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Prognostic value of lipoprotein-associated phospholipase A_2 mass for all-cause mortality and vascular events within one year after acute ischemic stroke

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ABSTRACT

Background and aims: We performed a prospective investigation of the longer-term prognostic value of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) mass for all-cause mortality and vascular events within one year after acute ischemic stroke.

Methods: We examined the Lp-PLA_2 mass among 3401 participants enrolled in the China Antihypertensive Trial in Acute Ischemic Stroke. The primary outcome was all-cause mortality. Cox proportional hazard ratios (HRs) and 95% confidence intervals (95% CIs) were constructed to assess the independent associations between the baseline Lp-PLA_2 mass and the outcomes after adjustment for variables in models 1, 2, and 3 [further adjusted for low-density lipoprotein cholesterol (LDL-C)].

Results: Overall, 3278 patients completed the follow-up, during which, 188 all-cause death events occurred. The Kaplan-Meier survival curve showed that the cumulative incidence rate of all-cause mortality increased across quartiles of Lp-PLA_2 mass (log-rank $p = 0.018$). Compared with the lowest quartile of Lp-PLA_2, the HRs (95% CIs) for the highest quartile of Lp-PLA_2 were 1.89 (1.22−2.91), 2.16 (1.31−3.55), and 2.17 (1.32−3.58) for all-cause mortality after adjusting for the covariables in models 1, 2, and 3, respectively. In addition, patients in the highest quartile of Lp-PLA_2 mass coupled with higher LDL-C had significantly highest risk of all-cause mortality (HR, 1.81; 95% CI, 1.05 to 3.11; $p = 0.032$).

Conclusions: The elevated Lp-PLA_2 mass was associated with all cause-death independently of other risk factors within one year after acute ischemic stroke.

1. Introduction

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), an inflammatory marker, is involved in the atherosclerotic process through inflammatory activities [1,2]. Experimental studies demonstrate that Lp-PLA_2 exerts its effect on cardiovascular disease (CVD) through involvement in the evolution of atherosclerosis [3]. Particularly, Lp-PLA_2 is capable of hydrolyzing the platelet-activating factor and

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phospholipids, which play protective functions, thus contributing to the prediction of future CVD events [4].

Accumulating epidemiological studies reported strong associations of Lp-PLA_2 with CVD and stroke in the general population, as well as in the populations of metabolic syndrome, diabetes, and coronary heart disease (CHD) [3,5–7]. The largest meta-analysis of 32 prospective studies found a positive association of Lp-PLA_2 activity and mass with incidence of CHD, stroke, and CVD mortality after adjustment for traditional risk factors [8]. Furthermore, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial demonstrated that Lp-PLA_2 activity was associated with a higher risk of CVD mortality [9].

Notably, high Lp-PLA_2 was also associated with increased risk for both first and recurrent CVD, CHD, and ischemic stroke [10]. A small prospective cohort study of 467 patients found that higher levels of Lp-PLA_2 mass were associated with a higher risk of recurrent stroke and combined outcome of recurrent stroke, myocardial infarction or vascular death after a first-ever ischemic stroke [11,12]. The CHANCE (Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events) trial showed that higher Lp-PLA_2 activity in the acute period was associated with increased risk of recurrent vascular events within 90 days since a transient ischemic attack or minor stroke [13].

However, little evidence on association of Lp-PLA_2 mass with longer-term risks of all-cause mortality and vascular events after acute ischemic stroke is currently available. It remains unclear whether higher levels of Lp-PLA_2 mass predict longer-term risks of all-cause mortality and vascular events in patients with acute ischemic stroke. We thus performed a large prospective multicenter study based on the China Antihypertensive Trial in Acute Ischemic Stroke (CATIS) [14], to explore prognostic value of the Lp-PLA_2 mass on all-cause mortality and vascular events within one year after acute ischemic stroke.

2. Patients and methods

2.1. Study subjects and data collection

The CATIS was a multicenter, single-blind, blinded end-point, randomized clinical trial conducted in 26 hospitals across China. Its design and major results were reported previously [14]. In brief, 4071 patients aged 22 years or older, who had ischemic stroke confirmed by computed tomographic scan or magnetic resonance imaging of the brain within 48 h of symptom onset, and who had an elevated systolic blood pressure (BP) between 140 and < 220 mmHg, were recruited for this trial. Patients with a BP $\geq$ 220/120 mmHg, severe heart failure, acute myocardial infarction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, or resistant hypertension and those in a deep coma were excluded. Since several patients refused to offer blood samples, or some collected samples were hemolyzed in storage or transport, or Lp-PLA_2 mass was not tested, a total of 3401 patients were included in this analysis. This study was approved by the institutional review boards at Tulane University in the United States and Soochow University, as well as the ethical committees of the 26 participating hospitals in China. Written consent was obtained from all study participants or their immediate family members. The CATIS is registered with clinicaltrials.gov (NCT01840072).

2.2. Measurements

Data related to demographic characteristics, lifestyle risk factors, and medical history was collected at the time of enrollment (baseline). Data related to medical history, BP, National Institutes of Health Stroke Scale (NIHSS) score, and modified Rank Scale score was obtained. Stroke severity was assessed at baseline by trained neurologists using the NIHSS, for which the scores range from 0 to 42, with higher scores indicating a more severe neurologic deficit [15]. Computed tomographic or magnetic resonance imaging of the brain was performed according to standard techniques to confirm the diagnosis of ischemic stroke in all trial participants. Three BP measurements were obtained at baseline by trained nurses according to a common protocol adapted from the procedures recommended by the American Heart Association [16].

2.3. Plasma glucose, blood lipids and plasma Lp-PLA_2 mass measurements

Blood samples were collected within 24 h of hospital admission after at least 8 h of fasting. The plasma glucose levels were measured using the modified hexokinase enzymatic method. Total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C) and triglycerides (TG) levels were analyzed enzymatically using commercial reagents. The glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation with an adjusted coefficient of 1.1 for the Chinese population [17].

All plasma and serum samples were frozen at −80 °C in the Central Laboratory until testing of plasma Lp-PLA_2 mass. The plasma Lp-PLA_2 mass was determined using a commercially available enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, Minnesota), which is based on the quantitative sandwich enzyme immunoassay technique. In this technique, a monoclonal antibody specific to human PLA2G7 is pre-coated onto a microplate. The intra-assay coefficient of variation for the Lp-PLA_2 assay is #2.3%, and the inter-assay coefficient of variation is #5.2%. Serum high sensitivity C-reactive protein (hsCRP) was measured by latex enhanced immuno-turbidimetric assay on the Cobas c 501 analyzer (Roche Diagnostics, Indianapolis, IN). The laboratory technicians were blinded to the clinical characteristics and outcomes of the study participants.

2.4. Outcome assessment

The participants were followed up one year after hospitalization by trained neurologists and research nurses who were unaware of the treatment assignment, as detailed elsewhere [14]. The primary outcome was death from any causes, and the secondary outcomes were vascular events (i.e., vascular deaths, nonfatal stroke, nonfatal myocardial infarction, and hospitalization and treatment for angina, congestive heart failure, or peripheral arterial disease) and recurrent stroke. Death certificates were obtained for the participants who died, and hospital data were abstracted for all vascular events. A trial-wide outcomes assessment committee, blinded to treatment assignment, reviewed and adjudicated vascular events based on the criteria established in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

2.5. Statistical analysis

Demographics and other baseline characteristics were summarized by quartiles of baseline Lp-PLA_2 mass. Categorical variables were presented as frequencies and percentages, continuous variables were reported as mean ± standard deviation (SD), and non−normally distributed variables were presented as medians and interquartile ranges. Tests for linear trends were performed using covariance analysis for continuous variables, and Chi-square trend analysis was performed for categorical variables.

The cumulative incidence risks of outcomes across baseline Lp-PLA_2 mass quartiles were estimated with Kaplan-Meier curves and