.254 ~ 1.634
TC (mmol/L)	1.072	0.146	4.251	0.005	0.142	1.221 ~ 1.833
TG (mmol/L)	0.393	0.049	4.624	0.042	1.469	1.318 ~ 1.538
HDL-C (mmol/L)	0.435	0.184	5.726	0.000	1.432	1.227 ~ 1.643
CRP (mg/L)	0.235	0.425	0.339	0.565	1.265	0.570 ~ 2.788
UA (μmol/L)	0.007	0.009	0.594	0.441	0.993	0.975 ~ 1.011
FINS (Um/mL)	0.196	0.734	0.069	0.791	0.829	0.205 ~ 2.325
HOMA-IR	0.378	0.749	0.256	0.615	1.457	0.336 ~ 5.314
Lp-PLA2 (ng/mL)	0.447	0.251	4.689	0.017	1.670	1.015 ~ 1.377

0.05). No significant differences were found in gender ratio, age, course of disease, and LDL-C level between the two groups of patients (p > 0.05) (Table 1).

Independent risk factors for MS in T2DM patients

The indicators with statistical difference in univariate analysis (p < 0.05) were incorporated to multivariate lo-

Table 3. Correlations of Lp-PLA2 level and metabolic indicators in T2DM complicated with MS.

Indicator	r	p
Gender	0.201	0.142
Age	0.060	0.617
Course of disease	0.007	0.962
BMI	0.263	0.074
Waist circumference	0.239	0.081
SBP	0.140	0.283
DBP	0.118	0.428
FBG	0.458	0.004
HbA1c	0.528	0.011
TC	0.434	0.000
TG	0.077	0.020
LDL-C	-0.477	0.000
HDL-C	0.084	0.015
CRP	0.264	0.087
UA	0.107	0.339
FINS	0.331	0.015
HOMA-IR	0.357	0.014

Table 4. Association between Lp-PLA2 level and T2DM complicated with MS.

Model	Lp-PLA2 ≤ 105.64 ng/mL	Lp-PLA 105.64 - 163.37 ng/mL		Lp-PLA ≥ 163.37 ng/mL	
		HR (95% CI)	p	HR (95% CI)	p
Model 1	1.000 (ref)	2.212 (0.768 ~ 6.360)	0.134	6.122 (2.964 ~ 12.131)	< 0.001
Model 2	1.000 (ref)	1.989 (0.683 ~ 5.747)	0.208	4.824 (2.818 ~ 8.689)	< 0.001
Model 3	1.000 (ref)	2.015 (0.704 ~ 5.767)	0.192	4.394 (2.213 ~ 9.609)	< 0.001
Model 4	1.000 (ref)	1.649 (0.575 ~ 4.726)	0.352	2.580 (1.325 ~ 6.432)	0.005

Model 1 - uncorrected, Model 2 - corrected for age and gender, Model 3 - corrected for model 2 and hypertension, hyperlipidemia, cardiovascular, and cerebrovascular diseases and course of disease, BMI waist circumference, SBP and DBP, Model 4 - corrected for model 3 and FBG, HbA1c, TC, TG, LDL-C, HDL-C, CRP, UA, FINS, HOMA-IR, etc., ref - reference group.

gistic regression analysis (stepwise regression method), and the results manifested that TC, TG, HDL-C, HbA1c, and Lp-PLA2 were independent risk factors for MS ($p < 0.05$) (Table 2).

Correlations of Lp-PLA2 level in T2DM patients and detection indicators

Spearman's correlation analysis was utilized to analyze the associations between the Lp-PLA2 level in T2DM patients and detection indicators. The results denoted that serum Lp-PLA2 was significantly positively correlated with FBG, HbA1c, TC, TG, HDL-C, FINS, and HOMA-IR ($p < 0.05$), but significantly negatively associated with LDL-C ($p < 0.05$) (Table 3).

Association between Lp-PLA2 level and T2DM complicated with MS

According to the tertiles of Lp-PLA2 level, patients were divided into Lp-PLA ≤ 105.64 ng/mL group, Lp-PLA: 105.64 - 163.37 ng/mL group, and Lp-PLA ≥ 163.37 ng/mL group. Multivariate Cox regression analysis was conducted using four models. The results displayed that among the four models, the risk of T2DM complicated with MS was higher in Lp-PLA ≥ 163.37 ng/mL group than that in other groups. Furthermore, in model 4, the risk of T2DM complicated with MS in Lp-PLA ≥ 163.37 ng/mL group was 2.580 times higher than that in Lp-PLA2 ≤ 105.64 ng/mL group [hazard ratio (HR) = 2.580, 95% CI: 1.325 - 6.432, p = 0.005]

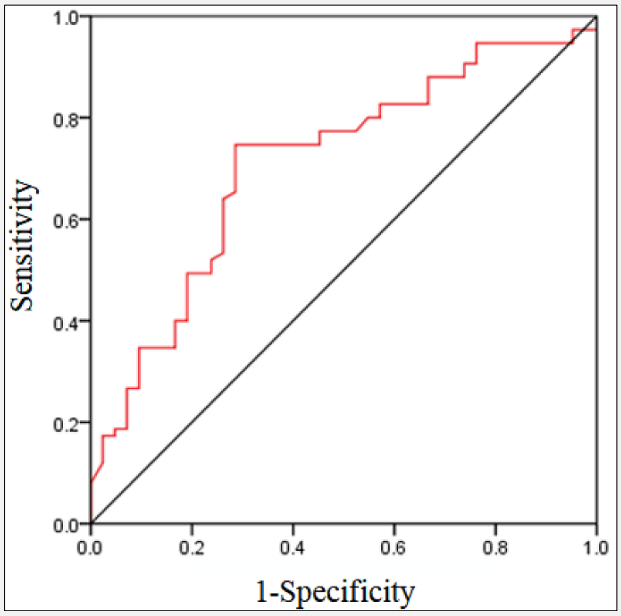

Figure 1. ROC curve of Lp-PLA2 level for predicting MS in T2DM patients.

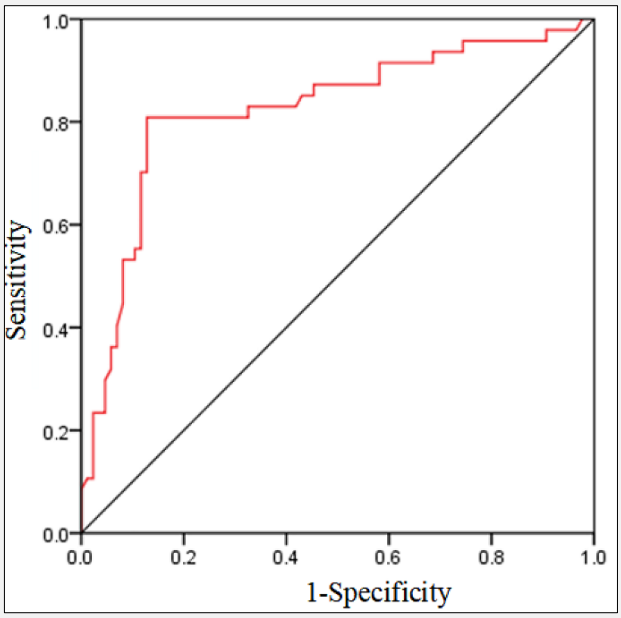

Figure 2. ROC curve of the prediction model for MS in T2DM patients.

(Table 4).

Optimal predictive value of Lp-PLA2 level for MS in T2DM patients

The area under the ROC curve of Lp-PLA2 for predicting MS in T2DM patients was 0.724 (95% CI: 0.625 - 0.826, $p < 0.05$). The optimal predictive value of Lp-PLA2 determined by the Youden index was 82.96 ng/mL, and the sensitivity, specificity, positive predictive value and negative predictive value were 73.7%, 85.4%, 77.56%, and 93.24%, respectively (Figure 1).

Risk prediction model of MS

The prediction model was constructed with the presence or absence of MS in T2DM patients as a dependent variable (assignment: yes = 1, no = 0) and TC, TG, HDL-C, HbA1c, and Lp-PLA2 as independent variables: predictive value = EXP [8.642 - 0.691 (TC) - 0.491 (TG) - 0.945 (HDL-C) - 0.369 (HbA1c) - 0.928 (Lp-PLA2)]/1 + EXP [8.642 - 0.691 (TC) - 0.491 (TG) - 0.945 (HDL-C) - 0.369 (HbA1c) - 0.928 (Lp-PLA2)], and assignments for TC, TG, HDL-C, HbA1c, and Lp-PLA2 were continuous variables.

The area under the ROC curve of the prediction model for MS in T2DM patients was 0.823, and the cutoff value, Youden index, sensitivity and specificity were 0.219, 0.656, 78.87% and 87.66%, respectively (Figure 2).

DISCUSSION

T2DM is mainly attributed to insufficient insulin secretion and insulin resistance. Compared with general population, such patients are more prone to MS because of higher possibility of metabolic disorders, such as obesity, hypertension, hyperlipidemia, and impaired glucose tolerance [8,9]. As a serine esterase secreted by intimal macrophages, T cells, and large cells, Lp-PLA2 can indirectly cause impairment of vascular endothelial cells by mediating inflammatory response [10], which has a certain value in evaluating ischemic stroke and carotid plaque stability in T2DM patients [11]. Lin et al. [12] demonstrated that the serum Lp-PLA2 level was found to be an independent risk factor for T2DM complications and could predict macrovascular diseases to a certain extent. As reported by Ding et al. [13], Lp-PLA2 was capable of reflecting the degree of insulin resistance in T2DM patients and served as a predictor of cardiovascular disease. Based on the findings above, it can be concluded that Lp-PLA2 may participate in the pathological process of DM-related complications. However, little literature exists regarding the correlation of the serum Lp-PLA2 level with MS in T2DM patients and its predictive value.

In the present study, the results confirmed that the incidence rate of MS was 61.15% in T2DM patients. The results of univariate analysis revealed that T2DM patients with MS had significantly higher BMI, SBP, DBP, FBG, HbA1c, TC, TG, HDL-C, CRP, UA, FINS, HOMA-IR, and serum Lp-PLA2 levels and larger waist circumference than those without MS, consistent with research by Zhou et al. [14]. It can be seen that serum Lp-PLA2 can serve as a predictor of the risk of MS in T2DM patients. Multivariate logistic regression analysis manifested that TC, TG, HDL-C, HbA1c, and Lp-PLA2 were independent risk factors for MS. Spearman's correlation analysis denoted that serum Lp-PLA2 was significantly positively related to FBG, HbA1c, TC, TG, HDL-C, FINS, and HOMA-IR, but significantly negatively associated with LDL-C. The findings indicated that Lp-PLA2 has close relationships with metabolic indicators such as TC, TG, and HDL-C, and has an indirect influence on insulin resistance in T2DM patients. After multiple confounding factors were corrected, the risk of MS in T2DM patients was subjected to simulation evaluation using four models, and the results displayed that the serum Lp-PLA2 level was considered to be an independent risk factor for MS in T2DM patients. In addition, among the four models, the risk of T2DM complicated with MS was higher in the Lp-PLA2 $\geq$ 163.37 ng/mL group than that in the other groups. Furthermore, in model 4, the risk of T2DM complicated with MS in the Lp-PLA2 $\geq$ 163.37 ng/mL group was 2.580 times higher than that in the Lp-PLA2 $\leq$ 105.64 ng/mL group (HR = 2.580, 95% CI: 1.325 - 6.432, $p = 0.005$). ROC curve illustrated that 82.87 ng/mL was the optimal cutoff value of Lp-PLA2 for predicting MS occurrence. If Lp-PLA2 > 82.87 ng/mL, T2DM patients were more likely to be complicated with MS. The area under the ROC curve of Lp-PLA2 for predicting MS in T2DM patients was larger than 0.7, and the sensitivity, specificity, positive predictive value and negative predictive value of Lp-PLA2 were 73.7%, 85.4%, 77.56%, and 93.24%, respectively, indicating that Lp-PLA2 is of certain value for predicting MS in T2DM patients. In light of multivariate analysis, the risk prediction model was constructed for T2DM patients with MS. The area under the ROC curve of the prediction model was 0.823, and the cutoff value, Youden index, sensitivity, and specificity were 0.219, 0.656, 78.87%, and 87.66%, respectively, indicating better predictive value.

CONCLUSION

In conclusion, the increased serum Lp-PLA2 level is an independent risk factor for MS in T2DM patients. Lp-PLA2 (82.87 ng/mL) has a certain predictive value for MS. Close attention should be paid in clinic to the serum Lp-PLA2 level of T2DM patients, and thorough evaluation regarding the risk of MS in such patients is also required, thus preventing MS by virtue of reasonable intervention measures.

Declaration of Interest:
The authors declare that they have no conflict of interest.

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