Synergetic Effect of Lipoprotein(a) and Lipoprotein-Associated Phospholipase A2 on Functional Outcomes in Patients with Ischemic Stroke

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Abstract

Background:

The relationship of lipoprotein(a) [Lp(a)] and stroke functional outcomes was conflicting. The relationship of Lp(a) and Lp-PLA\(_2\) levels to functional outcomes is unclear. The aim was to clarify whether high Lp(a) is associated with poor functional outcomes and examine the relationship of Lp(a) and Lp-PLA\(_2\) to functional outcomes in patients with ischemic stroke.

Methods:

A total of 10,422 individuals from the third China National Stroke Registry cohort were recruited. Plasma level of Lp(a) at admission was measured with enzyme-linked immunosorbent assay. The cut-off was set at the median for Lp(a). Functional outcome was assessed using the modified Rankin scale (mRS) at 3 months after stroke. The association between Lp(a) and stroke functional outcomes was evaluated using a multivariate Cox regression model.

Results:

The median age was 63.0 years, and 31.6% participants were women. Patients in higher Lp(a) group had higher incidences of poor functional outcome at 3 months (P<0.0001). In multivariate cox regression model, elevated Lp(a) levels were associated with poor functional outcomes at 3 months (Q4 vs. Q1: hazard ratio 1.39, 95% confidence interval 1.11-1.75). Subgroup analysis showed the significant effect of interaction of Lp-PLA\(_2\) level with Lp(a) level on functional outcomes (p=0.008). After stratification by Lp(a) and Lp-PLA\(_2\), the Lp(a) high/ Lp-PLA\(_2\) high group showed the highest incidence of poor functional outcomes at 3 months.

Conclusions:

Elevated Lp(a) level is associated with poor functional outcomes in patients with ischemic stroke. Lp(a) has a synergetic effect with Lp-PLA\(_2\) on functional outcomes after ischemic stroke.

Background

Lipoprotein(a) [Lp(a)] is composed of low-density lipoprotein (LDL)-like particle and apolipoprotein B-100 (apoB), which is linked to apolipoprotein(a) [apo(a)] by disulfide bond. The pathogenic characteristics of Lp(a) include proinflammatory, proatherogenic, and prothrombotic. The pro-inflammatory of Lp(a) is partially mediated by oxidized phospholipids attached to apo(a).\(^1\) Lp(a) has attracted considerable attention because of its several large clinical genetic observation studies, which confirmed that plasma Lp(a) level is positively correlated with increased risks of stroke,\(^2\) myocardial infarction,\(^3,4\) and aortic valve stenosis.\(^1,5,6\)
Inflammation is involved in the occurrence and development of poor functional outcomes in patients with ischemic stroke.\(^7\) Lipoprotein-associated phospholipase A\(_2\) [Lp-PLA\(_2\)], an inflammatory marker, is an independent predictor of ischemic stroke and coronary heart disease.\(^8,9\) More importantly, Lp-PLA\(_2\) is intimately associated with Lp(a) in atherosclerosis and cardiovascular disease.\(^10\) Although previous studies examined the association of Lp(a) with risk of poor functional outcome in patients with ischemic stroke,\(^11,12,13\) rare studies have conducted the relationship of Lp(a) and Lp-PLA\(_2\) levels to stroke functional outcomes.

In this study, we aimed to evaluate the hypothesis that a high level of Lp(a) is associated with poor functional outcome and Lp(a) high/ Lp-PLA\(_2\) high have a synergistic effect on functional outcomes in patients with ischemic stroke from the third China National Stroke Registry (CNSR-III) database.

**Methods**

**Data availability**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Study population**

We used the CNSR-III, a nationwide, prospective, multicenter, observational registration study based on etiology, imaging, and biology markers from patients with ischemic stroke and transient ischemic attack (TIA) between August 2015 and March 2018 in China.\(^14\) Specific information about the database has been described in detail in our previous studies.\(^14\) In brief, a total of 15,166 consecutive patients from 171 hospitals were recruited, among which 93.3% with ischemic stroke (n = 14,146) and 6.7% with TIA (n = 1020). All patients were enrolled within 7 days after symptom onset. We included 10,422 individuals with complete information on plasma Lp(a) measurements. According to the principles mentioned in the Declaration of Helsinki, the ethics committees of Beijing Tiantan Hospital and all other recruited participating centers approved the study protocol.\(^15\) Written informed consent was obtained from all participants (or guardians of participants) in this study.

**Baseline data collection**

An electronic data capture system by face-to-face interviews was used to collect CNSR-III clinical baseline data. The subsequent data were gathered from the registry database, including age, sex, body mass index (BMI), and smoking status; medical history of hypertension, diabetes mellitus, and lipid metabolism disorders; systolic blood pressure (SBP), fasting plasma glucose (FPG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), high-sensitivity C-reactive protein (hsCRP), Lp(a), and lipoprotein-associated phospholipase A\(_2\) [Lp-PLA\(_2\)]; stroke subtypes, classified as large artery atherosclerosis (LAA), and non-LAA according to the Trial of ORG 10172 in Acute
Stroke Treatment (TOAST) criteria, discharge medication rate of anticoagulant and antiplatelet drugs, and the National Institutes of Health Stroke Scale (NIHSS) score at admission.

**Functional outcomes of stroke evaluation**

The severity of ischemic stroke was evaluated using the NIHSS score at admission. Functional outcome was assessed with the modified Rankin scale (mRS) at 3 months and 1 year after stroke separately. The mRS scale ranges from 0 to 6, and the score parallels the severity of ischemic stroke. An mRS score of 0 was defined as no residual stroke symptoms; 5, severe disability; and 6, death.

**Laboratory analyses**

Fasting blood specimens from 11,261 patients were collected using EDTA anticoagulation tubes within 1 day after admission and were centrifuged on-site within 2 h of collection to separate plasma for subsequent testing. Standard hospital assays were used on fresh plasma samples to measure plasma FPG, LDL-C, HDL-C, TG, hsCRP, and Lp-PLA$_2$.

**Lp(a) measurement**

Lp(a) ELISA (Mercodia, Uppsala, Sweden) detects human Lp(a) and in terms of isoforms, is size-independent in terms of the kringle IV type 2 domain. The Mercodia ELISA is a solid phase two-site enzyme immunoassay and include a 5-point calibrator. The coefficient of variation (CV) was 7%.

**Statistical analyses**

Baseline characteristics categorized by Lp(a) levels were compared. Data on basic characteristics are presented as medians (interquartile ranges) for continuous variables. Categorical variables are presented as percentages. Nonparametric Wilcoxon test and chi-square test were used for comparisons of continuous and categorical variables between groups separately. The associations of Lp(a) with mRS at 3 months and 1 year were examined using a logistic regression model. We adjusted the potential confounders measured at baseline in the analysis. The model was adjusted for age, sex, BMI, FPG, LDL-C, HDL-C, TG, hsCRP, Lp-PLA$_2$, TOAST subtype, and NIHSS score at admission. The strength of the associations was demonstrated using hazard ratios (HRs) with 95% confidence intervals (CIs). The sensitivity analysis was used to rule out the effects of recurrence and TIA on the association between the levels of Lp(a) and outcomes at 3 months. Two-sided $p < 0.05$ was considered to be statistically significant. The above statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

**Results**

In the CNSR-III cohort of 15,166 patients with ischemic stroke or TIA, 12,603 patients from 171 sites were entered into a subgroup analysis of Lp(a) levels and functional outcomes. Blood samples from 11,261 of the 12,603 patients were collected and examined at the laboratory. According to the inclusion criteria, a total of 10,422 patients were included in the study, and the remaining 839 patients were excluded (Figure
In Table S1, the comparison of the included and excluded patients is shown. Compared with the excluded patients, the included patients showed significantly higher levels of LDL-C, Lp-PLA_2, lower rate of current smoker, and higher discharge medication rates of anticoagulant and antiplatelet drugs.

**Baseline characteristics**

Table 1 shows the baseline characteristics of the 10,422 individuals stratified by Quartiles of baseline plasma Lp(a) levels. With the increment in plasma Lp(a) levels, patients tended to be older and had lower levels of BMI and TG, a higher proportion of LAA, and higher LDL-C, HDL-C, hsCRP, and Lp-PLA_2.

**Association between the levels of Lp(a) and stroke outcomes at 3 months and 1 year**

Figure S2 demonstrates a positive correlation between the levels of Lp(a) and functional outcomes of stroke at 3 months. In the unadjusted model, elevated levels of Lp(a) were positively correlated with the poor clinical outcomes of stroke as evaluated using mRS score ≥ 3 at 3 months [Quartile 4 vs. Quartile 1, HR 1.58, 95% CI 1.35-1.86, p<.0001] (Table 2). Furthermore, elevated Lp(a) levels were significantly associated with the poor clinical outcomes of stroke as evaluated by mRS score ≥ 3 at 1 year [Quartile 4 vs. Quartile 1, HR 1.48, 95% CI 1.25-1.74, p<.0001]. After adjustment for age, sex, BMI, FPG, LDL-C, HDL-C, TG, hsCRP, Lp-PLA_2, TOAST subtype, and NIHSS score at admission, similar results were observed.

Elevated levels of Lp(a) were positively correlated with the poor clinical outcomes of stroke as evaluated by mRS score ≥ 3 at 3 months [Quartile 4 vs. Quartile 1, HR 1.39, 95% CI 1.11-1.75, p<.0001] and at 1 year [Quartile 4 vs. Quartile 1, HR 1.27, 95% CI 1.02-1.59, p<.0001]. Distribution of mRS scores at 3 months according to Lp(a) levels showed similar trends (Figure 1).

**Subgroup analysis for the association between Lp(a) levels and mRS ≥3 at 3 months**

Among all the subgroup detection indexes, only the variable Lp-PLA_2 was associated with both Lp(a) levels and functional outcomes of stroke (Table 3). We then used Lp-PLA_2 for subgroup analysis to further evaluate the relationship between Lp(a) levels and functional outcomes of stroke assessed using mRS ≥3 at 3 months.

**Concurrent assessment of Lp(a) levels and Lp-PLA_2 on stroke outcomes**

Table 4 shows concurrent analysis stratifying Lp(a) and Lp-PLA_2 into low vs. high levels (<median value vs. ≥median value). Good outcomes were observed among patients with Lp(a) low/ Lp-PLA_2 low group, whereas poor outcomes were observed among patients with Lp(a) high/ Lp-PLA_2 high group.

**Sensitivity analysis**

**Association between the levels of Lp(a) and outcomes at 3 months after removing patients with recurrent stroke and TIA**
To rule out the effect of recurrence and TIA on the association between the levels of Lp(a) and outcomes at 3 months, we excluded the 3 months recurrent stroke and TIA population for further analysis. As shown in Table S2, in the unadjusted model, elevated levels of Lp(a) were positively correlated with the poor clinical outcomes of stroke as evaluated by mRS score $\geq 3$ at 3 months. After adjustment for age, sex, BMI, FPG, LDL-C, HDL-C, TG, hsCRP, Lp-PLA$_2$, TOAST subtype, and NIHSS score at admission, similar results were observed. Elevated levels of Lp(a) were positively correlated with the poor clinical outcomes of stroke as evaluated by mRS score $\geq 3$ at 3 months.

**Discussion**

In the CNSR-III cohort study, we investigated the association between plasma Lp(a) levels and the functional outcomes of ischemic stroke. The results demonstrated a positive correlation between the levels of Lp(a) and functional outcomes evaluated by mRS at 3 months and 1 year after stroke. The association remained after excluding patients with recurrence of stroke and TIA at 3 months. More importantly, Lp(a) levels and Lp-PLA$_2$ showed a synergistic effect on functional outcomes in patients with ischemic stroke.

In recent years, several small clinical studies have demonstrated that elevated Lp(a) levels are positively correlated with poor functional outcomes in patients with ischemic stroke. In a clinical study by Wang et al. who included 232 consecutive patients with an acute ischemic stroke diagnosis complicated with type 2 diabetes, higher Lp(a) levels at admission are associated with increased risk of poor functional outcomes at 3 months according to mRS scores.$^{11}$ Similarly, in a study conducted by Wang et al., who investigated 153 patients with acute ischemic stroke and 120 controls, an increased risk of poor functional outcomes was associated with Lp(a) levels.$^{12}$ In another study that recruited 100 consecutive patients with acute ischemic stroke and 120 controls, a positive relationship is suggested between Lp(a) levels and poorer long-term prognosis of stroke.$^{17}$ By contrast, Kooten et al. failed to find any association of stroke prognosis with Lp(a) levels.$^{13}$ The association of stroke prognosis with Lp(a) level remains unclear. Therefore, a large sample cohort study is warranted to further clarify the relationship of ischemic stroke prognosis with Lp(a) levels. The current results demonstrated a positive correlation between the levels of Lp(a) and functional outcomes evaluated by mRS at 3 months and 1 year after stroke. To remove the effect of stroke recurrence and TIA on the conclusion, we further analyzed the relationship between Lp(a) levels and functional outcomes after excluding patients with stroke recurrence and TIA at 3 months, the relationship still existed. Our study confirmed a positive association between plasma Lp(a) levels and functional outcomes at 3 months and 1 year after ischemic stroke.

The mechanism through which Lp(a) levels are associated with functional outcomes of ischemic stroke remains unclear until now. Inflammation runs through the onset, process, and progression of acute ischemic stroke. In acute ischemic stroke, microglial activation and cell death products trigger an inflammatory cascade, which damages the brain and affects functional outcomes.$^7$ The pathogenic effect of Lp(a) is partly due to its pro-inflammatory effect, which is harmful to the progression of
ischemic stroke. The pro-inflammatory effect is mediated partially by its oxidized phospholipid content.\textsuperscript{18} In addition, other molecules are related to the effect of Lp(a) pro-inflammatory. Our study revealed that Lp(a) levels and Lp-PLA\textsubscript{2} have a synergistic effect on functional outcomes. As a pro-inflammatory indicator, Lp-PLA\textsubscript{2} is mainly expressed on the surface of inflammatory cells enriched in plaques, and it promotes the secretion of inflammatory mediators by degrading oxidized phospholipids to cause endothelial dysfunction.\textsuperscript{19} Endothelial dysfunction aggravates functional outcomes of ischemic stroke.\textsuperscript{20, 21} In a recent study, Schnitzler et al. demonstrated that oxidized phospholipids carried by Lp(a) drive endothelial inflammation.\textsuperscript{18} Lp-PLA\textsubscript{2} may be considered as the synergistic molecule mediator for pro-inflammatory properties of Lp(a). We also found that with the increase in Lp(a) levels, hsCRP levels also increased. Combining the results of the present study with the conclusions of previous studies further indicates that elevated Lp(a) levels disrupt functional outcomes after ischemic stroke mainly through inflammatory pathways.

The present study is the largest by far to evaluate the clear association between plasma Lp(a) levels and functional outcomes after ischemic stroke. However, it has several limitations. First, we only measured Lp(a) at admission, and no serial measurement of Lp(a) levels was performed. For this reason, we could not conclude any causal relationship of functional outcomes with high Lp(a) levels. We only demonstrated a positive association of poor functional outcomes after ischemic stroke with high Lp(a) levels. Second, the study samples comprised Chinese individuals, limiting the application of its conclusions to other races and populations. Third, genetic data were lacking because of the observational nature of the study. Future studies are warranted to further investigate the effect of these factors on Lp(a) and functional outcomes in patients with ischemic stroke.

Conclusions

Elevated Lp(a) level is associated with poor functional outcomes evaluated by mRS at 3 months and 1 year after ischemic stroke. Lp(a) has a synergetic effect with Lp-PLA\textsubscript{2} on functional outcomes after ischemic stroke. Further studies should be carried out regarding the inflammation mechanism between increased Lp(a) levels and poor functional outcomes in patients with ischemic stroke.

Abbreviations

Lp(a)=lipoprotein(a); CNSR-III=the third China National Stroke Registry; mRS=the modified Rankin scale; NIHSS=the National Institutes of Health Stroke Scale; TIA=transient ischemic attack; BMI=body mass index; TOAST=Trial of ORG 10172 in Acute Stroke Treatment; LAA=large artery atherosclerosis; SBP=systolic blood pressure; FPG=fasting plasma glucose; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; hsCRP=high-sensitivity C-reactive protein; Lp-PLA\textsubscript{2}=lipoprotein-associated phospholipase A\textsubscript{2}.

Declarations
Ethics approval and consent to participate

According to the principles mentioned in the Declaration of Helsinki, the ethics committees of Beijing Tiantan Hospital and all other recruited participating centers approved the study protocol. Written informed consent was obtained from all participants (or guardians of participants) in this study.

Consent for publication

All authors have approved this manuscript.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Y.J.W., and L.M.Z. contributed to the conception and design of the study. All authors (Y.J.W., L.M.Z., X.J., J.X., X.W.H., J.X., K.L., A.M.J., J.X.L., and X.M.) contributed to the acquisition and analysis of data. X.J., Y.J.W., and L.M.Z. contributed to drafting the text, preparing the tables and figures.

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Not applicable

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Tables

Due to technical limitations, table 1 to 4 is only available as a download in the Supplemental Files section.

Figures
Figure 1

(A)(B) Clinical outcomes at 3 months based on mRS, presented as percentage

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx
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