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Original Article

Clinical significance of lipoprotein associated phospholipase A2 and uric acid in patients with acute coronary syndrome

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Abstract: Objective: To investigate clinical significance of lipoprotein associated phospholipase A2 (Lp-PLA2) and uric acid in patients with acute coronary syndrome (ACS). Methods: The present prospective study included a total of 323 patients who were diagnosed with acute coronary syndrome from January 2014 to December 2015. All patients were divided into 3 groups of clinical diagnosis: the ST-elevation acute myocardial infarction (STEMI) group, the non-ST-elevation acute myocardial infarction (NSTEMI) group and the unstable angina (UA) group. Serum levels of Lp-PLA2, uric acid, C-reactive protein (CRP), NT-pro-B-type natriuretic peptide (BNP) and TnI were measured using commercial available ELISA kits. Kaplan-Meier curve was performed for analysis of cumulative MACE-free survival time. Spearman's analysis was used to determine the correlation between biomarkers. Results: Serum levels of both Lp-PLA2 and uric acid were significantly higher in all groups of ACS patients than those of the healthy control. Lp-PLA2 was dramatically higher in STEMI and NSTEMI groups than the UA group, and was the highest in STEMI patients. There was significant correlation between Lp-PLA2 and CRP, Lp-PLA2 and NT-proBNP, Lp-PLA2 and uric acid, as well as uric acid and NT-proBNP. In high Lp-PLA2 and uric acid groups, the MACE-free survival time was significantly shorter than that in low Lp-PLA2 and uric acid groups. Lp-PLA2 and uric were both risk factors for 1-year mortality of ACS patients. Conclusion: Both Lp-PLA2 and uric acid were risk factors for one-year mortality and MACE of ACS patients, Lp-PLA2 was correlated with uric acid, CRP and NT-proBNP, and statistical difference was only found for Lp-PLA2 in different patients of STEMI, NSTEMI and UA.

Keywords: Lp-PLA2, uric acid, acute coronary syndrome, ST-elevation acute myocardial infarction, non-ST-elevation acute myocardial infarction, unstable angina

Introduction

Despite development of medical and surgical techniques, as well as biomedical understanding, the cardiovascular diseases remain one of the leading causes for global death [1, 2]. It is reported that cardiovascular diseases accounted for 31% mortality worldwide in 2012, which caused death of 17.5 million people [3, 4]. Among cardiovascular diseases, acute coronary syndromes (ACS), including ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina (UA) remain to be a main threat due to its high morbidity and mortality rates [5, 6]. There are many well-known biomarkers for ACS, such as CK-MB, CRP, TnI, and NT-proBNP [7, 8]. However new biomarkers are still needed to give more accurate clinical diagnosis and deeper understanding for the pathology of ACS [9].

Both lipoprotein associated phospholipase A2 (Lp-PLA2) and uric acid are proven to play important roles in cardiovascular related diseases such as heart transplantation [10], atherosclerosis [11], diabetes [12] and hypertension [13]. It was considered that gene polymorphism of Lp-PLA2 was associated with acute myocardial infarction (AMI) patients [14]. Studies also showed that uric acid level was a cardiovascular risk factor in patients with

recent myocardial infarction [15] and was associated with mortality and heart failure hospitalizations in patients with complicated myocardial infarction [16]. Despite these researches, few studies focused on difference of Lp-PLA2 and uric acid in different kinds of ACS, like STEMI, NSTEMI and UA. In the present study, we aimed to conduct a prospective study to investigate clinical significance of Lp-PLA2 and uric acid in ACS patients. This study might give more clinical evidences for the role of Lp-PLA2 and uric acid in ACS patients.

Methods and materials

Patients

The present prospective study included a total of 323 patients who were diagnosed with acute coronary syndrome from January 2014 to December 2015. The patients were divided into 3 groups: 1) the ST-elevation acute myocardial infarction (STEMI) group, n = 152; 2) the non-ST-elevation acute myocardial infarction (NSTEMI) group, n = 82; 3) the unstable angina (UA) group, n = 89. All patients were sent to hospital within 48 h after morbidity. STEMI was defined as > 20 min idiopathic chest pain and typical ST segment elevation > 1 mm in at least two contiguous leads, as well as transient rise of creatine kinase MB (CK-MB) or troponin I (TnI); NSTEMI was defined as chest pain within 48 hours, associated with typical increase of the CK-MB or TnI and an electrocardiographic ST-segment depression or T-wave inversion, or transient (< 20 minutes) ST elevations; UA was defined as angina at rest or crescendo angina with a clinical indication of urgent (within 48 h) coronary angiography [17, 18]. Patients with malignant diseases, chronic informatory diseases and end-stage renal or pulmonary diseases, as well as patients who used uric acid resistant drugs or drugs that affect uric acid metabolism within 2 months before the study were excluded. Patients were excluded due to a lack of clinical data as well. Besides, 50 healthy individuals were recruited as healthy control. Informed consent was obtained from all patients. The present study was approved by ethic committee of the Shandong Provincial Hospital.

Measurement of serum Lp-PLA2 and uric acid and other biomarkers

The blood samples of all patients were collected within 24 h after admission. Serum levels of Lp-PLA2, uric acid, C-reactive protein (CRP), NT-pro-B-type natriuretic peptide (BNP) and TnI of patients were measured using commercial available ELISA kits (all purchased from Abcam, Cambridge, MA, USA) according to the manufacturer's protocols.

Data collection and follow-up

Baseline patient characteristics including age, gender, body mass index (BMI), medical history (hypertension and diabetes), left ventricular ejection fraction (LVEF) and Gensini scores were recorded. Major adverse cardiovascular events (MACE) were defined as cardiovascular death, heart failure, recurrence of angina or malignant arrhythmia, rehospitalization or percutaneous intervention [19]. For survival analysis, all course mortality was recorded from the admission. The follow-up lasted for 1 year from admission or until death.

Statistical analysis

Continuous variables were expressed by mean ± SD when normally distributed, and median (range) if otherwise. Chi square test was used to compare the counting materials and rates. Comparison between two groups of continuous data was performed using the Student *t*-test or Mann-Whitney U test. Comparison for three or more groups was conducted by one-way analysis of variance (ANOVA) followed by Tukey post hoc test. Kaplan-Meier curve was performed for analysis of cumulative MACE-free survival time and 1-year survival. Spearman's analysis was used to determine the correlation between biomarkers. Relationship between serum levels of Lp-PLA2 and uric acid and 1-year mortality of patients was analyzed using logistic regression model by a stepwise method. A *P*-value less than 0.05 was considered to be statistically significant. All calculations were made using SPSS 18.0.

Results

Patient characteristics

The present study included a total of 323 patients, mean age 61.4 ± 10.7, male:female 177:146. As shown in **Table 1**, no significant difference was found in age, gender, weight, and medical history among 3 different groups. However, LVEF (%) in UA group was significant higher than the STEMI and NSTEMI groups (P < 0.001). Meanwhile, levels of GRACE score,

Table 1. Basic clinical information for all ACS patients

Variables	STEMI, n = 152	NSTEMI, n = 82	UA, n = 89	P*
Age, year	62.1 ± 10.7	60.8 ± 10.0	60.8 ± 11.5	0.545
Male:female	82:70	46:36	49:40	0.952
BMI (kg/m^2)	23.6 ± 3.7	24.2 ± 3.6	24.0 ± 3.7	0.392
Medical history, n (%)				0.854
Hypertension	20 (13.2)	10 (12.2)	12 (13.5)	
Diabetes	47 (30.9)	19 (23.2)	22 (24.7)	
LVEF, (%)	53.5 ± 3.7	54.8 ± 3.7	59.7 ± 3.9	< 0.001
GRACE score	168.3 ± 22.8	166.2 ± 23.8	148.9 ± 20.9	< 0.001
NT-pro-BNP, ng/L	783 (323~1507)	756 (309~1493)	385 (215~576)	< 0.001
CRP, mg/L	9 (3~16)	8 (3~15)	5 (2~10)	< 0.001

*Comparison among three groups.

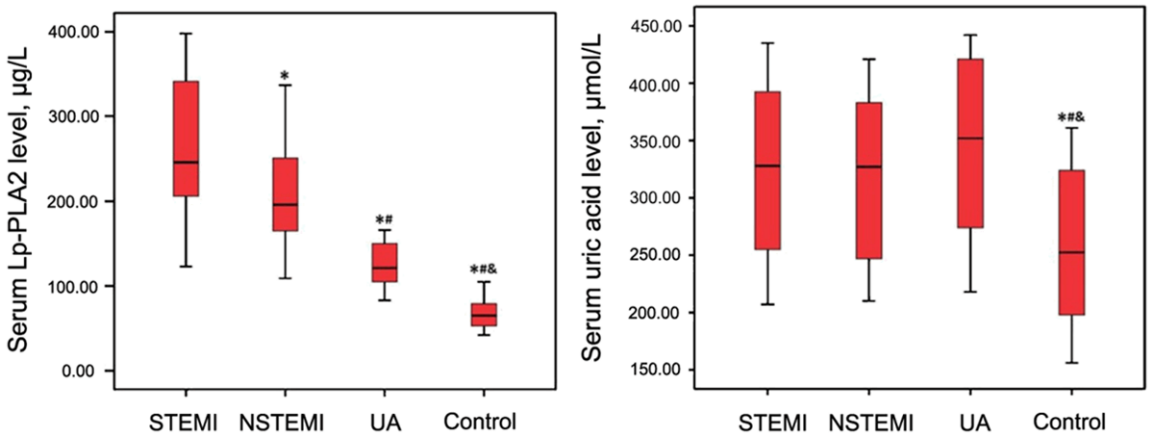

Figure 1. Serum Lp-PLA2 and uric acid among different groups of patients and the healthy control. *P < 0.05 *vs.* STEMI; #P < 0.05 *vs.* NSTEMI; &P < 0.05 *vs.* UA.

NT-pro-BNP, TnI and CRP were all significantly lower in UA patients compared with the two AMI groups (P < 0.001). No significant difference was observed between STEMI and NSTEMI groups.

Comparison of Lp-PLA2 and uric acid among different groups of patients

Then we compared serum levels of Lp-PLA2 and uric acid among different groups of patients and the healthy control. Results showed that, in all groups of ACS patients, serum levels of both Lp-PLA2 and uric acid were significantly higher than those of the healthy control (P < 0.001, **Figure 1**). Meanwhile, serum levels of Lp-PLA2 were dramatically higher in STEMI (mean: 245 μg/L, range: 123-398) and NSTEMI (mean: 197 μg/L, range: 109-337) groups than the UA group (mean: 124 μg/L, range: 83-166) (P < 0.001), and was the highest in STEMI patients (P < 0.001). However, no significant difference was found among the 3 patient groups for serum levels of uric acid. These results indicated both serum levels of Lp-PLA2 and uric acid might be associated with ACS, however only Lp-PLA2 might be associated with the severity of ACS.

Correlation among Lp-PLA2, uric acid and CRP, NT-proBNP

To further investigate the relationship of Lp-PLA2 and uric acid with ACS, we performed Spearman's analysis in all ACS patients to see whether Lp-PLA2 and uric acid were correlated with CRP and NT-proBNP. As shown in **Table 2**, there was significant correlation between Lp-PLA2 and uric acid, Lp-PLA2 and CRP, Lp-PLA2 and NT-proBNP, as well as uric acid

Table 2. Spearman's analysis for correlation among Lp-PLA2, uric acid and CRP, NT-proBNP

	Lp-PLA2	uric acid	CRP	NT-proBNP
Lp-PLA2	-	0.004	0.000	0.000
Uric acid	0.004	-	0.804	0.004
CRP	0.000	0.8046	-	0.000
NT-proBNP	0.000	0.004	0.000	-

and NT-proBNP. However, no significant correlation was found between uric acid and CRP.

One-year MACE and mortality for patients with high or low levels of Lp-PLA2 and uric acid

At last, we divided all patients into high/low Lp-PLA2 and uric acid groups according to the median value of serum Lp-PLA2 or uric acid levels. The K-M curve was used to show the cumulative MACE-free survival time between different groups. Results showed in high Lp-PLA2 and uric acid groups, the MACE-free survival time was significantly shorter than that in low Lp-PLA2 and uric acid groups ($P < 0.001$, **Figure 2**). Further logistic analysis also showed that Lp-PLA2 and uric were associated with 1-year mortality and were both risk factors for 1-year mortality of ACS patients (**Table 3**).

Discussion

Despite existing widely accepted biomarkers such as CK-MB, CRP, TnI, and NT-proBNP, new biomarkers are still needed to give more accurate clinical diagnosis, as well as providing deeper understanding for the pathology of ACS. Both Lp-PLA2 and uric acid were reported to be elevated in ACS patients and were associated with outcomes of ACS. However, few studies focused on difference of Lp-PLA2 and uric acid in different kinds of ACS, like STEMI, NSTEMI and UA. In the present study, we for the first time demonstrated that, in all groups of ACS patients, serum levels of both Lp-PLA2 and uric acid were significantly elevated than the healthy individuals, and both Lp-PLA2 and uric acid were risk factors for one-year mortality and MACE of ACS patients. However, statistical difference was only found for Lp-PLA2 in different patients of STEMI, NSTEMI and UA.

Clinical significance of Lp-PLA2 in ACS has been reported in several researches. Li et al demonstrated that Lp-PLA2 activity was higher in patients with ACS and was strongly and independently associated with major adverse cardiac events [20]. It was also considered that Lp-PLA2 was elevated in STEMI patients than NSTEMI patients [21]. Recently, a Chinese study showed that plasma Lp-PLA2 concentration was independently associated with coronary heart disease in Chinese patients [22]. However, clinical evidences are still lacking for Lp-PLA2 in UA patients compared with STEMI and NSTEMI patients. In the present research, we for the first time further confirmed that Lp-PLA2 was significantly higher in STEMI patients than NSTEMI and UA patients, and Lp-PLA2 was the lowest in UA patients than AMI patients. Meanwhile Lp-PLA2 was correlated with uric acid, CRP and NT-proBNP, and was an independent risk factor for mortality of ACS patients.

The prognostic value of uric acid in ACS patients was recently noticed in some studies. Magnoni et al showed that high uric acid level was associated with in-hospital mortality in ACS patients [23]. It was also found in ACS patients that, patients with high uric acid level had higher mortality rate [24]. Despite these studies, few study focused on difference of uric acid in difference ACS patients and its relationship with other biomarkers. In the present study, we confirmed that uric acid was an independent risk factor for mortality, and uric acid was also correlated with Lp-PLA2 and NT-proBNP, however no significant difference was found for uric acid in different ACS patients, and uric acid was not correlated with CRP.

In conclusion, we conducted a prospective study to investigate clinical significance of Lp-PLA2 and uric acid in ACS patients. Results showed that serum levels of both Lp-PLA2 and uric acid were significantly elevated in ACS patients than the healthy individuals. Both Lp-PLA2 and uric acid were risk factors for one-year MACE and mortality, and Lp-PLA2 was correlated with uric acid, CRP and NT-proBNP. However, statistical difference was only found for Lp-PLA2 in different patients of STEMI, NSTEMI and UA. This study might give more clinical evidences for Lp-PLA2 and uric acid in ACS patients.

Disclosure of conflict of interest

None.

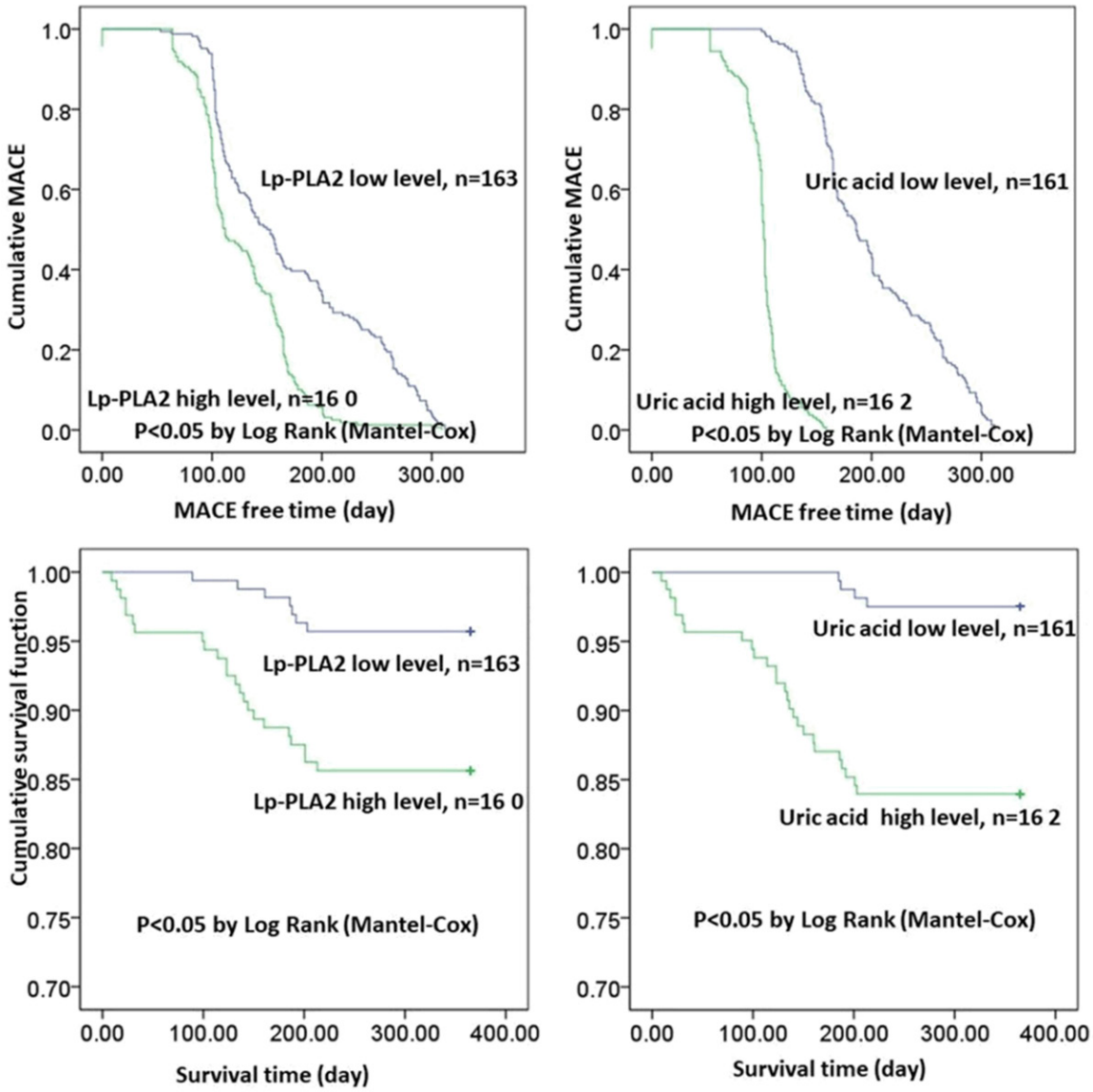

Figure 2. K-M curves for 1-year MACE and mortality of ACS patients with high/low Lp-PLA2 and uric acid.

Table 3. Correlation between Lp-PLA2 and uric acid with 1-year mortality for ACS patients by logistic regression analysis

	Wald	Odds ratio	95% CI	*P* value
Lp-PLA2	8.729	1.008	1.003~1.014	0.003
Uric acid	19.604	1.048	1.026~1.070	< 0.001

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