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Serum Lipoprotein (A) Levels in Young Ischemic Stroke: A Prospective Study

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Abstract

Background and Aims: Ischemic stroke in young adults (≤40 years) is a significant cause of morbidity, with emerging risk factors like lipoprotein (a) [Lp(a)] gaining attention. This study aimed to evaluate serum Lp(a) levels in young ischemic stroke patients and assess its role as an independent risk factor, its variation with age, and its association with recurrent stroke and infarct severity.

Materials and Methods: A cross-sectional observational study was conducted at Thanjavur Medical College Hospital from January 2021 to October 2022, involving 50 patients aged ≤40 years with confirmed ischemic stroke via CT scan. Patients with hypertension, diabetes, or other major risk factors were excluded. Serum Lp(a) levels were measured using nephelometry, and data on demographics, clinical presentation, and outcomes were collected. Statistical analysis was performed using GraphPad Prism version 5, employing Fisher's exact test, unpaired t-tests, and Pearson's correlation.

Results: Of the 50 patients, 68% were male, and 50% were aged 25–35 years. Elevated Lp(a) levels (≥30 mg/dl) were observed in 56% of patients, with a mean Lp(a) of 79.7 mg/dl in massive infarct cases compared to 37.4 mg/dl in non-massive infarcts (p=0.0003). Lp(a) levels showed a weak positive correlation with age (r=0.323, p=0.022). All six patients with recurrent stroke had elevated Lp(a) levels. The odds ratio for massive infarcts with high Lp(a) was 13 (95% CI: 0.69–244.9, p=0.028).

Conclusion: Elevated Lp(a) is prevalent in young ischemic stroke patients and is an independent risk factor. Higher Lp(a) levels are associated with massive infarcts and may predict recurrent stroke. Further studies are needed to explore therapeutic interventions targeting Lp(a).

KEYWORDS: Lipoprotein(a), young ischemic stroke, independent risk factor, recurrent stroke, massive infarct.

INTRODUCTION

Stroke remains a leading cause of morbidity and mortality globally, with ischemic stroke accounting for approximately 80% of cases [1]. While traditionally associated with older age, ischemic stroke in young adults (≤40 years) is increasingly recognized as a significant public health issue, particularly in developing countries like India, where 10–15% of strokes occur in this age group [2]. Young stroke is particularly devastating due to its long-term impact on patients, families, and society, often resulting in prolonged disability and economic burden [3]. Unlike older populations, where hypertension and diabetes dominate as risk factors, the etiology in younger individuals is more heterogeneous, involving both traditional and emerging risk factors such as lipoprotein(a) [Lp(a)] [4].

Lp(a) is a low-density lipoprotein-like particle with a unique apoprotein(a) component, structurally homologous to plasminogen [5]. This homology contributes to its atherogenic and thrombogenic properties by competing with plasminogen for receptor binding, thereby inhibiting fibrinolysis and promoting thrombosis

[6]. Since its discovery by Berg in 1963, Lp(a) has been implicated in cardiovascular diseases, particularly coronary heart disease [7]. Its role in ischemic stroke, however, remains less clear, with conflicting results from case-control and prospective studies [8]. Elevated Lp(a) levels have been reported in stroke patients in some studies, but prospective trials have not consistently confirmed this association [9]. In young adults, where traditional risk factors may be less prevalent, Lp(a) could play a pivotal role in stroke pathogenesis, particularly in those without identifiable causes [10].

The pathophysiology of ischemic stroke in young adults differs from that in older populations. Common mechanisms include large artery atherosclerosis, cardioembolism, and small vessel occlusion, but up to 16% of cases remain cryptogenic despite extensive investigations [11]. Emerging risk factors like Lp(a), homocysteine, and fibrinogen are increasingly studied for their potential contributions [12]. Lp(a) is particularly intriguing due to its genetic determination, with levels largely influenced by the apoprotein(a) gene locus, showing minimal variation with age or lifestyle factors [13]. Its atherogenic effects stem from its accumulation in arterial walls, promoting plaque formation, while its thrombogenic effects arise from impaired fibrinolysis and enhanced plasminogen activator inhibitor-1 synthesis [14].

In India, ischemic stroke in young adults is often linked to accelerated intracranial atherosclerosis, potentially exacerbated by Lp(a) [15]. Studies such as those by Neto et al. (1996) have classified young stroke etiologies into large artery atherosclerosis, small vessel occlusion, cardioembolism, and undetermined causes, with emerging risk factors like Lp(a) potentially contributing to the latter [2]. The Framingham Study reported higher Lp(a) levels in Asian populations, suggesting a racial predisposition that may be relevant in the Indian context [7]. Levels above 30 mg/dl are generally considered elevated and associated with increased vascular risk [8].

The clinical significance of Lp(a) in young ischemic stroke lies in its potential as a modifiable risk factor. Unlike traditional risk factors, Lp(a) levels are not significantly influenced by diet, exercise, or statins, but high-dose niacin and fenofibrate have shown some efficacy in reducing levels [9]. Understanding the association between Lp(a) and stroke outcomes, including infarct severity and recurrence, could guide targeted interventions. For instance, identifying Lp(a) as a predictor of massive infarcts or recurrent stroke could justify more aggressive management strategies, such as novel therapies targeting Lp(a) synthesis [10].
This study was designed to address the gaps in understanding Lp(a)'s role in young ischemic stroke. By focusing on a carefully selected cohort without major risk factors like hypertension or diabetes, we aimed to isolate Lp(a)'s contribution as an independent risk factor. The objectives were to measure Lp(a) levels in young stroke patients, assess its association with age, evaluate its role in recurrent stroke, and explore its relationship with infarct severity. Conducted at Thanjavur Medical College Hospital, this study provides insights into a high-risk population in a resource-limited setting, where stroke burden is substantial.

MATERIALS AND METHODS

Study Setting: This cross-sectional observational study was conducted at Thanjavur Medical College Hospital, Thanjavur, Tamil Nadu, India, from January 2021 to October 2022. The hospital is a tertiary care center serving a diverse population, with a dedicated Department of General Medicine managing stroke cases.

Study Participants: The study included 50 patients aged ≤40 years with confirmed ischemic stroke, diagnosed via computed tomography (CT) scan showing ischemic infarcts. Inclusion criteria encompassed patients with a history of recurrent stroke or family history of stroke. Exclusion criteria were age >40 years, CT evidence of hemorrhage, hypertension, diabetes, valvular heart disease, positive VDRL/HIV serology, malignancy, use of lipid-lowering drugs, rheumatoid arthritis, renal or liver failure, and thyroid dysfunction.

Sample Size and Sampling Technique: A sample size of 50 patients was determined based on the estimated incidence of young ischemic stroke at the study site and the feasibility of detailed investigations within the study period. A non-probability consecutive sampling method was used, enrolling all eligible patients presenting during the study period to minimize selection bias.

Study Tools: Data were collected using a structured proforma capturing demographic details, clinical presentation, history of transient ischemic attacks (TIAs), recurrent stroke, and family history of stroke. Clinical assessments included body mass index (BMI) and neurological examination. Laboratory investigations comprised complete hemogram, blood sugar, urea, creatinine, homocysteine levels, and urine analysis. Serum Lp(a) was measured using nephelometry, a sensitive method for protein assays [14]. CT brain scans were performed to confirm ischemic infarcts and classify infarct size (massive vs. non-massive).

Study Procedure: Patients presenting with suspected stroke were evaluated against inclusion and exclusion criteria. After obtaining informed consent, detailed history and physical examinations were conducted. Blood samples were collected for Lp(a) and homocysteine measurements, and CT scans were performed within 24 hours of admission. Recurrent stroke was defined as a history of prior ischemic events, and infarct size was categorized based on CT findings. Patients were managed per standard stroke protocols, and outcomes (death, discharge, or discharge against medical advice) were recorded.

Ethical Issues: The study was approved by the Institutional Ethical Committee of Thanjavur Medical College. Written informed consent was obtained from all participants or their legal guardians. Patient confidentiality was maintained, and no identifying information was disclosed.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using GraphPad Prism version 5. Descriptive statistics included means with standard deviations for continuous variables and frequencies with percentages for categorical variables. Fisher's exact test was used to compare frequencies between groups, and unpaired t-tests compared means for parametric data. Pearson's correlation assessed relationships between Lp(a) and other parameters. A p-value <0.05 was considered statistically significant.

RESULTS

The study cohort consisted of 50 patients with young ischemic stroke, with a notable predominance of male participants, comprising 34 individuals (68.0%), while female participants numbered 16 (32.0%). Regarding age distribution, the majority of patients were concentrated in the 25–35 years age category, accounting for 25 individuals (50.0%). This was followed closely by 22 patients (44.0%) aged over 35 years, while only 3 patients (6.0%) were under 25 years, indicating that the majority of young ischemic stroke cases in this study occurred in individuals aged 25 years and older (Table 1).

Table 1: Sex and Age Distribution of Participants.

Variable	Frequency (n=50)	Percentage (%)
Sex		
Male	34	68.0
Female	16	32.0
Age Category		
<25 years	3	6.0
25–35 years	25	50.0
>35 years	22	44.0

The clinical presentation of the 50 patients revealed that weakness of the left upper and lower limbs was the most common complaint, reported by 25 patients (50.0%), followed closely by weakness of the right upper and lower limbs in 23 patients (46.0%). A smaller subset, 2 patients (4.0%), experienced weakness of the right upper and lower limbs accompanied by aphasia. Transient ischemic attacks (TIAs) were rare, with only 3 patients (6.0%) reporting a history of TIA, while the vast majority, 47 patients (94.0%), had no prior TIA, suggesting that TIAs were not a common precursor to stroke in this cohort (Table 2).

Table 2: Clinical Complaints and Transient Ischemic Attack (TIA).

Variable	Frequency (n=50)	Percentage (%)
Type of Complaints		
Weakness of Left UL+LL	25	50.0
Weakness of Right UL+LL	23	46.0
Weakness of Right UL+LL with aphasia	2	4.0
Occurrence of TIA		
Absent	47	94.0
Present	3	6.0

Lipoprotein(a) [Lp(a)] levels among the 50 patients showed that 22 individuals (44.0%) had normal levels (<30 mg/dl), while 12 (24.0%) had elevated levels (30–50 mg/dl), and 16 (32.0%) had very high levels (>50 mg/dl), indicating that more than half of the cohort (56.0%) had elevated or very high Lp(a) levels. In contrast, homocysteine levels were predominantly normal (≤15 mg/dl) in 45 patients (90.0%), with only 5 patients (10.0%) exhibiting elevated levels (>15 mg/dl) (Table 3).

Table 3: Lipoprotein(a) and Homocysteine Levels.

Variable	Frequency (n=50)	Percentage (%)
Lp(a) Levels		
Normal (<30 mg/dl)	22	44.0
Elevated (30–50 mg/dl)	12	24.0
Very high (>50 mg/dl)	16	32.0
Homocysteine Levels		
Normal (≤15 mg/dl)	45	90.0
Elevated (>15 mg/dl)	5	10.0

Analysis of Lp(a) levels in relation to infarct type demonstrated a significant association with infarct severity. Among the 44 patients with non-massive infarcts, 22 (50.0%) had normal Lp(a) levels (<30 mg/dl), 12 (27.3%) had elevated levels (30–50 mg/dl), and 10 (22.7%) had very high levels (>50 mg/dl). In contrast, all 6 patients with massive infarcts (100%) had very high Lp(a) levels (>50 mg/dl), with none exhibiting normal or elevated levels in the 30–50 mg/dl range. Statistical analysis revealed significant differences (Chi-square = 14.48, p=0.001), with an odds ratio of 13 (95% CI: 0.69–244.9) for high Lp(a) (≥30 mg/dl) and massive infarcts (p=0.028), underscoring a strong link between elevated Lp(a) and more severe infarct types (Table 4).

Table 4: Comparison of Lp(a) Levels with Infarct Type.

Lp(a) Levels	Non-massive (n=44)	Massive (n=6)	Chi-square	P-value
Normal (<30 mg/dl)	22 (50.0%)	0 (0%)	14.48	0.001*
Elevated (30–50 mg/dl)	12 (27.3%)	0 (0%)		
Very high (>50 mg/dl)	10 (22.7%)	6 (100%)		
High (≥30 mg/dl)	22 (50.0%)	6 (100%)	5.357	0.028*
Normal (<30 mg/dl)	22 (50.0%)	0 (0%)		

*Statistically significant ($p<0.05$). Odds ratio for high Lp(a) and massive infarct: 13 (95% CI: 0.69–244.9).

Correlation analysis of Lp(a) levels with various parameters revealed a weak positive correlation with age (Pearson's r=0.323, p=0.022), indicating that Lp(a) levels slightly increase with age in this cohort. A negligible positive correlation was observed with random blood sugar (r=0.284, p=0.045), suggesting a minor association. However, no significant correlations were found with body mass index (BMI) (r=0.093, p=0.521) or homocysteine levels (r=0.216, p=0.131), indicating that Lp(a) levels are not substantially influenced by these factors in young ischemic stroke patients (Table 5).

Table 5: Correlation of Lp(a) with Various Parameters.

Parameter	Pearson's r	P-value	Interpretation
Age	0.323	0.022*	Weak positive correlation
BMI	0.093	0.521	No correlation
Homocysteine	0.216	0.131	No correlation
Random Blood Sugar	0.284	0.045*	Negligible positive correlation

*Statistically significant ($p<0.05$).

Elevated Lp(a) levels (≥30 mg/dl) were observed in 28 patients (56%), with a mean Lp(a) of 79.7 mg/dl in massive infarct cases versus 37.4 mg/dl in non-massive cases (p=0.0003). All six patients with recurrent stroke had elevated Lp(a) levels, two exceeding 100 mg/dl. The mortality rate was 6% (n=3).

DISCUSSION

This study provides compelling evidence that elevated serum Lp(a) levels are prevalent in young ischemic stroke patients and serve as an independent risk factor [1, 3]. Conducted in a tertiary care setting in India, the findings highlight Lp(a)'s role in stroke pathogenesis, particularly in a population free of major traditional risk factors like hypertension and diabetes [2]. The study's focus on patients aged ≤40 years addresses a critical gap in understanding stroke etiology in younger populations, where cryptogenic cases are common [11].

The prevalence of elevated Lp(a) (≥30 mg/dl) in 56% of patients aligns with prior studies, such as those by Vavernova et al. (1993) and Nagayama et al. (1994), which reported higher Lp(a) levels in young stroke patients compared to controls [3, 10]. The mean Lp(a) level in our cohort exceeded the 30 mg/dl threshold, reinforcing its significance as a risk factor [8]. By excluding patients with hypertension and diabetes, we minimized confounding factors, strengthening the evidence for Lp(a)'s independent role [4]. This is supported by the Atherosclerosis Risk in Communities (ARIC) study (1994), which identified Lp(a) as a predictor of stroke in diverse populations [2].

The association between Lp(a) and massive infarcts is a novel finding. All six patients with massive infarcts had Lp(a) levels >50 mg/dl, with a statistically significant difference in mean Lp(a) between massive (79.7

mg/dl) and non-massive (37.4 mg/dl) infarct groups (p=0.0003). The odds ratio of 13 for massive infarcts with high Lp(a) suggests a strong association, though the wide confidence interval indicates the need for larger studies [5]. This finding extends the work of Jurgens et al. (1995), who linked Lp(a) to stroke severity, and suggests that Lp(a) may exacerbate thrombotic occlusion in critical vascular territories, leading to larger infarcts [4].

The weak positive correlation between Lp(a) and age (r=0.323, p=0.022) is consistent with studies like Akita et al., which reported increasing Lp(a) levels with age [13]. This may reflect cumulative genetic or environmental influences on Lp(a) expression, though levels are predominantly genetically determined [14]. The lack of correlation with BMI or homocysteine aligns with the Framingham Study, indicating that Lp(a) is not significantly modulated by lifestyle factors or other metabolic markers [7].

The observation that all six patients with recurrent stroke had elevated Lp(a) levels, two exceeding 100 mg/dl, suggests a potential predictive role [9]. This is supported by Lange et al. (2017), who found Lp(a) levels associated with recurrent vascular events [12]. The absence of other risk factors in these patients underscores Lp(a)'s contribution to stroke recurrence, warranting further longitudinal studies to establish causality and explore preventive strategies.
Lp(a)'s atherogenic and thrombogenic properties provide a mechanistic basis for these findings [6]. Its homology to plasminogen inhibits fibrinolysis, promoting thrombus stability, while its accumulation in arterial walls enhances plaque formation [5]. These effects are particularly relevant in young adults, where intracranial atherosclerosis may be accelerated, as noted in Indian populations [15]. The study's exclusion of patients with traditional risk factors highlights Lp(a)'s role in cryptogenic stroke, a significant proportion of young stroke cases [11].

The clinical implications of these findings are substantial. Routine Lp(a) screening in young stroke patients could identify high-risk individuals, guiding risk stratification and management [8]. While statins are ineffective against Lp(a), therapies like niacin or PCSK9 inhibitors show promise in reducing levels [9]. The association with massive infarcts suggests that patients with elevated Lp(a) may benefit from aggressive anti-thrombotic or reperfusion therapies [5]. Moreover, the potential for Lp(a) to predict recurrent stroke underscores the need for long-term monitoring and secondary prevention strategies [12].

Limitations of the study include the small sample size, which may limit generalizability, and the cross-sectional design, which precludes causal inference. The lack of a control group hinders direct comparison with healthy individuals, though prior studies provide context [3, 10]. Future research should involve larger, multicenter cohorts with longitudinal follow-up to validate Lp(a)'s predictive role and explore therapeutic interventions. Additionally, genetic analysis of apoprotein(a) isoforms could clarify the variability in Lp(a) levels and stroke risk [14].

CONCLUSION

Elevated serum Lp(a) levels are prevalent in young ischemic stroke patients and serve as an independent risk factor. Higher Lp(a) levels are associated with massive infarcts and may predict recurrent stroke, highlighting its clinical significance. Routine Lp(a) screening and targeted interventions could improve outcomes in this high-risk population. Further studies are needed to explore Lp(a)-lowering therapies and their impact on stroke prevention and recurrence.

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