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ORIGINAL ARTICLE

Association between serum lipoprotein-associated phospholipase A2, ischemic modified albumin and acute coronary syndrome: a cross-sectional study

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Abstract

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a newly emerging biomarker with strong pro-inflammatory effects, and is an independent risk predictor of atherosclerotic plaque rupture and thrombosis. In addition, ischemic modified albumin (IMA) is another important marker for the evaluation of myocardial ischemia, and has been approved by the U.S. Food and Drug Administration. The objective of this study was to investigate serum Lp-PLA2 and IMA in the early diagnosis, progression and prognosis of acute coronary syndrome (ACS). Serum Lp-PLA2 and IMA were detected using an AU5800 automatic biochemical analyzer in samples from 180 patients with ACS [$n=60$ with unstable angina pectoris (UA), $n=56$ with non-ST segment elevation myocardial infarction (NSTEMI), and $n=64$ with ST segment elevation myocardial infarction (STEMI)] and 60 healthy control subjects. The relationship between Lp-PLA2 and IMA with Gensini score and the number of coronary artery lesions was explored, and logistic regression was conducted to identify risk factors for major adverse cardiovascular events (MACE). Serum Lp-PLA2 and IMA were significantly higher in all ACS subgroups compared to the control group ($P<0.05$), were positively associated with the severity of ACS based on the Gensini score ($P<0.05$), and were significantly higher in patients with double- and triple-vessel lesions compared to those with single-vessel lesions and healthy controls ($P<0.05$). Logistic regression identified Lp-PLA2, IMA, and troponin I levels as independent risk factors for MACE. Lp-PLA2 and IMA were predictive of the degree of myocardial ischemia in patients with ACS, and may provide important clinical significance for the early diagnosis of ACS and the choice of treatment strategy.

Keywords Acute coronary syndrome · Lipoprotein-associated phospholipase A2 · Ischemia-modified albumin · Gensini score · Major adverse cardiovascular events

Abbreviations

ACS	Acute coronary syndrome
CI	Confidence interval
HDL-C	High-density lipoprotein cholesterol
IMA	Ischemic modified albumin
LDL-C	Low-density lipoprotein cholesterol
Lp-PLA2	Lipoprotein-associated phospholipase A2
MACE	Major adverse cardiovascular events
NSTEMI	Non-ST segment elevation myocardial infarction
OR	Odds ratio
PCI	Percutaneous coronary intervention
STEMI	ST segment elevation myocardial infarction
TC	Total cholesterol
TG	Triglycerides
TnI	Troponin I
UA	Unstable angina pectoris

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Introduction

Acute coronary syndrome (ACS) refers to clinical symptoms that are compatible with acute cardiac ischaemia, with a spectrum ranging from unstable angina (UA) to a non-ST segment elevation myocardial infarction (NSTEMI) to ST segment elevation myocardial infarction (STEMI) [1, 2]. Due to the high incidence of ACS and high rate of in-hospital mortality, early risk stratification has important clinical value for prognosis and treatment strategies [3]. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a newly emerging biomarker with strong pro-inflammatory effects, and is an independent risk factor of coronary heart disease and ischemic stroke [4, 5]. Some studies have shown that Lp-PLA2 is closely related to the risk of coronary heart disease and major adverse cardiovascular events (MACE) [6, 7]. Ischemic modified albumin (IMA) is another important marker for the evaluation of myocardial ischemia, and has been approved by the U.S. Food and Drug Administration. IMA has potential clinical value in the early diagnosis, risk stratification, and prognosis of ACS [8, 9]. Lp-PLA2 and IMA have become research hotspots in the cardiovascular field [10–12]. Therefore, this study measured the levels of Lp-PLA2 and IMA in the serum of patients with ACS to explore its potential value in the early development, progression, and prognosis of ACS.

Materials and methods

Study subjects

A total of 180 consecutive subjects (120 males, 64.59 ± 12.42 years old) who underwent coronary angiography for ACS and were treated with primary or selective percutaneous coronary intervention (PCI) in the emergency and cardiovascular departments of Lianyungang Second People's Hospital from January 2016 to April 2018 were enrolled in the study. The inclusion criteria were diagnosis of ACS according to the American College of Cardiology's diagnostic criteria for ACS (2014 edition) [13]. According to American College of Cardiology/American Heart Association guidelines [14, 15], all patients were divided into three groups, including: (1) 60 patients with UA, presented as the negative results of troponin I (TnI), chest pain at rest or aggravated effort type angina within 1 month with the changes of definite ischemic electrocardiogram or recurrent angina pectoris; (2) 56 patients with NSTEMI, diagnosed as the results of TnI were higher than the 99th percentile of the upper limit of reference interval, accompanied by continuous ischemic chest pain, and the changes of electrocardiogram showed new ST segment depression or T wave flattening and inversion; and (3) 64 patients with STEMI, presented as the results of TnI were higher than the 99th percentile of the upper limit of reference interval, accompanied by the typical changes of electrocardiogram was ST segment arch-back elevation, and/or persistent ischemic chest pain, echocardiographic findings of abnormal segmental wall activity. Patients were also categorized by Gensini score as mild (n = 52, Gensini score ≤ 20), moderate (n = 75, 20 < Gensini score ≤ 40) or severe (n = 53, Gensini score > 40). Patients were also categorized based on the number of coronary lesions: one vessel (n = 58), two vessels (n = 78) or three vessels (n = 44). Over the same period, 60 control subjects with normal coronary artery findings and no changes of electrocardiogram ischemic ST-T. Patients with chest pain who received more than 6 h of treatment; patients with malignant tumors, immune system diseases, or severe organ failure; patients with severe infection or cerebrovascular disease; and patients with combined acute and chronic cardiovascular disease were excluded.

The present study was in accordance with the Helsinki Declaration of Human Rights and it was approved by the Medical Ethics Committee of the Second People's Hospital of Lianyungang. All subjects provided written informed consent.

Coronary angiography and Gensini score evaluation

Coronary angiography and outcome determination were performed in all patients by highly skilled clinicians. The severity of coronary stenosis was quantitatively evaluated using the Gensini scoring system [16], which was calculated according to stenosis severity: 1 point for < 25% stenosis, 2 points for 26–50% stenosis, 4 points for 51–75% stenosis, 8 points for 76–90% stenosis, and 32 points for total occlusion. The score was then multiplied by a weight coefficient reflecting the relative importance of the position of the lesion within the coronary artery system. For example, a weight of 5 was used for the left main coronary artery, 2.5 for the proximal region of the left anterior descending artery and left circumflex coronary artery, 1.5 for the middle region, and 1 for the distal region of the left anterior descending artery and mid-distal region of the left circumflex coronary artery. The Gensini score then was determined as the sum of the lesions and the degree of coronary artery stenosis. Patients were evaluated after PCI to determine their prognosis and evaluate MACE, including refractory angina, recurrent acute myocardial infarction, revascularization, and all-cause death.

Instruments and reagents

Serum Lp-PLA2 and IMA levels as well as serum urea, creatinine, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were determined using commercially available assay kits (Lp-PLA2 lot: Z170501, IMA lot: Z170601, Chongqing Zhongyuan Co., Ltd, China, urea lot: AUZ4979, creatinine lot: AUZ4025, TC lot: AUZ3958, TG lot: AUZ4776, HDL-C lot: AUZ5523, LDL-C lot: AUZ5522, Beckman Co., Ltd., USA) and an AU5821 automatic biochemical analyzer (Beckman Co., Ltd., USA). Troponin I (TnI) was measured using a commercially available assay kit (TnI lot: 1006063510, Merrie Co., Ltd., France) and a VIDAS30 automatic immunofluorescence analyzer (Merrie Co., Ltd., France). All instruments were effectively maintained and calibrated, and were met the testing requirements.

Specimen collection

A total of 5 mL of venous blood (including a separation hose) for the detection of serum TnI, Lp-PLA2, and IMA was collected in patients immediately. On day 2, an additional 5 ml of fasting venous blood was collected for the detection of urea, Crea, TC, TG, HDL-C, and LDL-C.

Statistical analyses

Data were analyzed using IBM SPSS Statistics 19.0 (Armonk, NY, USA). Data were checked for normality, and data that were normally distributed were expressed using the mean ± standard deviation. One-way analysis of variance was used to compare across multiple groups, and the least significant difference test was used for pairwise comparisons. Count data were analyzed using the χ^2 test, and independent correlation factors were analyzed using binary logistic regression analysis. A P value < 0.05 was considered statistically significant.

Results

Characteristics of patients with ACS and healthy controls

The essential characteristics of the patients with ACS and the healthy control group are presented in Table 1. There were no significant differences in sex, age, body mass index, systolic blood pressure, diastolic blood pressure, urea, Crea, TC, TG, HDL-C or LDL-C across the groups ($P > 0.05$). The proportion of individuals who smoke was significantly higher among patients with ACS compared to the control group ($P < 0.05$). In subgroups of ACS, the

Table 1 Characteristics of patients with ACS and healthy controls

Parameter	Control group ($n = 60$)	UA group ($n = 60$)	NSTEMI group ($n = 56$)	STEMI group ($n = 64$)	F/χ^2 value	P value
Gender (male/female)	32/28	39/21	37/19	44/20	3.65	0.30
Age (years)	59.68 ± 14.91	63.80 ± 13.28	65.13 ± 12.07	64.88 ± 12.04	2.21	0.09
History of smoking (Y/N)	22/38	25/35[a]	30/26[a]	39/25[a]	9.03	< 0.05
BMI (kg/m^2)	23.75 ± 1.72	24.05 ± 1.98	24.09 ± 1.87	23.53 ± 1.94	1.21	0.31
SBP (mm Hg)	125.40 ± 7.58	127.20 ± 8.07	126.30 ± 7.54	129.00 ± 8.28	2.43	0.07
DBP (mm Hg)	79.57 ± 4.73	80.87 ± 4.55	81.77 ± 4.64	81.45 ± 5.96	2.22	0.09
Gensini score	–	17.94 ± 9.67	28.48 ± 9.47[b]	38.43 ± 10.79[bc]	64.64	< 0.05
Single-vessel coronary lesions (Y/N)	–	45/15	9/47	4/60	76.73	< 0.05
Double-vessel coronary lesions (Y/N)	–	11/49	43/13	24/40	41.68	< 0.05
Triple-vessel coronary lesions (Y/N)	–	4/56	4/52	36/28	54.40	< 0.05
Urea (mmol/L)	5.23 ± 1.10	5.60 ± 1.31	5.41 ± 1.39	5.77 ± 1.31	2.05	0.11
Creatinine (μmol/L)	72.88 ± 7.47	74.82 ± 8.15	78.236 ± 17.42	77.36 ± 13.00	2.40	0.07
TC (mmol/L)	4.46 ± 0.62	4.57 ± 0.67	4.65 ± 1.03	4.90 ± 1.25	2.51	0.06
TG (mmol/L)	1.12 ± 0.36	1.27 ± 0.62	1.36 ± 0.67	1.39 ± 0.80	2.17	0.10
HDL-C (mmol/L)	1.24 ± 0.25	1.21 ± 0.28	1.14 ± 0.32	1.13 ± 0.29	2.21	0.09
LDL-C (mmol/L)	2.56 ± 0.54	2.77 ± 0.53	2.76 ± 0.67	2.82 ± 0.58	2.46	0.06
TnI (ng/mL)	0.01 ± 0.01	0.02 ± 0.01	4.27 ± 0.82[ab]	7.22 ± 1.34[abc]	19.48	< 0.05

All data are reported as the mean ± standard deviation

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TnI* troponin I, *UA* unstable angina pectoris, *NSTEMI* non-ST elevation myocardial infarction, *STEMI* ST elevation myocardial infarction

[a]Compared with control group, $P < 0.05$

[b]Compared with UA group, $P < 0.05$

[c]Compared with NSTEMI group, $P < 0.05$

incidence of coronary artery lesions was statistically different. With the severity of ACS, the number of coronary artery lesions increased significantly. Gensini score and serum TnI levels were significantly different across ACS subgroups: STEMI > NSTEMI > UA ($P < 0.05$).

Comparison of Lp-PLA2 and IMA levels

Serum Lp-PLA2 levels were significantly different across the groups ($P < 0.05$). Serum Lp-PLA2 levels were significantly higher in patients with ACS compared to the control group. Pairwise comparisons indicated that serum levels of Lp-PLA2 were significantly higher in the STEMI group compared to the UA and NSTEMI groups ($P < 0.05$), but were not significantly different between the UA and NSTEMI groups ($P > 0.05$). Serum IMA levels were significantly different across the groups ($P < 0.05$); levels increased with the severity of the lesion (STEMI > NSTEMI > UA) (Table 2).

Relationship between Lp-PLA2, IMA, and Gensini score

Patients with ACS were divided into mild, moderate, and severe groups according to the Gensini score. Serum Lp-PLA2 levels were significantly different ($P < 0.05$) across these three groups. In particular, serum Lp-PLA2 levels were significantly higher in the severe group compared to the mild and moderate groups; no significant difference was observed between the mild and moderate groups ($P > 0.05$). Similarly, serum IMA levels were significantly different ($P < 0.05$) across the three groups. In particular, serum IMA levels increased as the Gensini score increased (Table 3).

Relationship between Lp-PLA2, IMA, and the number of coronary lesions

Patients were divided into three groups based on the number of coronary lesions: one vessel, two vessels, or three vessels. Serum Lp-PLA2 and IMA levels were significantly different between subgroups of patients with ACS ($P < 0.05$), and increased with the number of coronary lesions. There was no significant difference in Lp-PLA2 and IMA levels between patients with one vessel lesion and the control group ($P > 0.05$) (Table 4).

Logistic regression analysis of risk factors for MACE during hospitalization

MACE were observed in 39 patients with ACS after PCI: 22 cases had refractory angina, 6 had recurrent acute myocardial infarction, 8 required revascularization and 3 died (all-cause death). Logistic regression analysis of MACE risk factors during hospitalization was performed using Lp-PLA2, IMA, TnI, TC, TG, HDL-C, and LDL-C as independent

Table 2 Comparison of Lp-PLA2 and IMA levels in each group

Parameter	Control group ($n = 60$)	UA group ($n = 60$)	NSTEMI group ($n = 56$)	STEMI group ($n = 64$)	F value	P value
Lp-PLA2 (U/L)	501.40 ± 90.34	569.90 ± 134.50[a]	596.70 ± 117.10[a]	666.00 ± 182.40[abc]	15.40	< 0.05
IMA (U/mL)	70.75 ± 3.14	72.86 ± 3.78[a]	74.60 ± 3.17[ab]	76.56 ± 3.15[abc]	34.28	< 0.05

All data are reported as the mean ± standard deviation

Lp-PLA2 lipoprotein-associated phospholipase A2, *IMA* ischemic modified albumin, *UA* unstable angina pectoris, *NSTEMI* non-ST elevation myocardial infarction, *STEMI* ST elevation myocardial infarction

[a]Compared with control group, $P < 0.05$

[b]Compared with UA group, $P < 0.05$

[c]Compared with NSTEMI group, $P < 0.05$

Table 3 Relationship between Lp-PLA2, IMA, and Gensini score

Parameter	Control group ($n = 60$)	Mild ($n = 52$) (Gensini score ≤ 20)	Moderate ($n = 75$) (20 < Gensini score ≤ 40)	Severe ($n = 53$) (Gensini score > 40)	F value	P value
Lp-PLA2 (U/L)	501.40 ± 90.34	570.20 ± 150.00[a]	584.30 ± 143.90[a]	682.30 ± 148.20[abc]	18.86	< 0.05
IMA (U/mL)	70.75 ± 3.14	72.63 ± 4.08[a]	74.83 ± 2.28[ab]	76.61 ± 3.90[abc]	33.95	< 0.05

All data are reported as the mean ± standard deviation

Lp-PLA2 lipoprotein-associated phospholipase A2, *IMA* ischemic modified albumin

[a]Compared with control group, $P < 0.05$

[b]Compared with mild group, $P < 0.05$

[C]Compared with moderate group, $P < 0.05$

Table 4 Relationship between Lp-PLA2, IMA, and the number of coronary lesions

Parameter	Control group ($n=60$)	Single-vessel group ($n=58$)	Double-vessel group ($n=78$)	Triple-vessel group ($n=44$)	F value	P value
Lp-PLA2 (U/L)	501.40 ± 90.34	538.40 ± 118.50	603.50 ± 73.53[ab]	725.60 ± 221.90[abc]	29.72	< 0.05
IMA (U/mL^)	70.75 ± 3.14	71.25 ± 2.62	74.91 ± 2.40[ab]	78.94 ± 1.72[abc]	111.4	< 0.05

All data are reported as the mean ± standard deviation

Lp-PLA2 lipoprotein-associated phospholipase A2, *IMA* ischemic modified albumin

[a]Compared with control group, $P<0.05$

[b]Compared with single-vessel group, $P<0.05$

[c]Compared with double-vessel group, $P<0.05$

variables and with or without MACE as an independent variable. Lp-PLA2, IMA, and TnI were independent predictors of MACE during hospitalization in patients with ACS. These three indicators also were independent risk factors for short-term prognosis ($P>0.05$) (Table 5).

Discussion

In this study, we investigated the association between serum Lp-PLA2, IMA and ACS. We provided evidence that the levels of serum Lp-PLA2 and IMA were significantly higher in patients with ACS compared to the control group. Our further analyses indicated that the levels of serum Lp-PLA2 and IMA were closely related to Gensini scores in patients with ACS, and gradually increased as the Gensini score increased. Our research also found that serum Lp-PLA2 and IMA levels increased as the number of coronary lesions increased and Lp-PLA2, IMA, TnI levels were identified as independent risk factors for MACE in ACS with important implications for short-term prognosis in patients with ACS. This finding is independent of traditional risk factors of MACE in ACS.

ACS is a complete or incomplete occlusive syndrome caused by the rupture of coronary atherosclerotic plaque, and is a clinically common critical illness. Due to its sudden onset, rapid progress, and high mortality, early diagnosis and prognosis are keys to ACS rescue and treatment [3, 17]. Therefore, new serum biomarkers are urgently needed to assess the early onset of ACS and its progression. Lp-PLA2 is also called platelet-activating factor acetylhydrolase, which is mainly synthesized and secreted by mature macrophages and lymphocytes. Its main function is to hydrolyze oxidized low-density lipoprotein and form oxidized fatty acids and lysophosphatidylcholine. The chemotaxis and activation of monocytes affect the migration, proliferation, and dysfunction of vascular smooth muscle cells, leading to changes in platelet aggregation and coagulation function, and thus promote the development of atherosclerosis [18, 19]. A study by Kocak et al. showed that the level of Lp-PLA2 activity was significantly different in patients with ACS compared to healthy controls ($P<0.05$), and may, therefore, have potential clinical predictive value in the early diagnosis of ACS [20]. Another study by Lu et al. also demonstrated that the levels of serum Lp-PLA2 exhibited predictive values in patients with ACS, and are associated with the severity of coronary artery stenosis [21]. Additionally, Li et al. Also found that serum level of Lp-PLA2 altered considerably during the early phase of ACS and increased Lp-PLA2 independently predicted cardiovascular outcome in patients with ACS after adjustment for

Table 5 Logistic regression analysis of risk factors for MACE during hospitalization

Independent variable	B	SE (b)	Wald χ^2	P value	OR (95% CI)
Lp-PLA2	0.009	0.003	8.614	0.003	1.009 (1.003–1.016)
IMA	0.294	0.092	10.189	0.001	1.342 (1.120–1.607)
TnI	0.134	0.054	6.239	0.012	1.144 (1.029–1.270)
TC	– 0.892	0.622	2.054	0.152	0.410 (0.121–1.388)
TG	– 0.007	0.520	0.000	0.989	0.993 (0.358–2.753)
HDL-C	1.607	1.108	2.105	0.147	4.989 (0.569–43.758)
LDL-C	0.448	0.557	0.648	0.421	1.566 (0.525–4.667)

MACE major adverse cardiovascular events, *Lp-PLA2* lipoprotein-associated phospholipase A2, *IMA* ischemic modified albumin, *OR* odds ratio, *CI* confidence interval, *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TnI* troponin I potential confounders [22]. Consistent with previous studies, our study indicated that serum Lp-PLA2 involved in the occurrence and progress of ACS and had potential to predict the occurrence of ACS. IMA is assumed "N-terminal modifed" albumin which is generated immediately following myocardial ischemia. The causes of the increases in IMA have been shown to be endothelial or extracellular hypoxia, acidosis, and free oxygen radicals. It is the only marker of myocardial ischemia approved by the U.S. Food and Drug Administration [23, 24]. One recent study found that IMA rose rapidly 5–10 min after myocardial ischemia and could be detected in the reversible stage of ACS. It is, therefore, a stable, early, sensitive, and inexpensive biomarker for ACS [25]. Wahab et al. showed that a distinct advantage of measuring IMA in patients presenting to the emergency department with acute chest pain to rule out a final diagnosis of ACS [26]. Several studies also indicated that IMA is a highly sensitive marker and has a high predictive value, which might prove the usefulness of this biomarker for early detection of myocardial ischemia [3, 27]. Their research data showed a possible role of the IMA test in the early triage of patients with chest pain. Additionally, Mehta et al. also reported that serum IMA levels are significantly higher in patients with ACS compared to healthy controls, and have important clinical value in the early diagnosis and risk stratification of ACS [28]. Consistent with above studies, our study indicated that serum IMA was closely related to the occurrence and severity of ACS and might become a novel marker for diagnosis of ACS.

However, the limitations of this study merit consideration. First, the number of subjects was relatively small, and we aim to recruit more subjects for in-depth research in the future. Second, because this was not a prospective study, hence the casuality between Lp-PLA2 levels, IMA levels and the incidence of ACS cannot be implied. In addition, the long-term prognosis of ACS was not evaluated, thus, a well-controlled longitudinal study is needed to determine the causality between Lp-PLA2 levels, IMA levels and the development of ACS. Although there are some limitations, our present study is still important as it provides an important basis for further studies about Lp-PLA2 levels, IMA levels in patients with ACS.

In conclusion, our present study is novel in showing that Lp-PLA2 and IMA were predictive of the degree of myocardial ischemia in patients with ACS, and may provide important clinical significance for the early diagnosis of ACS and the choice of treatment strategy. Hence high-quality, large-scale clinical studies are necessary to confirm the role of Lp-PLA2 and IMA in the presence of ACS.

Author contributions FY and QL conceived and designed the experiments. LZ, YW, and CZ performed the experiments. WZ, WL and LM analyzed the data. FY, LM, and QL wrote or revised the manuscript. All the authors approved the final submitted version of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest with this work.

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