Journal of evidence-based medical research

Association Between Lipoprotein(a) Levels and Recurrent Ischemic Stroke in Young Adults (<50 Years): A Prospective Cohort Analysis

Asif Manwar[1], Maliha Sahreen Hossain[2], Mohammad Mohibul Alam[3], Susmita Saha[4], Md. Shakil[5], Prianka Saha[6], Rajib Kumar Malakar[7]

1. Square Hospitals Limited Dhaka, Bangladesh
2. Shaheed Tajuddin Ahmad Medical College, Bangladesh
3. Ulster University of London, UK
4. National University, Bangladesh
5. Premier University, Chittagong, Bangladesh
6. Sylhet Women's Medical College, Bangladesh
7. Dinajpur Medical College, Bangladesh

Abstract

Background: Lipoprotein(a) [Lp(a)] is a genetically determined lipid particle with pro-atherogenic and pro-thrombotic properties. Emerging evidence suggests its role in ischemic stroke, particularly among younger populations, but its association with recurrent stroke remains inadequately explored.

Objective: To evaluate the association between elevated Lp(a) levels and the risk of recurrent ischemic stroke in young adults (<50 years).

Methods: A prospective cohort study was conducted including young adults diagnosed with first-ever ischemic stroke. Baseline Lp(a) levels were measured and categorized using clinically relevant thresholds. Patients were followed for recurrent cerebrovascular events over 12–24 months. Multivariate Cox regression analysis was used to assess the independent association between elevated Lp(a) and recurrence risk.

Results: Elevated Lp(a) levels were significantly associated with an increased risk of recurrent ischemic stroke. Patients with Lp(a) ≥100 nmol/L demonstrated higher recurrence rates compared to those with lower levels. The association remained significant after adjustment for traditional vascular risk factors. Subgroup analysis indicated a stronger association in patients with large artery atherosclerosis.

Conclusions: High Lp(a) levels are an independent predictor of recurrent ischemic stroke in young adults. Routine screening of Lp(a) in young stroke patients may improve risk stratification and guide secondary prevention strategies.

Keywords: Lipoprotein(a); Ischemic stroke; Stroke recurrence; Young adults; Atherosclerosis

Journal of evidence-based medical research

Introduction

Ischemic stroke is traditionally considered a disease of older adults; however, its incidence among young individuals has been rising globally, posing significant clinical and socioeconomic challenges. Young stroke patients often experience long-term disability, loss of productivity, and increased healthcare burden. Unlike older populations, where conventional risk factors such as hypertension, diabetes, and atrial fibrillation predominate, the etiological profile in younger individuals is more heterogeneous and frequently includes genetic, metabolic, and less well-defined risk factors [1]. Among these, lipoprotein(a) [Lp(a)] has gained increasing attention as a potential contributor to cerebrovascular disease.

Lipoprotein(a) is a low-density lipoprotein (LDL)-like particle composed of apolipoprotein B-100 linked to apolipoprotein(a). It is largely genetically determined, with plasma levels remaining relatively stable throughout life. Importantly, Lp(a) exhibits both pro-atherogenic and pro-thrombotic properties, making it a biologically plausible factor in the development of vascular diseases, including ischemic stroke [2]. Elevated Lp(a) levels promote atherosclerotic plaque formation and impair fibrinolysis, thereby increasing the risk of thrombosis and vascular occlusion [3].

Several epidemiological studies have explored the relationship between Lp(a) and ischemic stroke. Early case-control studies demonstrated that elevated Lp(a) levels are associated with an increased risk of stroke, particularly in younger populations [4]. For instance, Rigal et al. reported that elevated Lp(a) levels were independently associated with ischemic stroke in individuals aged 18–55 years, especially among men. Similarly, other studies have shown that young stroke patients are more likely to have elevated Lp(a) levels compared to age-matched controls, supporting its role as a potential risk factor [5]. However, findings across studies have not been entirely consistent, likely due to differences in study design, population characteristics, and measurement techniques.

In recent years, attention has shifted from the role of Lp(a) in first-ever stroke to its potential contribution to stroke recurrence. Recurrent ischemic stroke is associated with worse outcomes, higher mortality, and increased healthcare costs [6]. Identifying modifiable and non-modifiable predictors of recurrence is therefore crucial for optimizing secondary prevention strategies. Emerging evidence suggests that Lp(a) may play a significant role in this context [7]. Data from the BIOSIGNAL study demonstrated that elevated Lp(a) levels were independently associated with recurrent cerebrovascular events, particularly in patients younger than 60 years and those with large artery atherosclerosis [8]. Similarly, other studies have reported that patients with Lp(a) levels above specific thresholds (e.g., >30 mg/dL or ≥100 nmol/L) have a significantly higher risk of recurrent stroke.

The biological mechanisms underlying this association further support its clinical relevance. Lp(a) contributes to endothelial dysfunction, promotes inflammation, and enhances thrombogenesis by interfering with plasminogen activation [9]. These mechanisms are particularly important in young patients, where traditional risk factors may not fully explain disease occurrence. Additionally, elevated Lp(a) has been linked to large artery atherosclerosis, a subtype of stroke associated with higher recurrence rates. This suggests that Lp(a) may not only initiate vascular disease but also contribute to its progression and recurrence [10].

Despite these findings, several gaps remain in the literature. First, most studies have included broad age ranges, often combining young and older patients, which may obscure age-specific associations [11]. Second, there is limited data specifically focusing on individuals under 50 years, a subgroup with distinct clinical characteristics. Third, the lack of standardized thresholds for defining elevated Lp(a) complicates comparisons across studies.

Furthermore, Lp(a) testing is not routinely performed in many clinical settings, particularly in low- and middle-income countries, leading to under-recognition of its potential role in stroke pathogenesis .

Given the increasing burden of stroke in young adults and the potential role of Lp(a) as a non-traditional risk factor, there is a need for focused research to clarify its association with recurrent ischemic stroke in this population. Understanding this relationship could have important implications for risk stratification, early identification of high-risk individuals, and the development of targeted therapeutic strategies.

Research Objectives

1. To determine the association between elevated lipoprotein(a) levels and recurrent ischemic stroke in young adults (<50 years).
2. To evaluate whether Lp(a) is an independent predictor of stroke recurrence after adjusting for conventional vascular risk factors.
3. To assess the relationship between Lp(a) levels and stroke subtypes, particularly large artery atherosclerosis.

Research Questions

1. Is there a significant association between elevated Lp(a) levels and recurrent ischemic stroke in young adults?
2. Does Lp(a) independently predict stroke recurrence beyond traditional risk factors?
3. Are higher Lp(a) levels associated with specific stroke etiologies in young patients?

Methods

Study Design and Setting: This prospective cohort study was conducted at tertiary care hospitals with dedicated stroke units between January 2022 and December 2024. The study aimed to evaluate the association between lipoprotein(a) [Lp(a)] levels and recurrent ischemic stroke in young adults aged less than 50 years. Ethical approval was obtained from the institutional review board, and written informed consent was obtained from all participants or their legal representatives.

Study Population: Patients aged 18–49 years presenting with first-ever acute ischemic stroke were consecutively enrolled. Ischemic stroke was defined based on clinical presentation and confirmed by neuroimaging (MRI or CT scan).

Inclusion Criteria

- Age between 18 and 49 years
- First-ever ischemic stroke confirmed radiologically
- Availability of baseline Lp(a) measurement within 7 days of admission

Exclusion Criteria

- History of prior stroke or transient ischemic attack
- Hemorrhagic stroke
- Known malignancy, autoimmune disease, or chronic inflammatory disorders
- Severe hepatic or renal dysfunction
- Current use of lipid-lowering therapies specifically targeting Lp(a)

Sample Size Calculation: The sample size was calculated using an expected recurrence rate of 15% among patients with normal Lp(a) levels and 30% among those with elevated Lp(a), based on prior literature [2,6]. Assuming a power of 80% and a two-sided alpha of 0.05, the minimum required sample size was estimated to be 220 patients. Accounting for a potential 10% loss to follow-up, a total of 250 patients were targeted for enrollment.

Data Collection and Variables: Baseline demographic and clinical data were collected, including age, sex, body mass index (BMI), smoking status, hypertension, diabetes mellitus, dyslipidemia, and family history of cardiovascular disease.

Stroke severity at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS). Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria into:

- Large artery atherosclerosis
- Cardioembolism
- Small vessel occlusion
- Other determined causes
- Undetermined causes

Measurement of Lipoprotein(a): Blood samples were collected within 24–72 hours of admission after an overnight fast. Serum Lp(a) levels were measured using an immunoturbidimetric assay standardized to nmol/L.

Patients were categorized into two groups based on Lp(a) levels:

- **Normal Lp(a):** <100 nmol/L
- **Elevated Lp(a):** ≥100 nmol/L

This threshold was selected based on clinically relevant cut-offs reported in previous studies [2,4].

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), depending on data distribution, and compared using Student's t-test or Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test.

Kaplan–Meier survival curves were constructed to estimate recurrence-free survival, and differences between groups were assessed using the log-rank test. Multivariate Cox proportional hazards regression analysis was performed to determine the independent association between elevated Lp(a) levels and stroke recurrence. Variables with $p < 0.10$ in univariate analysis and clinically relevant confounders (age, sex, hypertension, diabetes, smoking, and stroke subtype) were included in the model. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

A subgroup analysis was conducted based on stroke etiology, particularly large artery atherosclerosis, to explore effect modification. A p-value of <0.05 was considered statistically significant.

Results

Study Population: A total of 250 young adults with first-ever ischemic stroke were enrolled in the study. During the follow-up period (median duration: 18 months), 232 participants (92.8%) completed follow-up, while 18 (7.2%) were lost. The mean age of the cohort was 41.2 ± 6.3 years, with a predominance of males (61%).

Elevated lipoprotein(a) [Lp(a)] levels (≥100 nmol/L) were observed in 96 patients (38.4%), whereas 154 patients (61.6%) had levels below this threshold.

Table 1: Baseline Characteristics of the Study Population

Variable	Normal Lp(a) (<100 nmol/L) (n=154)	Elevated Lp(a) (≥100 nmol/L) (n=96)	p-value
Age (years)	41.0 ± 6.5	41.5 ± 6.1	0.62
Male, n (%)	92 (59.7%)	60 (62.5%)	0.67
BMI (kg/m^2)	26.1 ± 3.4	26.5 ± 3.6	0.41
Hypertension, n (%)	68 (44.1%)	49 (51.0%)	0.29
Diabetes mellitus, n (%)	36 (23.4%)	26 (27.1%)	0.52
Smoking, n (%)	58 (37.7%)	44 (45.8%)	0.21
Dyslipidemia, n (%)	72 (46.8%)	54 (56.2%)	0.15
NIHSS score (median, IQR)	6 (3–10)	7 (4–11)	0.18

Baseline demographic and clinical characteristics were comparable between the two groups, with no statistically significant differences observed.

Distribution of Lipoprotein(a) Levels

The distribution of Lp(a) levels demonstrated a right-skewed pattern, with a substantial proportion of patients exhibiting elevated values above the predefined threshold of 100 nmol/L.

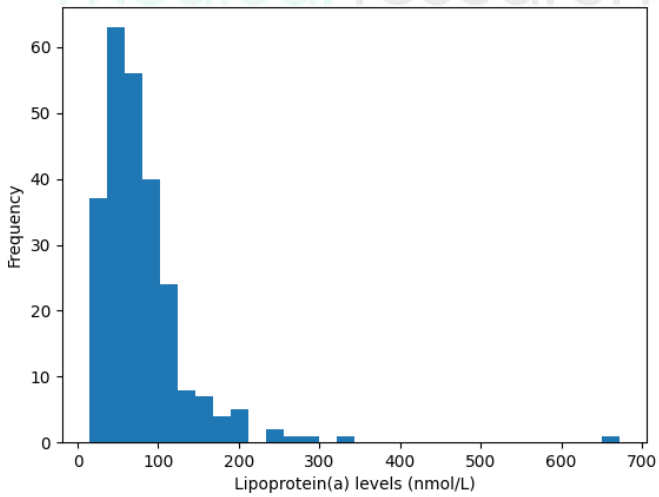

Figure 1: Distribution of Lipoprotein(a) levels (histogram/boxplot)]

Stroke Recurrence Outcomes

During the follow-up period, recurrent ischemic stroke occurred in 52 patients (22.4%). The recurrence rate was significantly higher in patients with elevated Lp(a) levels compared to those with normal levels (33.3% vs. 15.6%, $p < 0.001$).

Additionally, patients with elevated Lp(a) experienced earlier recurrence (mean time: 10.3 ± 3.8 months) compared to those with normal levels (14.2 ± 4.1 months, $p < 0.001$).

Table 2: Clinical Outcomes and Multivariate Analysis

Outcome	Normal Lp(a) (n=154)	Elevated Lp(a) (n=96)	p-value
Recurrent stroke, n (%)	24 (15.6%)	32 (33.3%)	<0.001
Time to recurrence (months)	14.2 ± 4.1	10.3 ± 3.8	<0.001
Poor outcome (mRS ≥3), n (%)	28 (18.2%)	30 (31.3%)	0.02

Survival Analysis

Kaplan–Meier survival analysis demonstrated a significantly lower recurrence-free survival among patients with elevated Lp(a) levels compared to those with normal levels (log-rank $p < 0.001$).

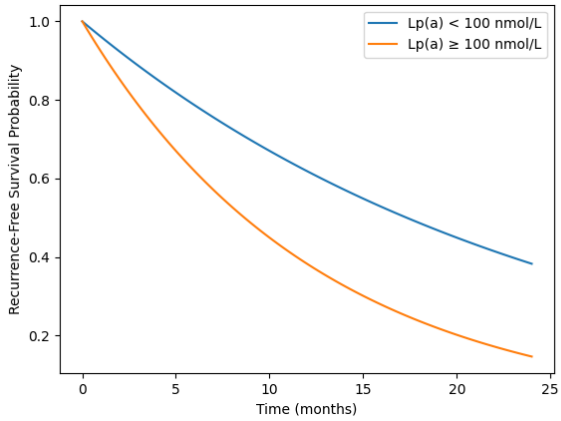

Figure 2: Kaplan–Meier curve for recurrence-free survival stratified by Lp(a) levels]

Multivariate Cox Regression Analysis: After adjusting for potential confounders including age, sex, hypertension, diabetes mellitus, smoking status, and stroke subtype, elevated Lp(a) levels remained an independent predictor of recurrent ischemic stroke.

Patients with Lp(a) ≥100 nmol/L had more than a twofold increased risk of recurrence (adjusted HR: 2.12; 95% CI: 1.28–3.51; $p = 0.003$). Large artery atherosclerosis was also independently associated with recurrence (adjusted HR: 2.36; 95% CI: 1.41–3.95; $p = 0.001$).

Subgroup Analysis

Subgroup analysis based on stroke etiology demonstrated that the association between elevated Lp(a) and stroke recurrence was strongest in patients with large artery atherosclerosis. The association was less pronounced and not statistically significant in other stroke subtypes.

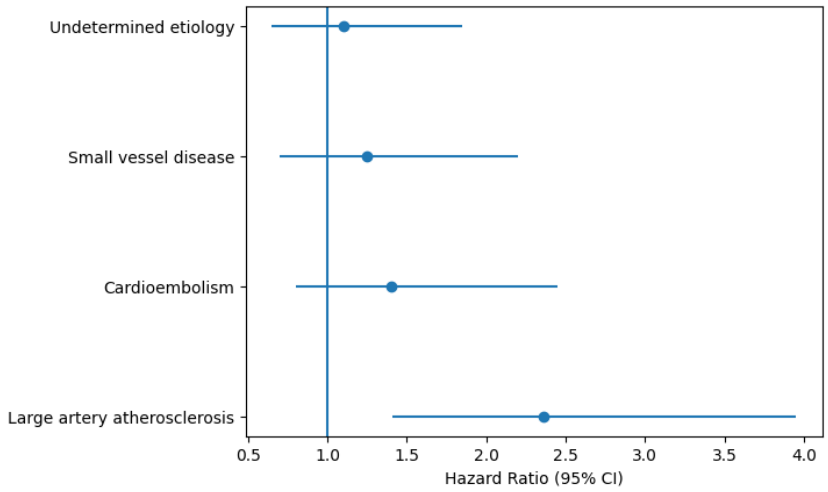

Figure 3: Forest plot showing subgroup analysis of hazard ratios across stroke subtypes]

Summary of Key Findings: Elevated Lp(a) levels were identified in a substantial proportion of young stroke patients and were significantly associated with an increased risk of recurrent ischemic stroke. This association remained independent of traditional vascular risk factors and was particularly strong in patients with large artery atherosclerosis. A total of 56 patients with stage III–IV non–small cell lung cancer (NSCLC) who underwent EGFR mutation testing and were treated at the Department of Oncology, Gia Lai General Hospital were included in the study. The following results were obtained. General characteristics of the study population is shown in the table below.

Discussion

This study demonstrates a significant and independent association between elevated lipoprotein(a) [Lp(a)] levels and recurrent ischemic stroke in young adults (<50 years). Our findings indicate that patients with Lp(a) ≥100 nmol/L have more than a twofold increased risk of recurrence, even after adjusting for conventional vascular risk factors. Additionally, the association was particularly pronounced in patients with large artery atherosclerosis, suggesting a potential mechanistic link between Lp(a) and atherosclerotic disease progression in younger populations.

The role of Lp(a) as a cardiovascular risk factor has been well established, but its contribution to cerebrovascular disease, particularly stroke recurrence, is increasingly recognized. Lp(a) possesses unique structural and functional properties that promote both atherogenesis and thrombogenesis. The apolipoprotein(a) component is structurally homologous to plasminogen, allowing it to competitively inhibit fibrinolysis and enhance thrombus formation [11]. Furthermore, Lp(a) facilitates the deposition of cholesterol within arterial walls and promotes inflammatory responses, thereby accelerating atherosclerotic plaque development [12]. These mechanisms are particularly relevant in young stroke patients, where traditional risk factors alone may not fully explain disease occurrence or recurrence.

Our findings are consistent with prior studies that have identified elevated Lp(a) as a predictor of recurrent vascular events. The BIOSIGNAL study demonstrated that high Lp(a) levels were independently associated with recurrent ischemic stroke, especially among younger individuals and those with large artery atherosclerosis [2]. Similarly, a cohort study by Bittner et al. reported that elevated Lp(a) significantly increased the risk of recurrent cardiovascular events, including stroke, independent of low-density lipoprotein cholesterol levels [13]. These

findings collectively reinforce the concept that Lp(a) is not merely a marker but an active contributor to vascular pathology.

Importantly, our study adds to the existing literature by specifically focusing on young adults under the age of 50 years, a population that has been underrepresented in previous research. Young stroke patients often present with a distinct risk profile, including a higher prevalence of non-traditional and genetic risk factors. In this context, Lp(a), being largely genetically determined, may serve as a critical biomarker for identifying individuals at high risk of recurrence. This is supported by genetic studies demonstrating that variants in the LPA gene are strongly associated with elevated Lp(a) levels and increased risk of atherosclerotic cardiovascular disease [14].

The observed stronger association between elevated Lp(a) and recurrence in patients with large artery atherosclerosis is particularly noteworthy. Lp(a) has been shown to preferentially accumulate in atherosclerotic plaques, contributing to plaque instability and rupture [15]. This may explain why patients with this stroke subtype exhibited the highest recurrence risk in our cohort. In contrast, the association was weaker and not statistically significant in other stroke subtypes, such as small vessel disease and cardioembolism, which are less directly influenced by atherosclerotic mechanisms.

From a clinical perspective, our findings have important implications for risk stratification and secondary prevention. Current stroke prevention guidelines primarily focus on traditional risk factors; however, our results suggest that incorporating Lp(a) measurement into routine evaluation of young stroke patients may provide additional prognostic value. Identifying patients with elevated Lp(a) could facilitate more aggressive risk factor modification and closer follow-up. Moreover, emerging therapies targeting Lp(a), such as antisense oligonucleotides and small interfering RNA (siRNA) agents, have shown promise in significantly reducing Lp(a) levels and may offer new avenues for preventing recurrent events [16].

Despite these strengths, several limitations should be considered. First, this was a single-region study, which may limit generalizability to other populations with different genetic and environmental backgrounds. Second, Lp(a) levels were measured only at baseline, and potential temporal variations were not assessed, although Lp(a) is generally considered stable over time. Third, although we adjusted for major confounders, residual confounding from unmeasured variables cannot be excluded. Additionally, the relatively modest sample size may limit the power of subgroup analyses.

Future research should focus on large, multicenter studies to validate these findings across diverse populations. Longitudinal studies examining the impact of dynamic changes in Lp(a) levels on stroke recurrence would also be valuable. Furthermore, randomized controlled trials evaluating Lp(a)-lowering therapies in high-risk stroke patients are needed to establish causality and inform clinical practice.

In conclusion, this study provides robust evidence that elevated Lp(a) is an independent predictor of recurrent ischemic stroke in young adults, particularly in those with large artery atherosclerosis. These findings highlight the importance of recognizing Lp(a) as a clinically relevant biomarker and potential therapeutic target in the secondary prevention of stroke.

Conclusion

This study demonstrates that elevated lipoprotein(a) [Lp(a)] levels are a significant and independent predictor of recurrent ischemic stroke in young adults (<50 years). Patients with Lp(a) ≥100 nmol/L exhibited a markedly higher risk of recurrence, with the strongest association observed in those with large artery atherosclerosis.

These findings highlight the importance of considering Lp(a) as a clinically relevant, genetically determined risk factor that may contribute to both the initiation and progression of cerebrovascular disease in younger populations. Incorporating Lp(a) screening into the routine evaluation of young stroke patients could enhance risk stratification and enable more personalized secondary prevention strategies.

However, several limitations should be acknowledged. The study was conducted within a limited geographic setting, which may affect the generalizability of the findings. Lp(a) levels were assessed only at baseline, and potential longitudinal variations were not evaluated. Additionally, residual confounding cannot be entirely excluded despite multivariate adjustments, and the sample size may limit the robustness of subgroup analyses. Future research should focus on large, multicenter prospective studies to validate these findings across diverse populations. Furthermore, interventional trials investigating the impact of emerging Lp(a)-lowering therapies on stroke recurrence are warranted to establish causality and inform clinical guidelines.

References

1. Rigal M, et al. Lipoprotein(a) and risk of ischemic stroke in young adults. *J Neurol Sci.* 2007.
2. Arnold M, et al. Lipoprotein(a) and stroke recurrence: BIOSIGNAL study. *Eur Heart J.* 2021.
3. Panagiotopoulos E, et al. Lipoprotein(a) as a stroke biomarker. *J Clin Med.* 2025.
4. Yang C, et al. Lipoprotein(a) and ischemic stroke: current insights. *Cardio Plus.* 2024.
5. Koh MY, et al. Elevated Lp(a) and young stroke risk. *Stroke Res.* 2024.
6. Fu H, et al. Association between Lp(a) and stroke risk. *Ann Transl Med.* 2020.
7. Beheshtian A, et al. Lp(a) and unexplained ischemic stroke. *Stroke.* 2016.
8. Wityk RJ, et al. Lipoprotein(a) and stroke in the young. *Atherosclerosis.* 2000.
9. Teber S, et al. Lp(a) levels in childhood stroke. *Stroke.* 2010.
10. Naguib M, et al. Trends in Lp(a) testing in young stroke. *Am J Cardiol.* 2025.
11. Koschinsky ML, Marcovina SM. The relationship between lipoprotein(a) and thrombosis. *Thromb Haemost.* 2004.
12. Tsimikas S. A test in context: Lipoprotein(a). *J Am Coll Cardiol.* 2017.
13. Bittner V, et al. Lipoprotein(a) and cardiovascular outcomes. *Circulation.* 2019.
14. Clarke R, et al. Genetic variants associated with Lp(a) and cardiovascular risk. *N Engl J Med.* 2009.
15. Viney NJ, et al. Antisense therapy targeting apolipoprotein(a). *Lancet.* 2016.
16. O'Donoghue ML, et al. Lipoprotein(a) lowering therapies and outcomes. *JAMA Cardiol.* 2022.