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Association between Lp-PLA2 and coronary heart disease in Chinese patients

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Abstract

Objective: To evaluate the association between plasma lipoprotein-associated phospholipase A2 (Lp-PLA2; known to release inflammatory mediators that promote atherosclerosis) and coronary heart disease (CHD) in Chinese patients.

Methods: This observational, cross-sectional study included a patient cohort who were assessed by coronary angiography and divided into patients with coronary heart disease and patients with normal coronary angiography (controls). Data for several biochemical indicators were collected. Plasma Lp-PLA2 concentrations were measured by enzyme-linked immunosorbent assay. Univariate and multivariate logistic regression were used to analyse the association between Lp-PLA2 concentration and CHD.

Results: A total of 531 patients were included, comprising 391 with CHD and 140 with normal coronary angiography (controls). Plasma Lp-PLA2 concentration was significantly higher in patients with CHD versus controls (median, 251 μg/l versus 219 μg/l, respectively), and particularly among patients with acute myocardial infarction and stable angina pectoris (249 μg/l and 266 μg/l, respectively). Multivariate analysis showed that Lp-PLA2 $\geq$ 292 μg/l (upper quartile of the whole cohort) was independently associated with CHD (odds ratio 2.814, 95% confidence interval 1.519, 5.214).

Conclusion: Plasma Lp-PLA2 concentration was independently associated with CHD in Chinese patients.

Keywords

Lipoprotein-associated phospholipase A2, coronary heart disease, atherosclerosis

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Introduction

Coronary heart disease (CHD) has a significant impact on human health, with a lifetime risk of 67% in both males and females aged >55 years.[1] In 2008, CHD was responsible for 12.7% of all deaths worldwide.[2]

Atherosclerosis is the pathological basis of CHD,[3,4] and the formation, development, and rupture of an atherosclerotic plaque involves inflammatory factors.[5–8] Epidemiological studies of traditional markers of inflammation confirmed that inflammatory processes are associated with the formation of coronary atherosclerotic plaques and the occurrence of acute cardiovascular events related to CHD.[9–12] Vulnerable plaques display a thin fibrous cap and a sizeable, necrotic, lipid-rich core containing a large amount of inflammatory and thrombotic mediators, while stable plaques display a thick fibrous cap.[13] Plaque remodelling is an ongoing process that involves many factors.[14,15]

Lipoprotein-associated phospholipase A2 (Lp-PLA2), a phospholipase enzyme encoded by the phospholipase A2 group VII (*PLA2G7*) gene, is a mediator of inflammatory reactions.[16] Accumulating evidence suggests a role of Lp-PLA2 in promoting atherosclerosis. Lp-PLA2 was initially recognized for its action in hydrolysing a platelet-activating factor, and was first named platelet-activating factor acetylhydrolase. Secreted by monocytes, macrophages, and T cells, Lp-PLA2 is a member of the phospholipase A2 (PLA2) superfamily and comprises 441 amino acid residues with a relative molecular mass of 45.4 kD.[16] Following secretion, Lp-PLA2 enters the blood circulation and binds to lipoprotein particles, mainly low-density lipoproteins (LDL; approximately 80%) and high-density lipoproteins (HDL).[17] Lp-PLA2 can generate pro-inflammatory molecules such as lyso-phosphatidylcholine and oxidized free fatty acids,[16] and these inflammatory factors promote atherosclerosis through several pathways.[18] High levels of Lp-PLA2 have been associated with an increased risk of atherosclerosis.[19–21]

Although a relationship between the *PLA2G7* gene and CHD has been demonstrated in the Chinese population,[22–24] the relationship between serum Lp-PLA2 levels and CHD remains poorly understood in this population. The aim of the present study was to evaluate the association of Lp-PLA2 with CHD and coronary plaque stability in a Chinese population, in an attempt to provide novel clues regarding atherosclerosis development and eventual future therapeutic approaches.

Patients and methods

Study population

The present retrospective, observational cohort study included consecutively enrolled patients who underwent diagnostic coronary angiography for evaluation of CHD at the No. 2 Department of Cardiology, Tianjin Chest Hospital, Tianjin, China between February 2012 and July 2012. Patients diagnosed with CHD and patients with normal coronary angiography (control group) were included.

Diagnosis of CHD was based on vascular stenosis $\geq 50\%$ in the left main artery, left anterior descending artery, left circumflex artery, and/or right coronary artery. The following clinical indicators of CHD were considered: (1) ischemic symptoms; (2) new ischemic electrocardiogram (ECG) changes (new ST-T wave changes or new left bundle branch block); (3) ECG pathological Q waves; (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; and (5) coronary angiography or autopsy confirmation of thrombus in the coronary artery.[25]

For subgroup analyses, patients with CHD were further divided into those with

stable angina pectoris (defined as angina during effort without evidence of recent worsening, or angina at rest in the preceding 3 months), unstable angina pectoris (defined as the presence of angina at rest that occurred during the preceding 48 hours with significant transient ischemic ST-segment and/or T-wave changes without a significant increase in serum creatine kinase level [Braunwald's class III-B]), or acute myocardial infarction (defined as the presence of >30 min continuous chest pain, ST-segment elevation >2.0 mm on ≥ 2 contiguous electrocardiographic leads, and serum creatine kinase level >150 IU/dl).

Diabetes was diagnosed according to diagnostic criteria of the China Guideline for Type 2 Diabetes (2010 edition):[26] (1) patients with diabetes symptoms (including typical symptoms such as polydipsia, polyuria, and unexplained weight loss) and (a) random blood glucose (without considering the last meal time, any time-of-day) blood glucose >11.1 mmol/, or (b) fasting blood glucose (fasting state at least 8 h without calorie consumption) >7 mmol/l, or (c) glucose 2 h following glucose load test >11.1 mmol/l; and (2) in patients without symptoms of diabetes, a repeated examination to obtain a clear diagnosis.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or the use of anti-hypertensive drugs.

Patients meeting any of the following criteria were excluded: (1) primary myocardiopathy, endocarditis, or severe valvular heart disease; (2) coronary arteritis or diseases that may cause non-atherosclerotic coronary artery stenosis; (3) any autoimmune disease; (4) acute or chronic infectious disease within 2 weeks prior to study participation; (5) severe liver or renal insufficiency such as aminotransferase levels greater than twice the upper limit of normal, or creatinine clearance < 50 ml/min; or (6) malignant tumour.

The study was approved by the ethics committee of Tianjin Chest Hospital, and written informed consent was obtained from all patients.

Evaluation of coronary angiography and coronary stenosis

Coronary angiography was performed within 24 h of symptom onset using a LAUNCHER® coronary catheter (Medtronic, Minneapolis, MN, USA) and the standard Judkins technique.[27] All patients were routinely injected with 2 000 U of sodium heparin using a standard transradial or femoral artery approach. The visual method was used with an angiography catheter as a reference (6 F angiography catheter, 1 F = 0.33 cm) to estimate the reference vessel diameter and pathological segment diameter stenosis at the following positions: left anterior oblique, 30°; left anterior oblique 30° + head position, 30°; left anterior oblique, 45° + foot position, 45°; front right oblique, 30° + head position, 30°; right anterior oblique, 30° + foot position, 30°; and other body positions.

Data collection and blood biochemistry

Data regarding smoking, alcohol consumption, hypertension, and diabetes were collected from all patients. Height, weight, and body mass index (BMI) were measured. Venous blood (10 ml) was collected prior to coronary angiography. Blood samples were allowed to stand at room temperature for 30 min to allow clotting, then serum was immediately collected and analysed for the following parameters: serum total bilirubin, total cholesterol, triglycerides, LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), lipoprotein(a), apolipoprotein A1, apolipoprotein B, C-reactive protein (CRP), and fibrinogen were determined. Biochemistry analyses were performed using a

MODULAR P-800 autoanalyser and associated reagents (Roche Diagnostics, Basel, Switzerland) according to the manufacturer's instructions.

Lp-PLA2 measurement

Prior to coronary angiography (and within 24 h of symptom onset), a 2-ml venous blood sample was drawn from each patient into a tube containing 1.8 mg/ml ethylenediaminetetra-acetic acid, and stored at 4°C. Within 24 h of collection, blood samples were centrifuged at 15 000 *g* for 10 min at 4°C, then plasma was collected and stored at –80°C. Plasma Lp-PLA2 concentration was measured using an enzyme-linked immunosorbent assay (ELISA) kit (Tianjin Kangerke Bioscience, Tianjin, China) according to the manufacturer's instructions. ELISA results were measured using an iMark™ Microplate Absorbance Reader (Bio-Rad, CA, USA).

Statistical analyses

Kolmogorov–Smirnov test was used to analyse data normality. Continuous variables are presented as mean ± SD or median (interquartile range), as appropriate. Independent Student's *t*-tests were used to compare between-group means, and three or more groups were compared using one-way analysis of variance with Bonferroni adjustment for multiple comparisons. Categorical variables are presented as *n* (%) prevalence and between-group differences were analysed using χ^2-test. Univariate and multivariate logistic regression analyses were performed to determine the factors independently associated with the presence of CHD. All analyses were performed using SPSS software, version 19.0 (IBM, Armonk, NY, USA). Two-sided *P* values < 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 531 patients were included (Table 1): 391 with CHD (median age, 62 years) and 140 with normal coronary angiography results (controls; median age, 59 years). Compared with controls, patients with CHD were older, showed a higher prevalence of male patients, diabetes, hypertension, and smoking (all $P < 0.01$), showed higher levels of triglycerides, fibrinogen, and CRP (all $P < 0.01$), and showed lower HDL-C levels ($P = 0.002$).

Plasma Lp-PLA2 levels were significantly higher in patients with CHD than in controls (median 250.6 versus 219.2 μg/l, respectively; $P = 0.001$). Among patients with CHD, subgroup analyses of patients with stable angina pectoris, unstable angina pectoris, or acute myocardial infarction revealed no statistically significant between-group differences in terms of age, sex, smoking, BMI, diabetes, or hypertension. A significantly higher proportion of patients with unstable angina pectoris had hypertension ($P = 0.035$), and patients with unstable angina pectoris had significantly higher total cholesterol and HDL-C levels, versus patients with stable angina pectoris or acute myocardial infarction ($P < 0.05$; Table 2). Patients with acute myocardial infarction had higher CRP levels versus patients with stable angina pectoris ($P < 0.001$; Table 2), and a higher proportion of patients with acute myocardial infarction and unstable angina pectoris were treated with probucol versus patients with stable angina pectoris ($P = 0.001$). In addition, compared with Lp-PLA2 concentrations in the control group (median, 219.2 μg/l), Lp-PLA2 concentrations in patients with acute myocardial infarction or stable angina pectoris were significantly higher (249.5 μg/l and 266.4 μg/l; $P = 0.046$ and $P = 0.008$, respectively; Figure 1).

Table 1. Demographic and clinical characteristics of 531 Chinese patients who underwent coronary angiography and were diagnosed with coronary heart disease (CHD) or had normal coronary angiography (controls)

	Patient group		
Parameter	CHD ($n = 391$)	Control ($n = 140$)	Statistical significance
Age, years	62 (30–83)	59 (31–81)	$P = 0.001$
Sex, male	271 (69.3%)	58 (41.4%)	$P < 0.001$
Diabetes	122 (31.2%)	21 (15.0%)	$P < 0.001$
Hypertension	266 (68.0%)	80 (57.1%)	$P = 0.008$
Smoking	220 (56.3%)	57 (40.7%)	$P < 0.001$
BMI, kg/m^2	25.9 (18.4–48.6)	25.4 (16.9–34.1)	NS
Total cholesterol, mmol/l	4.58 (0.86–8.07)	4.59 (0.92–10.03)	NS
Triglycerides, mmol/l	1.52 (0.48–11.69)	1.25 (0.44–16.31)	$P = 0.001$
HDL-C, mmol/l	1.25 (0.33–3.33)	1.38 (0.79–2.93)	$P = 0.002$
LDL-C, mmol/l	2.55 (0.24–5.34)	2.49 (0.72–4.81)	NS
Lipoprotein(a), g/l	0.20 (0.02–0.92)	0.20 (0.05–0.97)	NS
Fibrinogen, g/l	3.45 (1.63–8.72)	3.28 (0.96–7.68)	$P = 0.003$
CRP, ng/l	0.82 (0–52.07)	0.36 (0.02–11.30)	$P < 0.001$
Lp-PLA2, μg/l	250.6 (8.8–762.9)	219.2 (1.6–620.0)	$P = 0.001$
$\geq$292 μg/l[a]	127 (32.5%)	30 (21.4%)	$P = 0.015$
Probucol treatment	49 (12.5%)		

Data presented as median (range) or *n* (%) prevalence.

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A2.

[a]292 μg/l represents the upper quartile of Lp-PLA2 concentration in all patients.

NS, no statistically significant between-group difference ($P > 0.05$; Student's independent *t*-test).

Lp-PLA2 concentration is independently associated with CHD

Risk factors for CHD were first assessed by univariate analyses of variables (Table 3). Variables with P values < 0.15 were then included in a multivariate regression model (Table 4). Among the cohort of 391 patients with CHD, following adjustment for age and sex, multiple regression analysis showed that age (odds ratio (OR) 1.06, 95% confidence interval (CI) 1.03, 1.09; $P < 0.001$), male sex (OR 4.98, 95% CI 2.76, 9.01; $P < 0.001$), diabetes (OR 3.59; 95% CI 1.89, 6.84; $P < 0.001$), CRP levels (OR 1.22, 95% CI 1.05, 1.43; $P = 0.012$), and Lp-PLA2 concentration ≥ 292 μg/l (upper quartile of the whole cohort; OR 2.81; 95% CI 1.52, 5.21; $P = 0.001$) were independently associated with CHD (Table 4).

Discussion

In the present study, the association between CHD and Lp-PLA2, a novel inflammatory biomarker associated with atherosclerosis, was investigated. Lp-PLA2 concentration was found to be higher in patients with CHD versus control patients with normal coronary angiography. Multivariate analyses showed that Lp-PLA2 concentration was independently associated with CHD in the present population of Chinese patients undergoing coronary angiography.

The Lp-PLA2 phospholipase enzyme is an inflammatory marker associated with

Table 2. Demographic and clinical characteristics of Chinese patients who underwent coronary angiography and were diagnosed with coronary heart disease, subdivided into patients with stable angina pectoris, unstable angina pectoris, or acute myocardial infarction

Parameter	Patient subgroup			Statistical significance
	Stable angina pectoris ($n = 65$)	Unstable angina pectoris ($n = 254$)	Acute myocardial infarction ($n = 72$)	
Age, years	64 (42–82)	62 (33–83)	59 (30–83)	NS
Sex, male	40 (61.5)	171 (67.3)	53 (73.6)	NS
Diabetes	21 (32.3)	77 (30.3)	23 (31.9)	NS
Hypertension	36 (55.4)	180 (70.9)	44 (61.1)	$P = 0.035$[b]
Smoking	32 (49.2)	138 (54.3)	47 (65.3)	NS
BMI, kg/m^2	27.2 (20.6–33.2)	25.8 (18.4–33.5)	26.0 (19.0–48.6)	NS
Total cholesterol, mmol/l	4.27 (1.94–7.33)	4.69 (1.92–8.07)	4.43 (0.86–7.04)	$P = 0.030$[b]
Triglycerides, mmol/l	1.36 (0.52–0.41)	1.565 (0.48–11.69)	1.55 (0.74–9.68)	NS
HDL-C, mmol/l	1.13 (0.52–2.09)	1.31 (0.33–3.33)	1.13 (0.66–2.34)	$P < 0.001$[b]
LDL-C, mmol/l	2.38 (0.75–4.07)	2.55 (0.60–5.34)	2.66 (0.24–4.53)	NS
Lipoprotein(a), g/l	0.20 (0.05–0.74)	0.2 (0.03–0.92)	0.23 (0.02–0.79)	NS
Fibrinogen, g/l	3.39 (2.44–4.97)	3.46 (1.63–8.72)	3.48 (2.18–7.51)	NS
CRP, ng/l	0.4 (0.1–9.5)	0.66 (0–26.5)	1.6 (0.1–52.07)	$P < 0.001$[c]
Lp-PLA2, μg/l	266.44 (46.43–476.83)	250.58 (8.75–762.94)	249.46 (8.75–502.28)	NS
$\geq$ 292 μg/l[a]	23 (35.4)	82 (32.3)	18 (25.0)	NS
Probucol treatment	2 (3.1)	30 (11.8)	17 (23.6)	$P = 0.001$[d]

Data presented as median (range) or *n* (%) prevalence.

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A2.

[a]292 μg/l represents the upper quartile of Lp-PLA2 concentration in all patients.

[b]Patients with unstable angina pectoris versus other groups; [c]patients with acute myocardial infarction versus other groups;[d]patients with unstable angina pectoris or acute myocardial infarction versus stable angina pectoris.

NS, no statistically significant between-group difference ($P > 0.05$; Student's independent *t*-test, one-way analysis of variance or χ^2-test, as appropriate).

atherosclerosis, and is mainly produced by inflammatory cells.[20,28–30] Lp-PLA2 concentration had been shown to alter considerably during the early phase of acute coronary syndrome;[31] plasma Lp-PLA2 concentration decreased gradually in patients with acute coronary syndrome over the first 3 days following hospital admission and then remained stable. Long-term intensive therapy with statins decreases Lp-PLA2 concentration in addition to LDL-C levels, and change in Lp-PLA2 has been correlated with change in LDL-C.[32–34] These studies suggest that Lp-PLA2 plays an active role in the pathogenesis of atherosclerosis and CHD.

Vulnerable plaques are associated with Lp-PLA2, and higher Lp-PLA2 concentration is associated with more severe atherosclerosis, higher cardiovascular risk, and more vulnerable plaques.[35] By measuring activity of Lp-PLA2 and lysophosphatidylcholine in the left main coronary artery and coronary sinus,[36] the role of Lp-PLA2 in local vascular inflammation and early atherosclerosis has been demonstrated; patients with CHD were found to have higher Lp-PLA2 activity and lysophosphatidylcholine levels than controls. Lp-PLA2 is likely to be an inflammatory biomarker in coronary arteries, and probably has an effect on

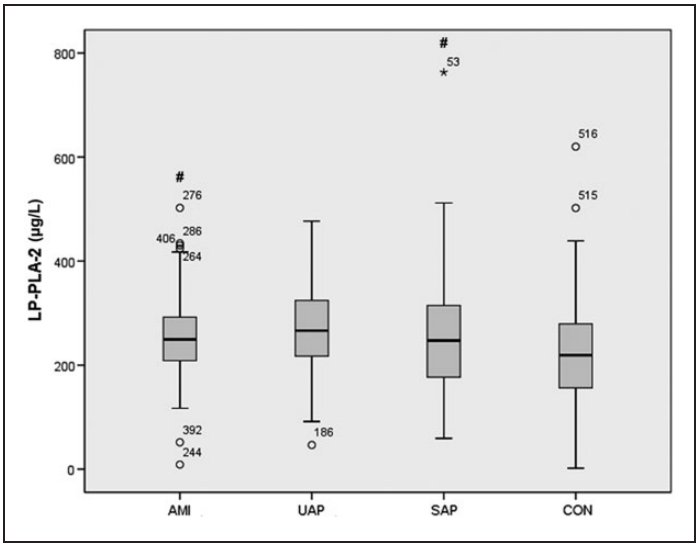

Figure 1. Box-whisker plots showing levels of Lp-PLA2 (μg/l) in Chinese patients who underwent coronary angiography and were diagnosed with coronary heart disease, divided into patients with acute myocardial infarction (AMI; $n = 72$), unstable angina pectoris (UAP; $n = 254$) or stable angina pectoris (SAP; $n = 65$), compared with a control group of patients with normal coronary angiography (CON; $n = 140$). #$P < 0.05$ versus controls. Central black horizontal line within the box, median; box extremities, upper and lower-quartiles; error bars, 1.5 times the interquartile range; ○, mild outlier; and *, extreme outlier

atherosclerotic plaques and thus the development of CHD.

Activity of Lp-PLA2 has been associated with Framingham score.[37] In addition to its role in inflammation, Lp-PLA2 might be directly or indirectly involved in plaque remodelling,[33] but the exact role of Lp-PLA2 remains controversial. Specifically, two studies have indicated that Lp-PLA2 could be cardioprotective because it hydrolyses platelet-activating factor and oxidized phospholipids on LDL particles.[38,39] In addition, a recent phase III trial using an Lp-PLA2 inhibitor reported no benefit in patients in terms of secondary prevention.[40] A Japanese study showed that Lp-PLA2 activity was associated with carotid plaques, but a Mendelian randomization analysis suggested that Lp-PLA2 was not a causative factor for atherosclerosis.[41] In the present study, and in accordance with other published studies,[32–34,41,42] Lp-PLA2 concentration was independently associated with CHD.

The present study results may be limited by the following factors. The sample size was relatively small and all patients were from a single centre. In addition, the cross-sectional study design did not allow for determining a cause-and-effect relationship. The observational nature of the study and a number of uncontrolled factors could have influenced the results. Therapeutic drugs and natural supplements could also have influenced the associations being observed; unfortunately, data regarding patient medication and supplements were unavailable, due to the retrospective nature of the study. Finally, despite presenting with normal coronary angiography, the control patients had a medical condition that prompted the need for coronary angiography, which may have biased the results.

Table 3. Univariate regression analysis of factors associated with coronary heart disease (CHD) in 531 Chinese patients who underwent diagnostic coronary angiography for evaluation of CHD

Characteristic	OR	95% CI	Statistical significance
Age, years	1.031	1.011, 1.052	$P = 0.002$
Sex, female	0.291	0.194, 0.435	$P < 0.001$
Diabetes	2.667	1.599, 4.45	$P < 0.001$
Hypertension	1.721	1.152, 2.571	$P = 0.008$
Smoking	2.029	1.366, 3.013	$P < 0.001$
BMI, kg/m^2	1.045	0.982, 1.111	NS
Total cholesterol, mmol/l	1.026	0.856, 1.229	NS
Triglycerides, mmol/l	1.182	0.967, 1.444	NS
HDL-C, mmol/l	0.419	0.242, 0.726	$P = 0.002$
LDL-C, mmol/l	1.079	0.864, 1.346	NS
Lipoprotein(a), g/l	0.683	0.235, 1.982	NS
Fibrinogen, g/l	1.41	1.096, 1.815	$P = 0.008$
CRP, ng/l	1.236	1.084, 1.409	$P = 0.002$
Lp-PLA2 $\geq$ 292 μg/l[a]	1.752	1.109, 2.766	$P = 0.016$

OR, odds ratio; CI, confidence interval; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A2.
[a]292 μg/l represents the upper quartile of Lp-PLA2 concentration in all patients.
NS, no statistically significant association ($P > 0.05$).

Table 4. Multivariate logistic regression analysis of risk factors for coronary heart disease (CHD) in 531 Chinese patients who underwent diagnostic coronary angiography for evaluation of CHD

	Adjusted			Unadjusted		
Characteristic	OR	95% CI	Statistical significance	OR	95% CI	Statistical significance
Age, years	1.056	1.025, 1.088	$P < 0.001$			
Sex, female	0.201	0.111, 0.362	$P < 0.001$			
Diabetes	3.592	1.887, 6.837	$P < 0.001$	2.889	1.608, 5.191	$P < 0.001$
Hypertension	1.029	0.598, 1.769	NS	1.407	0.861, 2.299	NS
Smoking	1.473	0.834, 2.601	NS	2.271	1.407, 3.667	$P = 0.001$
Triglycerides, mmol/l	1.111	0.897, 1.376	NS	1.031	0.863, 1.233	NS
HDL-C, mmol/l	0.561	0.273, 1.154	NS	0.584	0.304, 1.124	NS
Fibrinogen, g/l	1.396	0.994, 1.962	NS	1.353	0.997, 1.836	NS
CRP, ng/l	1.224	1.046, 1.433	$P = 0.012$	1.248	1.068, 1.458	$P = 0.005$
Lp-PLA2 $\geq$ 292 μg/l[a]	2.814	1.519, 5.214	$P = 0.001$	2.391	1.349, 4.239	$P = 0.003$

OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A2.
[a]292 μg/l represents the upper quartile of Lp-PLA2 concentration in all patients.
NS, no statistically significant association ($P > 0.05$).

In conclusion, Lp-PLA2 concentration was independently associated with CHD in Chinese patients. Additional studies are necessary to validate these results across the spectrum of CHD.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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