Biomarkers for Prediction of Cardiovascular Events in Community-Dwelling Adults Aged 40 or Older

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Summary

Lipoprotein-associated phospholipase A2 (Lp-PLA2) and high-sensitivity C-reactive protein (hs-CRP) have been reported to be associated with cardiovascular disease (CVD). However, whether the combination of these two markers can improve the prediction of CVD is unknown.

A total of 1,921 participants without CVD, aged 40 years or older, were enrolled from 2010 to 2011. Plasma Lp-PLA2 and hs-CRP were measured at baseline. Participants were subsequently followed until December 2015. We identified a total of 148 cardiovascular events (myocardial infarction, stroke, and all-cause death). Cox proportional-hazard models were used to determine the association between two independent markers and cardiovascular outcomes. The C statistic, Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI) were used to determine the utility of the two markers in predicting cardiovascular risk.

After adjustment for potential confounders, compared with the first quartile, hazard ratios (HRs) with 95% confidence interval (CI) for the third and fourth quartiles for Lp-PLA2 were 2.09 (1.17-3.73) and 2.62 (1.48-4.67), respectively, and HRs with 95%CI for the fourth quartile for hs-CRP was 1.78 (1.08-4.67). Compared with conventional risk factors, the combination of hs-CRP and Lp-PLA2 provided greater incremental information, and the C statistic increased by 0.013. The NRI and IDI were also statistically significant for cardiovascular events (P = 0.004 and P < 0.001, respectively).

Hs-CRP and Lp-PLA2 have complementary effects in predicting cardiovascular outcomes in adults aged 40 years or older.

Key words: Cardiovascular disease, Lipoprotein-associated phospholipase A2, High-sensitivity C-reactive protein

CVD is the primary cause of mortality and disability.1-5 It has been thought to be markers of inflammation, including Lp-PLA2 and hs-CRP, have been evaluated for their association with atherosclerotic CVD and their ability to improve cardiovascular risk stratification.2-4

Lp-PLA2, an enzyme that participates in cleaving fatty acids and initiating inflammation, seems to be a promising candidate. Several prospective studies5-8 provided evidence that Lp-PLA2 is an independent predictor of adverse cardiovascular events. CRP is widely used to monitor different inflammatory states and the effects of inflammation treatment. Some9-11 but not all studies12,13 showed that elevated hs-CRP levels were significantly associated with increased risk of CVD. Indeed, cardiovascular risk prediction was improved when hs-CRP was added to the Framingham risk score.14 Lp-PLA2 and hs-CRP may be additive or complementary in their ability to predict risk of cardiovascular outcomes.14,15 However, there is no definite conclusion on the effectiveness of the combination of these two markers.

Therefore, this study was aimed to identify their ability to improve cardiovascular risk stratification and to evaluate whether the combination of hs-CRP and Lp-PLA2 has a greater predictive value on cardiovascular events is essential. We studied a middle-aged, Chinese population-based cohort without CVD and evaluated the potential impact of either hs-CRP or Lp-PLA2 in predicting cardiovascular events during a 6 year follow-up period in the Asymptomatic Polyvascular Abnormalities Community (APAC) study. In secondary analyses, the C statistic, NRI, and IDI were used to determine the utility of the combination of these two markers in predicting cardiovascular risk.
Methods

Ethics: The study was approved by the Kailuan General Hospital and the Beijing Tiantan Hospital Ethics Committees and was performed in accordance with the guidelines of the Helsinki Declaration.

Study design and subjects: The APAC study was a community-based, long-term follow-up observational study conducted to investigate the epidemiology of asymptomatic multivessel abnormalities in middle-aged Chinese adults. The APAC study protocol has been previously reported in detail.\(^{16,17}\) A total of 1,921 participants were randomly recruited from the APAC study performed from January 2010 until December 2015. Primary inclusion criteria for the participants were: (1) aged ≥ 40 years; (2) complete basic information, hs-CRP and Lp-PLA2 levels available; and (3) no history of cancer, coronary disease, stroke, myocardial infarction, transient ischemic attack, or neurological deficits.\(^{8,19}\)

Measurement for plasma levels of Lp-PLA2 and hs-CRP: Fasting blood samples were collected in ethylene-diaminetetraacetic acid (EDTA) tubes before 9:00 AM. Tubes were centrifuged at 3,000 r/min for 5 minutes within 2 hours of collection, and plasma was isolated, placed in 1 mL Eppendorf tubes and stored at -80°C until analysis. The human Lp-PLA2 enzyme immunoassay kits (CUSABIO, Wuhan, China) were used to measure the plasma level of Lp-PLA2. The plasma Lp-PLA2 level for all participants was measured twice by the professional technicians at Beijing Tiantan Hospital. Experimental procedures and measures were performed strictly according to the manufacturer’s instructions.

The whole-blood level of hs-CRP was measured on the day of the medical examination by high-sensitivity nephelometry assay (Cias Latex CRP-H, Kanto Chemical Co. Inc, Tokyo, Japan) at the central laboratory of the Kailuan General Hospital. All laboratory technicians who performed these measurements were trained and certified. Experimental procedures and measures were performed strictly according to the manufacturer’s instructions.

Assessment of covariates: Subjective information was collected using questionnaires. Demographic variables, including history of disease, smoking, alcohol drinking, and drug history, were investigated at baseline. Clinical characteristics and biochemical indicators, including alcohol drinking, blood pressure, diabetes, blood lipids, total cholesterol (TC), body mass index (BMI), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), white blood cell (WBC) count, homocysteine (Hcy), triglyceride (TG), and uric acid (UA), were measured at Kailuan General Hospital. The definitions of covariates have been described in detail previously.\(^{16,17,20}\)

Follow-up procedures: A face-to-face interview at every 2 year ordinary medical examination was performed in this cohort until December 31, 2015 or until the cardiovascular outcomes. Physicians and nurses who conducted these follow-ups were blinded to baseline data. Participants who were unable to attend the interview were investigated and registered according to medical records from the hospital and Medicare. Composite endpoints included the first occurrence of stroke, myocardial infarction (MI), and all-cause death. Stroke was diagnosed by the combination of brain computed tomography and magnetic resonance confirmation in light of the World Health Organization (WHO) criteria.\(^{21}\) MI was diagnosed in light of the 2007 Universal Definition.\(^{22}\) Deaths were confirmed by the death certificates through provincial vital statistics offices. All clinical outcomes were examined by the Data Safety Monitoring Board.

Data management and statistical analyses: Continuous variables with normal distribution were presented as the mean (standard deviation [SD]). Data with non-normal distribution were expressed as medians (interquartile range [IQR]), whereas categorical variables were expressed as percentages. The Cox proportional hazards regression model was used to examine the independent risk factors and the risk for cardiovascular outcomes. Other potential confounding factors were adjusted in the Cox regression models. The results were presented as HRs and 95% CI. To assess utility of inflammatory markers in predicting cardiovascular events, we calculated the C statistic, NRI, and IDI.\(^{20}\)

All data management and analyses were performed using SAS software (version 9.3; SAS Institute, Cary, North Carolina, USA), except for the C statistics, NRI, and IDI. These were generated using the ROCR package for R. All statistical tests were two-sided, and \(P < 0.05\) was considered statistically significant.

Results

During an average follow-up of 59 months, 148 participants (44 strokes, 13 MIs, and 91 deaths, respectively) had composite endpoints among 1,921 participants with complete demographic and blood sample information.

Baseline characteristics: The baseline characteristics of the study participants are summarized in Table I. Compared with the non-cardiovascular events group, the participants who had a cardiovascular event were more likely to be older, male, have a medical history and medications in use of diabetes and hypertension, and have a higher level of TC, UA, HCY, WBC, hs-CRP, and Lp-PLA2 (\(P < 0.05\)). It is worth mentioning that significant differences for BMI, smoking, drinking, HDL-C, and LDL-C were not found among groups (\(P > 0.05\)).

Single analysis for the association of hs-CRP and Lp-PLA2 with cardiovascular outcomes: Multivariate Cox proportional hazards models were used to analyze the independence and association of Lp-PLA2 and hs-CRP for cardiovascular risk (Figure 1). Compared with the first quartile for Lp-PLA2 in the unadjusted model, HRs with 95% CI for the second, third, and fourth quartiles were 1.44 (0.77-2.68), 2.64 (1.50-4.62), and 4.06 (2.38-6.93), respectively (\(P < 0.001\)). The strength of the association attenuated after adjustment for age, sex, hypertension, diabetes, antihypertensive agents, hypoglycemic agents, UA, HCY, hs-CRP, and WBC count. Compared with the first quartile, HRs with 95% CI for the second, third, and fourth quartiles were 1.34 (0.72-2.51), 2.15 (1.20-3.83), and 2.69 (1.51-4.78), respectively (\(P < 0.001\)).

Hs-CRP also showed a graded association for the
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Figure 1. Multivariate-adjusted hazard ratios for events according to quartile of inflammatory factor. Lp-PLA2 indicates lipoprotein-associated phospholipase A2; Hs-CRP, high-sensitivity C-reactive protein; adjusted for age, sex, hypertension, diabetes, antihypertensive agents, hypoglycemic agents, TC, UA, WBC count, and HCY (additional: when calculated the HR (95%CI) of one of the inflammatory factors, adjust another inflammatory factor).

Table 1. Baseline Characteristics of Study Participants

| Characteristics | Total n=1,921 | No-Cardiovascular events n=1,773 | Cardiovascular events n=148 | P-value |
|-----------------|--------------|-----------------------------------|----------------------------|--------|
| Age, (mean ± SD), years | 60 (12) | 60 (11) | 67 (13) | <0.01 |
| Male, n (%) | 1412 (73.5) | 1290 (72.8) | 122 (82.4) | 0.01 |
| Smoking, n (%) | 729 (38.0) | 669 (37.7) | 60 (40.5) | 0.50 |
| Drinking, n (%) | 312 (16.2) | 285 (16.1) | 27 (18.2) | 0.49 |
| BMI, (mean ± SD), kg/m² | 24.9 (3.2) | 24.9 (3.2) | 25.2 (3.6) | 0.52 |
| Hyperlipidemia, n (%) | 225 (11.7) | 208 (11.7) | 17 (11.5) | 0.93 |
| TC, (mean ± SD), mmol/L | 5.2 (1.1) | 5.1 (1.1) | 5.3 (1.2) | 0.04 |
| HDL, (mean ± SD), mmol/L | 1.6 (0.5) | 1.6 (0.5) | 1.6 (0.5) | 0.27 |
| LDL, (mean ± SD), mmol/L | 2.6 (0.8) | 2.7 (0.8) | 2.6 (0.7) | 0.31 |
| TG, median (IQR), umol/L | 1.3 (0.9-1.9) | 1.3 (0.9-1.9) | 1.3 (1.0-2.1) | 0.31 |
| UA, median (IQR), umol/L | 297.0 (240.0-358.0) | 295.0 (237.0-356.0) | 336.0 (270.0-396.0) | <0.001 |
| Hypertension, n (%) | 621 (32.3) | 557 (31.4) | 64 (43.2) | 0.003 |
| Diabetes, n (%) | 202 (10.5) | 175 (9.9) | 27 (18.2) | 0.001 |
| Antihypertensive Agents, n (%) | 482 (25.1) | 434 (24.5) | 48 (32.4) | 0.03 |
| Hypoglycemic Agents, n (%) | 157 (8.2) | 136 (7.7) | 21 (14.2) | 0.01 |
| Antilipemic Agents, n (%) | 28 (1.5) | 26 (1.5) | 2 (1.4) | 0.28 |
| WBC count, median (IQR), 10⁹/L | 6.2 (5.2-7.3) | 6.2 (5.2-7.2) | 6.5 (5.5-8.0) | 0.005 |
| HCY, median (IQR), µmol/L | 140.7 (131.7-158.2) | 140.0 (131.5-156.2) | 151.1 (139.4-179.8) | <0.001 |
| Lp-PLA2, median (IQR), ng/mL | 11.1 (0.6-2.4) | 11.1 (0.6-2.3) | 11.6 (0.8-4.6) | <0.001 |

BMI indicates body mass index; TC, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; UA, uric acid; TG, triglyceride; Lp-PLA2, lipoprotein-associated phospholipase A2; Hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; and HCY, homocysteine. Categorical variables are expressed as percentage. Values of continuous variables are expressed as mean ± SD or median (IQR).

Figure 1. Multivariate-adjusted hazard ratios for events according to quartile of inflammatory factor. Lp-PLA2 indicates lipoprotein-associated phospholipase A2; Hs-CRP, high-sensitivity C-reactive protein; adjusted for age, sex, hypertension, diabetes, antihypertensive agents, hypoglycemic agents, TC, UA, WBC count, and HCY (additional: when calculated the HR (95%CI) of one of the inflammatory factors, adjust another inflammatory factor).

risk of cardiovascular events (Figure 1). Compared with the first quartile in the unadjusted model, HRs with 95% CI for the second, third, and fourth quartiles were 1.31 (0.76-2.26), 1.72 (1.04-2.87), and 2.58 (1.60-4.16), respectively (P < 0.001). The strength of the association attenuated after adjustment for age, sex, hypertension, dia-
betes, antihypertensive agents, hypoglycemic agents, UA, HCY, Lp-PLA2, and WBC count. Compared with the first quartile, HRs with 95% CI for the second, third, and fourth quartiles were 1.17 (0.67-2.04), 1.30 (0.77-2.20), and 1.78 (1.08-2.94), respectively ($P < 0.01$).

Cumulative incidence of cardiovascular events based on quartiles of plasma levels of Hs-CRP and Lp-PLA2 are shown in Figure 2A and B. Cumulative incidence of cardiovascular events based on median plasma levels of Hs-CRP and Lp-PLA2 are shown in Figure 2C.

**Figure 2.** Kaplan-Meier analysis for the cardiovascular events. Hs-CRP indicates high-sensitivity C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A2. A: Cumulative incidence for the cardiovascular events based on the quartiles of Lp-PLA2. B: Cumulative incidence for the cardiovascular events based on the quartiles of Hs-CRP. C: Cumulative incidence for the cardiovascular events based on Lp-PLA2 combined with Hs-CRP. Define the median of Hs-CRP and Lp-PLA2 as the threshold, and combine them into “lp-crp-,” “lp-crp + ,” “lp + crp + ,” and “lp + crp + ” groups.

**Table II.** Incremental Information with Hs-CRP and Lp-PLA2

| Biomarkers Retained by Backward Elimination | C Statistic | NRI | IDI |
|-------------------------------------------|-------------|-----|-----|
| Conventional risk factors*                |             |     |     |
| + Hs-CRP                                  | 0.009       | < 0.001 | 30.7 | < 0.001 | 2.6 | < 0.001 |
| + Lp-PLA2                                 | 0.006       | < 0.001 | -64.6 | 0.40 | 0.2 | 0.37 |
| + Hs-CRP + Lp-PLA2                        | 0.013       | < 0.001 | 41.5 | 0.004 | 2.7 | < 0.001 |

NRI indicates Net Reclassification Improvement; IDI, Integrated Discrimination Improvement; Lp-PLA2, lipoprotein-associated phospholipase A2; and hs-CRP, high-sensitivity C-reactive protein. *Conventional risk factors including age, sex, UA, TC, hypoglycemic agents, hypertension, diabetes (significant predictors of events after performing Cox proportional hazards regression with stepwise backward elimination). Increment in C statistic in a model with conventional risk factors and the biomarker set, compared with conventional risk factors alone (C = 0.701). $^1P$ value for increase in NRI or IDI in a model with conventional risk factors and the biomarker set, compared with conventional risk factors alone.

Our study confirmed that in a large community population, inflammatory factors can significantly increase prediction of the risk of major cardiovascular events. Of the inflammatory markers, the combination of hs-CRP and Lp-PLA2 provided the greatest increment.

**Discussion**

Many studies investigated the association of inflammatory markers with cardiovascular outcomes. Hs-CRP was used to predict CVD in a non-cardiovascular population according to the current treatment guidelines and helped prevent one additional event over a period of 10 years for every 400 to 500 people screened. Lp-PLA2 is a unique phospholipase that circulates primarily bound to low-density lipoprotein (approximately 80%). This phospholipase participates in the process of endothelial cell death, endothelial dysfunction, and atherosclerotic plaque...
formation by binding to low-density lipoprotein. The ARIC study showed that AUC improved when hs-CRP or Lp-PLA2 was added to the TRF-alone model (0.743 and 0.752, respectively). However, Melander, et al. suggested that Lp-PLA2 was not involved in contributing to the incremental information for predicting first cardiovascular events in the community. Lp-PLA2 level was significantly different in white and Hispanic subjects compared with that of black subjects. In that study, one of the key confounding factors was race. Discrepant findings, including conventional risk factors such as BMI, smoking, HDL-C, and LDL-C not significantly associated with CVD events, might be likely attributed to race or ethnicity. Previous reports have included similar results in the Chinese population. Our study, consisting of Chinese adults, demonstrated an independent correlation and incremental information of inflammatory factors for predicting CVD.

Most studies examined the role of hs-CRP and Lp-PLA2 in predicting CVD. Our findings were similar to previous studies. We showed that the significant association between higher plasma levels of hs-CRP and Lp-PLA2 with the risk of cardiovascular events remained after multivariable adjustments, demonstrating the independent role of Lp-PLA2 and hs-CRP in cardiovascular events. They showed that HCY was also a marker to predict cardiovascular events. However, HCY has no ability to improve the risk stratification of complex cardiovascular events in our study (Supplemental Table I). Furthermore, we examined the utility of hs-CRP and Lp-PLA2 in predicting CVD risk. Compared with conventional risk factors, the combination of hs-CRP and Lp-PLA2 provided the greatest incremental information. Ballantyne, et al. studied 12,819 healthy people in the ARIC study. They showed that Lp-PLA2 and CRP may be complementary in predicting coronary heart disease in a low LDL-C population. Koenig, et al. also suggested that Lp-PLA2 and CRP may be additive in their ability to predict risk of coronary heart disease. Our results provided direct evidence for the preceding conjecture. Hs-CRP in combination with Lp-PLA2 can provide greater incremental information compared with Hs-CRP or Lp-PLA2. With the addition of HCY, there is no statistically significant change in incremental information (Supplemental Table II). Hs-CRP and Lp-PLA2 are complementary in predicting cardiovascular outcomes in adults aged 40 years or older.

In addition, a defined, plant-based diet, PCSK9 inhibitors, high dose atorvastatin, ezetimibe, and niacin have resulted in significant reductions in Lp-PLA2. Early intervention is one of the important ways to reduce the burden of CVD.

Our study has several limitations. All-cause death included cardiovascular and unknown reasons, all of which have different pathogeneses. Lp-PLA2 combined with hs-CRP seems to be completely predictive of the occurrence of composite outcomes. The current study included only Chinese adults 40 years old and above living in the Kaifuan community; therefore, the population may not be representative. However, the homogeneous nature of our cohort could help to reduce potential confounding due to racial and health care disparities.

**Disclosure**

No conflicts of interest to declare.

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**Supplemental Files**

Supplemental Tables I, II

Please see supplemental files; [https://doi.org/10.1536/ihj.19-240](https://doi.org/10.1536/ihj.19-240)