

Lipoprotein-Associated Phospholipase A₂ Is Related to Plaque Stability and Is a Potential Biomarker for Acute Coronary Syndrome

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Purpose: Plasma lipoprotein-associated phospholipase A₂ (Lp-PLA₂) binds to low-density lipoprotein. The levels of Lp-PLA₂ reflect the plaque burden, and are upregulated in acute coronary syndrome (ACS). We investigated the diagnostic value of Lp-PLA₂ levels and found that it might be a potential biomarker for ACS. **Materials and Methods:** We classified 226 study participants into three groups: patients without significant stenosis (control group), patients with significant stenosis with stable angina (SA group), and patients with ACS (ACS group). **Results:** Lp-PLA₂ and high-sensitivity C-reactive protein (hs-CRP) levels were significantly greater in the ACS group than in the SA group ($p=0.044$ and $p=0.029$, respectively). Multivariate logistic regression analysis revealed that Lp-PLA₂ levels are significantly associated with ACS (odds ratio=1.047, $p=0.013$). The addition of Lp-PLA₂ to the ACS model significantly increased the global χ^2 value over traditional risk factors (28.14 to 35.602, $p=0.006$). The area under the receiver operating characteristic curve for Lp-PLA₂ was 0.624 ($p=0.004$). The addition of Lp-PLA₂ level to serum hs-CRP concentration yielded an integrated discrimination improvement of 0.0368 ($p=0.0093$, standard error: 0.0142) and improved the ability to diagnose ACS. **Conclusion:** Lp-PLA₂ levels are related to plaque stability and might be a diagnostic biomarker for ACS.

Key Words: Lp-PLA₂, acute coronary syndrome, biomarker, coronary atherosclerotic plaque instability

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INTRODUCTION

Cardiovascular disease is the major cause of death in most industrialized nations. Coronary heart disease (CHD) appears either as a stable disease, progressing slowly over several years, or as an unstable disease, progressing rapidly and resulting in

acute coronary syndrome (ACS), such as myocardial infarction, which may cause sudden death. Progression to ACS seems to depend most on exaggerated inflammatory changes within atherosclerotic plaques.¹⁻³

In recent studies, lipoprotein-associated phospholipase A₂ (Lp-PLA₂) was found to play a crucial role in the incidence of CHD in people whose low-density lipoprotein (LDL) concentrations were not predictive of high CHD risk.⁴ Earlier reports suggested a relation between Lp-PLA₂ and CHD risk;⁴⁻⁷ however, recent studies have shown that Lp-PLA₂ is an independent predictor of CHD.^{5,8} As a biomarker for coronary artery disease (CAD), Lp-PLA₂ levels are notably increased in ACS in particular, because Lp-PLA₂ activity is associated with vulnerable atherosclerotic plaques.⁸ Liu, et al.⁹ demonstrated that Lp-PLA₂ level is associated with vulnerable coronary atherosclerotic plaques and that Lp-PLA₂ could be a strong predictive biomarker for ACS.¹⁰ In addition, recent studies have shown that Lp-PLA₂ levels are elevated in ACS, which suggests that Lp-PLA₂ may be a clinical biomarker for ACS. The clinical diagnostic value of Lp-PLA₂ for ACS; however, has yet to be fully evaluated in comparison with other biomarkers, such as high-sensitivity C-reactive protein (hs-CRP) or lipoprotein concentration. hs-CRP is an accepted biomarker of inflammation and can be used as a potential biomarker of plaque instability; nevertheless, a question of tissue specificity has arisen for hs-CRP. Specifically, it is unclear as to whether hs-CRP is a plaque-specific inflammatory marker or a systemic inflammatory marker. Lp-PLA₂ is specific for vascular inflammation because it is made by macrophages in the plaque, in contrast to other markers of inflammation like CRP, which are made in the liver. Lp-PLA₂ may hold the potential to be a useful, vascular tissue-specific biomarker, if its measurement could be standardized.^{11,12} Therefore, this study was conducted to evaluate the diagnostic value of Lp-PLA₂ as an independent biomarker of ACS by comparing it to hs-CRP, which is widely used as a pro-inflammatory marker for coronary plaques.

MATERIALS AND METHODS

Subjects & clinical analysis

We studied 226 consecutive patients scheduled to undergo coronary angiography at Gangnam Severance Hospital in Seoul, Korea, from 2010 to 2012. Demographic data and clinical history were obtained for each patient through chart

review, with attention to clinical presentation, CAD risk factors, and medication, including lipid-lowering agents. Study participants were classified into three groups on the basis of their clinical presentation: 1) 53 cases with no significant stenotic lesions of the coronary arteries (control group); 2) 57 cases of stable angina (SA group); and 3) 116 cases of ACS including 60 cases of unstable angina (UA) and 56 cases of acute myocardial infarction (AMI) (ACS group). The age range was 36–92 years (mean age 62.69±10.59 years); 139 subjects were male and 87 were female. For all study groups, the exclusion criteria were malignant tumors, inflammatory disorders, severe liver disease (plasma alanine aminotransferase level ≥100 IU/L), renal disease (plasma creatinine ≥2.2 mg/dL), and hypersensitivity to contrast dye.

The study subjects were divided into ACS, SA, and control groups. In this study, the non-ACS group included both the control and SA groups. The control group was composed of patients who did not have significant coronary artery stenosis despite chest pain—likely atypical pattern. SA was defined as no changes in angina symptoms in the preceding 6 weeks, with no biomarkers of necrosis. Patients who underwent follow-up coronary angiography 9–12 months after the previous procedure, due either to residual stenotic lesions or to a history of stenting, were also included in the SA group. In contrast, ACS was characterized by typical chest pain, generally occurring at rest or with minimal exertion. The subtypes of ACS included UA and AMI. We defined UA as the presence of 1) angina at rest, 2) new onset accelerated angina within the past two months, or 3) chronic stable angina in patients who developed accelerated angina but had not experienced angina at rest during the preceding two months (according to the Braunwald classification).¹³ Subjects with elevated cardiac biomarkers [e.g., troponins, creatine kinase (CK), and CK-MB] were categorized as AMI patients, and the remaining patients were regarded as UA patients.^{14,15} In addition, we defined heart failure as the presence of New York Heart Association (NYHA) class II–IV symptoms accompanying cardiomegaly with pulmonary congestion on chest X-ray, decreased left ventricular (LV) systolic function (EF <50%), LV diastolic dysfunction suggestive of increased LV filling pressure, or cardiogenic shock. We defined metabolic syndrome using the National Cholesterol Education Program—Third Adult Treatment Panel (NCEPATP III) criteria. The definition of central obesity was modified to a body mass index ≥25 kg/m² because waist circumference was not measured in most patients. Other criteria included high blood pressure (≥130/85 mm Hg or taking an-

ti/hypertensive medication), hyperglycemia (≥ 110 mg/dL or being on hypoglycemic medication or insulin therapy), hypertriglyceridemia (≥ 150 mg/dL or taking a lipid-lowering agent), and low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL in men, < 50 mg/dL in women or taking a lipid-lowering agent). We classified patients as having metabolic syndrome when they met three or more of these five criteria.

Biochemical tests

For measurement of Lp-PLA₂ concentration in plasma, 5 mL of fasting blood samples were drawn before coronary angiography was performed. The blood samples, collected in EDTA, were centrifuged at $1000\times g$ for 15 minutes at -20°C within 30 minutes of collection, and the separated samples were stored at -80°C . Plasma concentrations of Lp-PLA₂, which was the mass level of Lp-PLA₂, was determined using a commercially available Lp-PLA₂ enzyme-linked immunosorbent assay (ELISA) kit (CUSABIO Biotech, Wuhan, China), an ELISA test with two specific monoclonal antibodies.^{16,17} Each sample was measured twice and the mean of the two values was calculated to minimize error. The interassay coefficient of variation was 16.11%. hs-CRP levels were measured using the latex-enhanced immunoturbidimetric method (Denka Seiken Co., Ltd., Tokyo, Japan) with a detection limit of 0.09 mg/L in serum, using a Hitachi 7600-110 automatic analyzer (Hitachi Co., Tokyo, Japan). Total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels in serum were measured using the standard enzymatic method (Daiichi Sankyo Co., Ltd., Tokyo, Japan for total, LDL and HDL cholesterol; Roche Diagnostics, Indianapolis, IN, USA for triglycerides) with a Hitachi 7600-110 analyzer (Hitachi Co., Tokyo, Japan).

Statistical analyses

Data are presented as a percentage or mean value \pm standard error. Two group comparisons were made using the Student's *t*-test for continuous variables or the χ^2 test for categorical variables. Multiple group comparisons were performed by analysis of variance, followed by Tukey-Kramer post-hoc analysis. To assess the relation between Lp-PLA₂ and serum hs-CRP levels, we conducted bivariate correlation analysis. Univariate and multivariate logistic regression analyses were performed to identify the risk factors for ACS. In addition, univariate and multivariate Cox regression analyses were used to identify diagnostic tools of ACS. To identify the incremental value of Lp-PLA₂ in diagnosis of ACS, three models were designed: 1) Model I: traditional

risk factors, including male gender, age, hypertension, and smoking, which were identified as meaningful diagnostic tools of ACS in our study using multivariate logistic regression analysis; 2) Model II: traditional risk factors+elevated CRP; and 3) Model III: traditional risk factors+elevated CRP+elevated Lp-PLA₂ level. Receiver operating characteristic (ROC) analysis was performed to identify the optimal cut-off values for Lp-PLA₂ level and hs-CRP level for diagnosis of ACS. We also constructed an ROC curve for the combination of hs-CRP and Lp-PLA₂ levels to evaluate whether it showed an improved ability to diagnose ACS. Additionally, we used new statistical analysis methods, calculation of integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices, to increase the discriminative value of the new biomarker, Lp-PLA₂ levels. The NRI index is calculated from the net of differences between the "upward" movement in categories for event subjects and the "downward" movement in those for non-event subjects. The IDI index is the difference in Yates discrimination slopes between the new and old models.^{18,19} Analyses were performed using the statistical software SPSS version 18.0 for Windows (IBM Canada Ltd., Markham, Ontario, Canada) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance was assumed for values of $p < 0.05$.

RESULTS

Baseline characteristics

The baseline characteristics and selected laboratory values of the study patients are presented in Table 1. There were significant differences among the three groups in age, history of hypertension, smoking, metabolic scores, heart failure, statin users (%), and serum HDL cholesterol levels. Mean Lp-PLA₂ mass level was 15.96 ± 10.88 IU/mL.

Association with acute coronary syndrome

The level of Lp-PLA₂ was significantly greater in the ACS group than in the SA group (18.00 ± 12.22 IU/mL vs. 13.75 ± 7.68 IU/mL, $p=0.040$). Lp-PLA₂ level was also higher in the ACS group than in the control group, but this difference was not statistically significant (18.00 ± 12.22 IU/mL vs. 14.21 ± 10.07 IU/mL, $p=0.087$) (Fig. 1A). Within the ACS group, Lp-PLA₂ levels tended to be higher in the AMI group (19.86 ± 14.19 IU/mL in the AMI group vs. 16.27 ± 9.85 IU/mL in the UA group, $p=0.090$) (Fig. 1B). Lp-PLA₂ level was

Table 1. Baseline Characteristics

Characteristics	Control (n=53)	SA (n=57)	ACS (n=116)	p value
Age, yrs	58.04±7.83	63.51±8.48	64.32±11.98	0.001
Male, n (%)	27 (50.9)	32 (56.1)	80 (69.0)	0.052
Hypertension, n (%)	32 (60.4)	47 (82.5)	68 (58.6)	0.006
Diabetes mellitus n (%)	9 (17.0)	18 (31.6)	39 (33.6)	0.079
Dyslipidemia, n (%)	0 (37.7)	32 (56.1)	46 (39.7)	0.077
Tot. cholesterol, mg/dL	178.20±32.18	162.11±38.44	168.40±42.73	0.109
TG, mg/dL	134.35±91.11	137.48±88.30	122.05±90.73	0.534
HDL, mg/dL	48.04±11.32	43.60±13.28	41.49±10.35	0.004
LDL, mg/dL	108.41±32.11	94.84±33.25	100.60±32.02	0.147
Smoking, n (%)	18 (34.0)	25 (43.9)	63 (54.3)	0.042
Metabolic syndrome, n (%)	26 (49.1)	37 (64.9)	72 (62.1)	0.182
Metabolic score	2.44±1.43	3.11±1.31	2.97±1.29	0.044
Heart failure, n (%)	3 (5.7)	5 (8.8)	35 (30.2)	0.000
Statin user, n (%)	16 (30.2)	30 (52.6)	42 (36.2)	0.038
Lp-PLA ₂ , IU/mL	14.21±10.07	13.75±7.68	18.00±12.22	0.020

SA, stable angina; ACS, acute coronary syndrome; Lp-PLA₂, lipoprotein-associated phospholipase A₂.

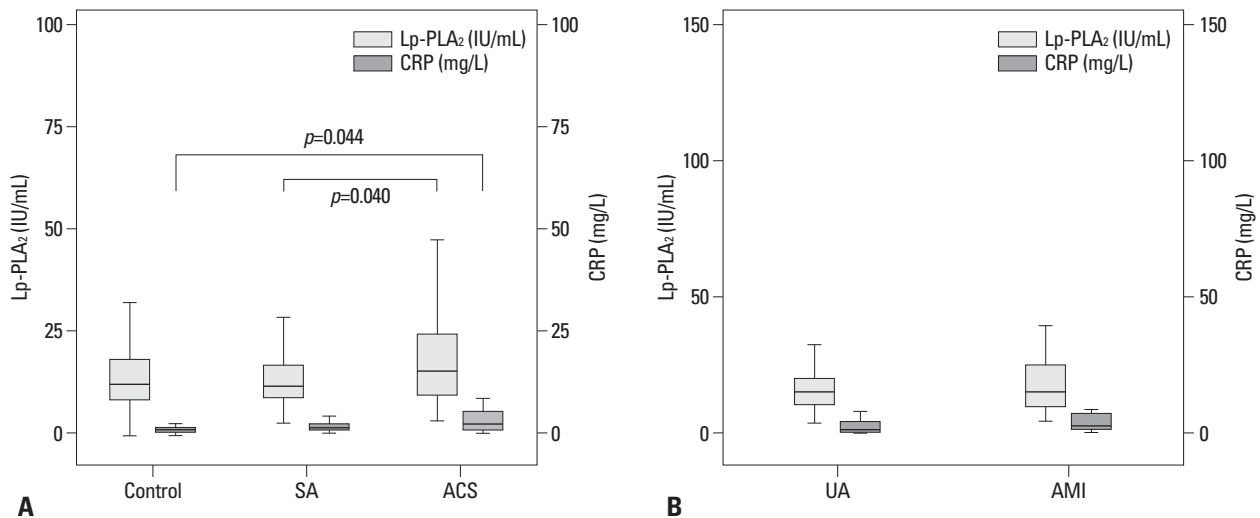


Fig. 1. Lp-PLA₂ and hs-CRP levels in each group. (A) Levels of Lp-PLA₂ and CRP in control, SA, and ACS groups. In Lp-PLA₂, $p=0.040$, compared with SA group. In CRP, $p=0.044$, compared with control group. (B) Levels of Lp-PLA₂ and CRP in ACS group including UA and AMI groups. Lp-PLA₂, lipoprotein-associated phospholipase A₂; SA, stable angina; ACS, acute coronary syndrome; hs-CRP, high-sensitivity C-reactive protein; UA, unstable; AMI, acute myocardial infarction.

insignificantly higher in the UA group than in the SA group (16.27±9.85 IU/mL in the UA group vs. 13.75±7.68 IU/mL in the SA group, $p=0.124$). In addition, serum hs-CRP concentration was significantly higher in the ACS group than in the control group (7.57±18.03 IU/mL vs. 1.86±3.20 IU/mL, $p=0.044$) and higher in the ACS group than in the SA group, but this latter difference was not statistically significant (7.57±18.03 IU/mL vs. 2.73±5.54 IU/mL, $p=0.087$) (Fig. 1A). The relation between Lp-PLA₂ and hs-CRP levels was not statistically significant either within the group of ACS patients ($r=0.056$, $p=0.607$) or within the population of patients as a whole ($r=0.065$, $p=0.387$).

Using univariate logistic regression analysis, male sex,

old age, Lp-PLA₂ level, hs-CRP level, smoking, and heart failure were significantly associated with ACS (Table 2). Multivariate logistic regression analysis showed that old age and Lp-PLA₂ level were significantly associated with ACS. Lp-PLA₂ level was associated with the prevalence of ACS with an odds ratio (OR) of 1.047 [95% confidence interval (CI): 1.010–1.086, $p=0.013$], and this association was statistically significant (Table 2).

To evaluate the incremental value of Lp-PLA₂ as a biomarker for diagnosis of ACS over traditional risk factors and CRP, we measured global χ^2 values. Significant increases in global χ^2 values were observed with elevated hs-CRP level over traditional risk factors (male sex, age, hy-

Table 2. Odds Ratio (OR) as a Biomarker for Diagnosis of ACS Using Univariate Logistic Analysis and Multivariate Logistic Analysis

Variables	Univariate			Multivariate		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Age	1.033	1.007–1.060	0.014	1.050	1.013–1.089	0.008
Male gender	1.897	1.101–3.268	0.021	1.759	0.652–0.746	0.265
Hypertension	0.548	0.314–0.956	0.034	0.519	0.244–1.105	0.089
Diabetes mellitus	1.577	0.882–2.820	0.124			
LDL-cholesterol	0.999	0.991–1.007	0.843			
Lp-PLA ₂	1.039	1.011–1.068	0.007	1.047	1.010–1.086	0.013
CRP	1.080	1.014–1.151	0.017	1.065	0.998–1.135	0.057
Smoking	1.823	1.073–3.097	0.026	1.420	0.569–3.546	0.453
Metabolic syndrome	1.204	0.706–2.051	0.495			
Heart failure	5.578	2.452–12.690	0.000	3.046	1.116–8.311	0.030
Statin nonuser	0.800	0.468–1.369	0.416			

ACS, acute coronary syndrome; CI, confidence interval; CRP, C-reactive protein.

pertension, and smoking) for diagnosis of ACS (Model I vs. Model II: 18.413 vs. 28.14, incremental global χ^2 value: 9.727, $p=0.002$) and with elevated Lp-PLA₂ level over traditional risk factors and elevated hs-CRP level (Model II vs. Model III: 28.14 vs. 35.602, incremental global χ^2 value: 7.462, $p=0.006$) (Fig. 2).

To determine the sensitivity and specificity of Lp-PLA₂ levels for diagnosis of ACS, we performed ROC analysis. The area under the ROC curve (AUC) of Lp-PLA₂ levels for ACS was 0.624 (95% CI: 0.542–0.706, $p=0.004$). ROC analysis showed that the optimal cut-off value for Lp-PLA₂ level was 15.41 IU/mL, and the sensitivity and specificity for diagnosis of ACS were 51.8% and 74%, respectively. We also evaluated the optimal cut-off value of hs-CRP levels: the AUC for ACS was 0.673 (95% CI: 0.594–0.752, $p=0.000$), the optimal cut-off value of hs-CRP was 1.85 IU/mL, and the sensitivity and specificity for diagnosis of ACS were 57.6% and 70.8%, respectively (Fig. 3). As compared with hs-CRP level, combination of Lp-PLA₂ with serum hs-CRP levels tended to increase the AUC (0.695, 95% CI: 0.618–0.772, $p=0.017$) for diagnosis of ACS (Fig. 3). However, when using new statistical analysis methods (NRI and IDI indices), we found that the addition of Lp-PLA₂ level to hs-CRP level improved the ability to diagnose ACS. The addition of Lp-PLA₂ level to hs-CRP level yielded an IDI of 0.0368% ($p=0.0093$, SE: 0.0142) and an NRI of 0.0854% ($p=0.2046$, SE: 0.0673).

Effect of statins (statin users vs. statin non-users)

We analyzed the levels of Lp-PLA₂ according to statin use at the time of coronary angiography. The study patients were treated with atorvastatin, simvastatin, or rosuvastatin. Al-

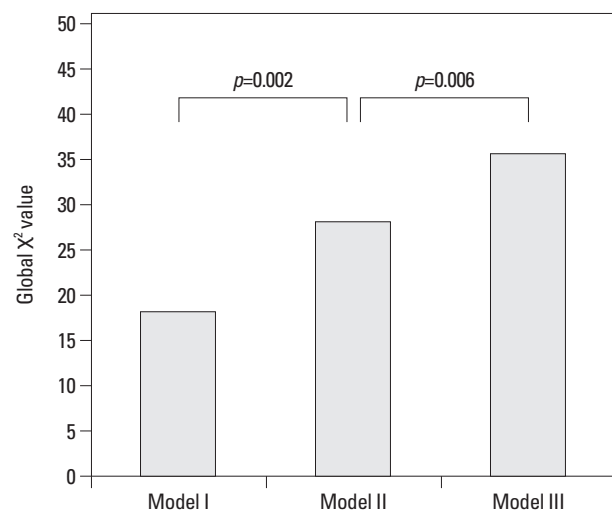


Fig. 2. Bar chart comparing global χ^2 values with three models for diagnosis of ACS. CRP had incremental value over traditional risk factors (Model I vs. Model II: 18.413 vs. 28.14, incremental global χ^2 value: 9.727, $p=0.002$), and Lp-PLA₂ level had incremental value over traditional risk factors and CRP (Model II vs. Model III: 28.14 vs. 35.602, incremental global χ^2 value: 7.462, $p=0.006$). ACS, acute coronary syndrome; CRP, C-reactive protein; Lp-PLA₂, lipoprotein-associated phospholipase A₂.

though the differences were not statistically significant, Lp-PLA₂ levels tended to be lower in statin users than in statin non-users in each group (14.19±12.70 vs. 14.21±8.91, 12.43±6.87 vs. 15.22±8.38, and 15.78±10.22 vs. 19.26±13.12 IU/mL in the control, SA, and ACS groups, respectively) ($p=0.996$, 0.178, 0.116, respectively).

DISCUSSION

The main pathophysiological mechanism of ACS is erosion and rupture of the atherosclerotic plaque, which results in

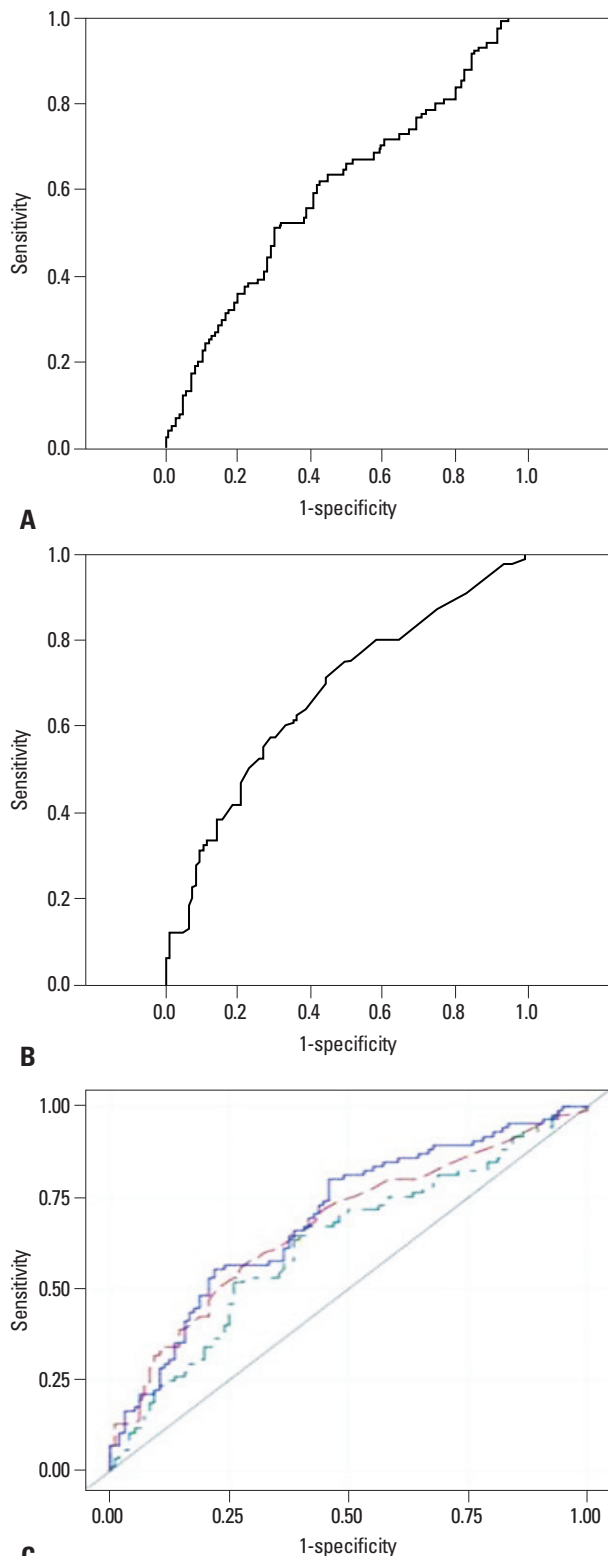


Fig. 3. Receiver operating characteristic (ROC) curves. ROC curve for Lp-PLA₂. (A) Area under the ROC curve for Lp-PLA₂ was 0.624 [95% confidence interval (CI): 0.542–0.706, $p=0.004$]. ROC curve for hs-CRP. (B) Area under the ROC curve for hs-CRP was 0.673 (95% CI: 0.594–0.752, $p=0.000$). (C) ROC curves for Lp-PLA₂ (green line), hs-CRP (red line), and Lp-PLA₂+hs-CRP (blue line). Area under the ROC curve for Lp-PLA₂+hs-CRP was 0.695 (95% CI: 0.618–0.772). Lp-PLA₂, lipoprotein-associated phospholipase A₂; hs-CRP, high-sensitivity C-reactive protein.

myocardial hypoperfusion.²⁰ Lp-PLA₂ is an enzyme found in atherosclerotic plaques, and it exists in the bloodstream bound to LDL.^{11,21,22} Numerous studies have shown that ruptured plaques contain more immune and inflammatory effector cells than do intact plaques and that Lp-PLA₂ may be an essential factor in the association between lipoproteins and inflammation.²³ Lp-PLA₂ is abundantly expressed within the atherosclerotic plaques,^{9,24,25} and its enzymatic products take part in the progression of inflammation and cell death, rendering the plaque vulnerable to rupture.^{23,26} Therefore, the amount of plasma Lp-PLA₂ reflects the plaque burden and inflammatory activity of atherosclerosis and enables the prediction of cardiovascular outcomes in patients with CHD. Herein, we measured plasma Lp-PLA₂ mass levels, which have been shown to have a strong positive correlation with plasma Lp-PLA₂ activity.^{16,27} Plasma Lp-PLA₂ activity is related to plaque rupture, and it may be a marker for vulnerable plaques.²⁸ In this study, we investigated the possible role of Lp-PLA₂ levels as a diagnostic biomarker for ACS with vulnerable plaques. Our analysis of 226 participants showed that Lp-PLA₂ levels are associated with risk of ACS. We found that Lp-PLA₂ levels were significantly increased in the ACS group, and within this group, Lp-PLA₂ levels were greater in the AMI group than in the UA group. This finding may be a result of the relation between vulnerable plaque rupture and Lp-PLA₂ level.¹⁴ To exclude the effect of the myocardial injury, we compared Lp-PLA₂ levels between the SA group and UA group, omitting the AMI group. Lp-PLA₂ levels tended to be higher in the UA group than in the SA group, which suggest Lp-PLA₂ is associated with plaque vulnerability, regardless of myocardial injury. There was no significant difference in Lp-PLA₂ levels between the ACS group and the control group, which might have resulted from the small number of enrolled patients.

Achieving target LDL cholesterol concentrations according to personal cardiovascular disease risk, based on the Framingham risk criteria, is very important for the prevention of primary and secondary atherosclerotic vascular diseases, including CHD. For those with moderate risk, a target LDL cholesterol concentration of <130 mg/dL is recommended, based on the Framingham risk calculator. The ATP III 2004 guidelines, however, recommend measurement of pro-inflammatory biomarkers, specifically Lp-PLA₂, as an adjustment to classical risk factor assessment. For those patients classified as having moderate risk, Lp-PLA₂ should be measured to allow for reclassification and to identify

those patients in relatively high-risk groups.²⁹

CRP is a representative risk factor for atherosclerotic inflammation, and its concentrations are known to be significantly greater in patients with ACS than in those without ACS.^{30,31} Similarly, because the concentration of Lp-PLA₂ is greater in patients with ACS, Lp-PLA₂ may be a good biomarker for diagnosis of ACS, as is CRP. In this study, we used more sensitive tests to evaluate improvement in model performance and usefulness of the new biomarker.¹⁸ We evaluated the ability of Lp-PLA₂ in combination with CRP to diagnose ACS by calculation of net reclassification improvement and integrated discrimination improvement indices. Although the diagnostic power was lower, as compared with serum hs-CRP concentration, the addition of Lp-PLA₂ level to serum hs-CRP concentration could significantly improve the ability to diagnose ACS, as shown by IDI indices.

Traditional risk factors such as LDL cholesterol or HDL cholesterol cannot be used to directly assess plaque-rupturing tendency, but greater amounts of Lp-PLA₂ signify plaque instability. Interventions to decrease Lp-PLA₂ activity, such as statin administration, might be useful for stabilizing vulnerable plaques in patients with ACS; thus, intensified lipid-lowering therapy might be emphasized. Lp-PLA₂ level tended to be lower in statin users than in statin non-users in each group in our study, although this result was not statistically significant. Patients with hypercholesterolemia have elevated levels of oxidized LDL (OxLDL) in the plasma. OxLDL can induce the expression of the procoagulant protein tissue factor (TF) in human monocytes and can also activate the coagulation system. Statins reduce the levels of OxLDL and thus inhibit inducible TF expression in the aorta and in atherosclerotic lesions.³² Reduced OxLDL levels and reduced TF expression lead to the inactivation of the coagulation system and should inhibit the development of a prothrombotic state. Therefore, statins can reduce inflammation and thrombogenicity in patients with hypercholesterolemia, and it is suggested that statins may lower the risk of advanced cardiovascular disease, including ACS. Indeed, more evidence of a statin effect was shown in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. A substudy with analysis of the MIRACL trial cohort revealed that high-dose atorvastatin significantly decreases Lp-PLA₂ mass and activity after ACS.³³ Currently, Lp-PLA₂ inhibition is thought to lead to reduced phospholipid oxidation and reduced expression of adhesion molecules that accelerate atherogenesis. Therefore, specific

Lp-PLA₂ inhibitors, such as darapladib, have been developed.^{8,34} Darapladib was suggested that it might produce sustained inhibition of circulating Lp-PLA₂ activity in dyslipidemic patients, and be associated with reduction in plaque burden in CHD.^{8,35,36} Darapladib has undergone evaluation in the coronary atherosclerosis imaging trial, in which it prevented necrotic core expansion, a crucial determinant of plaque vulnerability.⁸ Now, phase III clinical trials, investigating the effects of darapladib on cardiovascular outcome in CHD, are ongoing.³⁷⁻³⁹ In our study, as mentioned above, although the finding was not statistically significant, Lp-PLA₂ level tended to be lower in statin users than in statin non-users in each of the groups. Among ACS patients, there were patients with low Lp-PLA₂ levels who had taken statins previously. The previous statin users had taken normal doses of various statins, and Lp-PLA₂ levels were measured only at the time of coronary angiography in this study. Therefore, we could not measure Lp-PLA₂ after ACS, but we could guess that statin usage would reduce Lp-PLA₂ levels, as garnered from simultaneous comparisons between statin users and non-users in each group. Because some people take statins for primary prevention, assessing ACS risk solely on the basis of Lp-PLA₂ would not be appropriate. Indeed, patient usage of various medications that may interfere with cholesterol production should also be considered.

The limitations of this study merit consideration. First, because this was not a prospective study, we could not compare sequential measurements of Lp-PLA₂ level in the same patient. Furthermore, there may be differences in baseline Lp-PLA₂ levels among individuals. Therefore, we cannot be sure that statins reduce Lp-PLA₂ levels. In addition, Lp-PLA₂ levels were slightly greater in the control group. Such an unexpected result might be attributable to the small number of enrolled patients in this study. Also, although coronary angiography is one of the most commonly performed procedures for illustrating luminal narrowing and arterial anatomy and is considered the gold standard, it only offers information about the vessel lumen and does not provide information on plaque components or on plaque burden within the vessel wall.⁴⁰ Additionally, coronary angiography was performed because the patients in the control group might have had chest pain or a positive treadmill test. Therefore, microvascular angina or syndrome X is a possible diagnosis for those patients, even though their coronary arteries did not have significant narrowed lesions. Finally, it is known that myocardial damage or death induces inflammatory cells from the bone marrow, which could also affect Lp-

PLA₂ level. To discriminate which factor was related to increased Lp-PLA₂ levels, identification of tissue characteristics, such as by MRI, might be needed.

In conclusion, Lp-PLA₂ may be of use as a meaningful biomarker to diagnose ACS independent of hs-CRP and lipid profiles. Although Lp-PLA₂ measurement is not widely used in the clinic, use of this biomarker could help tailor an individualized treatment approach to patients with ACS. Specifically, patients with higher levels of Lp-PLA₂ at baseline could appear to have an increased risk of cardiovascular events. Thus, we could select, at an early stage, patients with high levels of Lp-PLA₂ who might benefit from aggressive lifestyle modification and more robust risk reduction strategies, such as intensified lipid-lowering therapy, with the overall effect of reducing the morbidity and mortality of cardiovascular disease.

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