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Lipid Tetrad Index as a predictor of Stroke severity and Outcomes in Patients with Acute Ischemic Stroke: A Hospital based Prospective study

Dr. Navin Kumar S[1], Dr. Mayilanathi K[2], Dr. Mohan Rao VR[3]

[1]Junior Resident, Department of General Medicine, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Tamil Nadu, India

[2]Professor, Department of General Medicine, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Tamil Nadu, India

[3]Professor, Department of General Medicine, Chettinad Hospital and Research Institute, Chettinad Academy of Research

[*]**Corresponding author:**

Dr. Navin Kumar S

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ABSTRACT

Background: Dyslipidaemia plays a crucial role in the pathophysiology of acute ischemic stroke, influencing both stroke severity and patient outcomes. The lipid tetrad index (LTI) has emerged as potential biomarkers for assessing stroke prognosis.

Objectives: To evaluate the association between LTI, stroke severity and outcomes among acute ischemic stroke patients presenting to a tertiary healthcare facility.

Methods: This was a hospital based, prospective study conducted in the Department of General Medicine, Chettinad Hospital And Research Institute, for a duration of 2 months between March and May 2025.

Results: The study included 40 acute ischemic stroke patients with a mean age of 62.5 years, of whom 90% were older than 40 years. Males constituted 65% of the population. Among the participants, 45% had a history of smoking, 35% consumed alcohol, 70% had hypertension, and 55% had diabetes. Laboratory investigations revealed mean values of lipoprotein A (38.4 mg/dL), total cholesterol (192.5 mg/dL), serum triglycerides (146.7 mg/dL), HDL cholesterol (42.3 mg/dL), and LDL cholesterol (118.6 mg/dL). The mean LTI was 15,200. Stroke severity, assessed by NIHSS, had a mean score of 9.8, while functional outcomes measured by mRS averaged 3.2, indicating moderate to severe disability. Correlation analysis showed that LTI had the strongest positive association with stroke severity (NIHSS: rp=0.506, p=0.002) and functional outcomes (mRS: rp=0.478, p=0.004). Lipoprotein A was also significantly associated with both NIHSS and mRS. ROC analysis identified LTI as a strong predictor of stroke severity (AUC=0.782) and functional outcomes (AUC=0.753), with high sensitivity and specificity.

Conclusion: This study highlights the significant association between LTI, lipoprotein A, and stroke severity and outcomes, suggesting their potential as predictive biomarkers in acute ischemic stroke.

Keywords: *Acute ischemic stroke, Lipid tetrad index, Lipoprotein A, Stroke severity, Functional outcomes, Biomarkers*

1. INTRODUCTION

Stroke remains a major global health concern, contributing significantly to mortality and long-term disability worldwide. According to the World Health Organization (WHO), stroke is the second leading cause of death and a major cause of disability, with an estimated 12.2 million new cases occurring annually.(1) Low- and middle-income countries bear the highest burden, accounting for nearly 80% of global stroke-related deaths.(2) In India, the burden of stroke has been rising sharply over the past few decades, paralleling an increase in non-communicable diseases such as hypertension, diabetes, and dyslipidaemia. Epidemiological studies suggest that stroke prevalence in India ranges from 84 to 262 per 100,000 population,(3) with ischemic stroke being the most common subtype, accounting for approximately 87% of all stroke cases.(4) The growing burden of stroke in India is exacerbated by factors such as increasing life expectancy, urbanization, changing dietary patterns, and inadequate access to healthcare facilities, making early risk stratification and prognostication crucial for optimizing patient outcomes.

Stroke severity and outcomes are influenced by a multitude of factors, including demographic variables, comorbidities, clinical presentation, and laboratory biomarkers. Several predictors have been extensively studied, including age, gender, hypertension, diabetes, smoking status, atrial fibrillation, and prior stroke history.(5) Biomarkers such as inflammatory markers, oxidative stress indicators, and components of the lipid profile have also been implicated in stroke pathophysiology and prognosis.(6) Among these, dyslipidaemia has gained significant attention due to its well-established role in atherosclerosis and cerebrovascular events. Traditional lipid parameters such as total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides have been used to assess cardiovascular and cerebrovascular risk.

In recent years, composite lipid indices have emerged as better predictors of cardiovascular and cerebrovascular risk compared to individual lipid parameters.(7) The Lipid Tetrad Index (LTI), a novel lipid-derived marker, is calculated using the formula: total cholesterol × triglycerides × lipoprotein(a) / HDL.(8) LTI integrates multiple lipid components, providing a more robust measure of lipid-related atherogenicity and thrombotic risk. Several studies have suggested that elevated LTI is associated with an increased risk of coronary artery disease,(9) and emerging evidence indicates its potential role in cerebrovascular diseases. Given that atherothrombosis is a key mechanism underlying ischemic stroke, LTI may serve as a valuable marker for assessing stroke severity and predicting functional outcomes. Against this background, this study aims to evaluate the association between LTI, stroke severity (assessed using National Institutes of Health Stroke Scale (NIHSS)) and outcomes (assessed using modified Rankin Scale (mRS)) among acute ischemic stroke patients presenting to a tertiary healthcare facility.

2. MATERIALS AND METHODS

This was a hospital based, prospective study conducted in the outpatient department and/or inpatient wards of the Department of General Medicine, Chettinad Hospital And Research Institute, Chettinad Academy of Research and Education, for a duration of two months. The study was approved by the Institutional Human Ethics Committee (IHEC) with reference number IHEC-I/3590/25 dated 20/03/2025. The participants were given the Participant Information Sheet (PIS) in their native language, and its contents were verbally explained to ensure their understanding and satisfaction. Enrolment into the study proceeded upon receipt of written informed consent. All patients more than 18 years of age, of both gender, with acute ischemic stroke presenting within 48 hours of symptom onset were included. However, patients with haemorrhagic stroke or other non-ischemic cerebrovascular events (e.g., transient ischemic attack, cerebral venous thrombosis); with a history of chronic liver disease, chronic kidney disease, or malignancy; patients on lipid-lowering therapy (e.g., statins, fibrates) for more than 3 months prior to stroke onset; with severe infections, systemic inflammatory conditions, or autoimmune diseases; and with a history of genetic or familial dyslipidaemia syndromes were excluded.

The sample size was calculated using the formula for correlation studies, considering a 95% confidence level and 80% power. Fisher's Z transformation was applied with an expected correlation coefficient of 0.500. The minimum required sample size was determined to be 40 patients, accounting for 10% attrition. The patients were enrolled using nonprobability sampling technique – complete enumeration of acute ischemic stroke patients. Upon admission, demographic and clinical data, including medical history and risk factors, were collected. Stroke severity was assessed using the NIHSS, and blood samples were obtained within 48 hours to measure lipid parameters for LTI calculation. Functional outcomes were assessed at discharge using the mRS, with all data recorded in a structured case report form.

Statistical analysis: The collected data was manually entered into Microsoft Excel and analyzed using Software for Statistics and Data Science (Stata) v16 (StataCorp, 2019). Descriptive analysis was presented using numbers and percentages for categorical variables and mean with standard deviation (SD) for continuous variables, based on normality tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests. The Chi-square test (two-sided) was applied for categorical variables, while independent 't' tests were used for continuous variables to assess associations. Pearson or Spearman's correlation coefficient was used to evaluate correlations between LTI, NIHSS, and mRS, and ROC analysis determined the area under the curve of LTI in predicting stroke severity and outcomes, with statistical significance set at $p<0.05$.

3. RESULTS

The study included a total of 40 acute ischemic stroke patients with a mean age of 62.5 ± 10.8 years. Among them, 90% were older than 40 years, while 10% were younger than 40 years. The majority of the participants were male (65%), whereas females constituted 35% of the study population. Regarding lifestyle factors, 45% of the patients had a history of smoking, and 35% reported alcohol consumption. Hypertension was present in 70% of the participants, while 30% were non-hypertensive. Diabetes mellitus was observed in 55% of the patients, whereas 45% did not have diabetes. Laboratory investigations revealed a mean lipoprotein A level of 38.4 ± 12.6 mg/dL, total cholesterol of 192.5 ± 28.3 mg/dL, serum triglycerides of 146.7 ± 32.4 mg/dL, HDL cholesterol of 42.3 ± 8.5 mg/dL, and LDL cholesterol of 118.6 ± 25.7 mg/dL. The lipid tetrad index had a mean value of 15,200 ± 5,600. Stroke severity, assessed using the NIHSS, had a mean score of 9.8 ± 4.2, indicating moderate stroke severity. Functional outcomes measured using the mRS showed a mean score of 3.2 ± 1.1, reflecting moderate to severe disability among the study participants.

Table 1: Characteristics of the patients with acute ischemic stroke

		Number (N = 40) (n)	**Percentage (%)**
Age (years), Mean (SD)		62.5 (10.8)	
Age (years)	<40	4	10.0
	≥40	36	90.0
Gender	Male	26	65.0
	Female	14	35.0
Smoking	Yes	18	45.0
	No	22	55.0
Alcohol	Yes	14	35.0
	No	26	65.0
Hypertension	Present	28	70.0
	Absent	12	30.0
Diabetes	Present	22	55.0
	Absent	18	45.0
Laboratory investigations			
Lipoprotein A (mg/dL), Mean (SD)		38.4 (12.6)	
Total cholesterol (mg/dL), Mean (SD)		192.5 (28.3)	
Serum triglyceride (mg/dL), Mean (SD)		146.7 (32.4)	
HDL cholesterol (mg/dL), Mean (SD)		42.3 (8.5)	
LDL cholesterol (mg/dL), Mean (SD)		118.6 (25.7)	
Lipid tetrad index, Mean (SD)		15,200 (5,600)	
Stroke severity and functional outcome			
NIHSS scores		9.8 (4.2)	
Modified Rankin Scale		3.2 (1.1)	
SD, Standard deviation; NIHSS, National Institutes of Health Stroke Scale			

Correlation analysis revealed a significant positive association between lipoprotein A and both stroke severity (NIHSS: rp=0.421, p=0.008) and functional outcome (mRS: rp=0.351, p=0.022). Similarly, the LTI demonstrated the strongest correlation with NIHSS (rp=0.506, p=0.002) and mRS (rp=0.478, p=0.004), both of which were statistically significant. Serum triglyceride levels showed a significant positive correlation with NIHSS (rp=0.334, p=0.041), but its association with mRS was not statistically significant (p=0.052). LDL cholesterol also exhibited a significant correlation with NIHSS (rp=0.312, p=0.043), while its relationship with mRS was marginally insignificant (p=0.058). Total cholesterol levels did not show a statistically significant correlation with either NIHSS (p=0.074) or mRS (p=0.091). Conversely, HDL cholesterol had a weak negative correlation with both NIHSS (rp=−0.220, p=0.153) and mRS (rp=−0.193, p=0.225), though these associations were not statistically significant.

Table 2: Correlation between lipid parameters, NIHSS scores and mRS scores

	NIHSS scores		mRS scores	
	Pearsons's correlation coefficient (rp)	**P value**	**Pearsons's correlation coefficient (rp)**	**P value**
Lipoprotein A	0.421	0.008*	0.351	0.022*
Total cholesterol	0.283	0.074	0.262	0.091
Serum triglyceride	0.334	0.041*	0.306	0.052
HDL cholesterol	-0.220	0.153	-0.193	0.225
LDL cholesterol	0.312	0.043*	0.295	0.058
Lipid tetrad index	0.506	0.002*	0.478	0.004*
*Statistically significant at p<0.05				

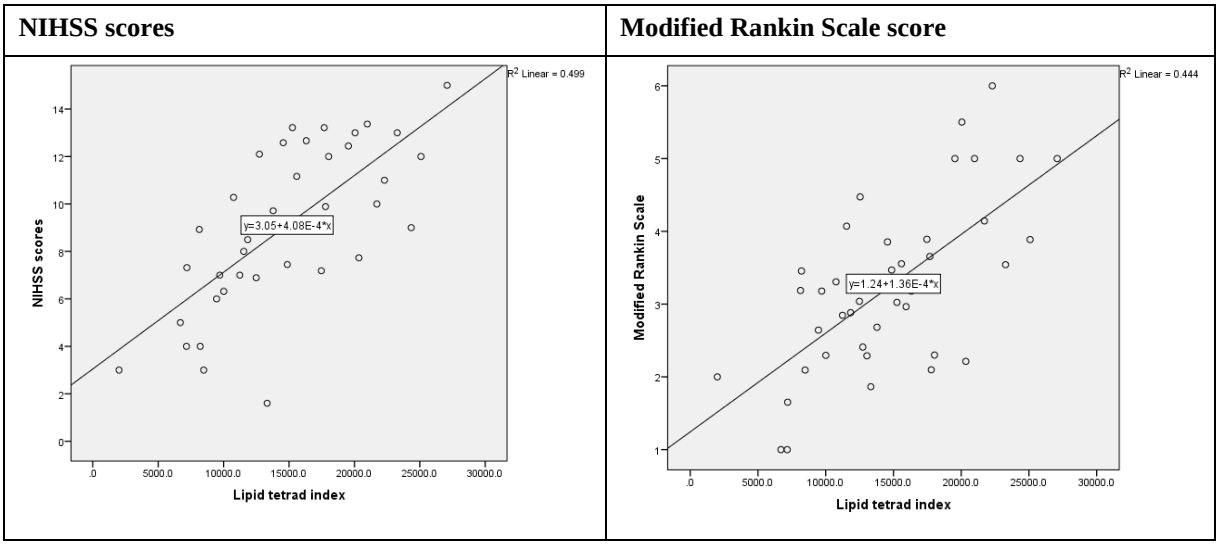


Figure 1: Correlation between lipid tetrad index, NIHSS and mRS scores

ROC analysis demonstrated that the lipid tetrad index was a significant predictor of both stroke severity and functional outcomes. For identifying moderate to severe stroke based on NIHSS, the AUC was 0.782 (95% CI: 0.661–0.894), with an optimal cutoff value of >12,500. At this threshold, the sensitivity and specificity were 82.5% and 74.5%, respectively, with a highly significant p-value of <0.001. Similarly, for predicting moderate to severe disability or death based on mRS, the AUC was 0.753 (95% CI: 0.631–0.865), with a cutoff value of >11,800. This cutoff demonstrated a sensitivity of 79.0% and specificity of 70.5%, with a statistically significant p-value of 0.003. These findings suggest that LTI is a reliable biomarker for assessing both stroke severity and functional outcomes in acute ischemic stroke patients.

Table 3: ROC analysis to determine the AUC of lipid tetrad index in predicting moderate to severe stroke (based on NIHSS) and moderate to severe disability or death (based on mRS)

	AUC (95% CI)	Cut off	Sensitivity (%)	Specificity (%)	P value
Moderate to severe stroke (based on NIHSS)	0.782 (0.661 to 0.894)	>12,500	82.5	74.5	<0.001*
Moderate to severe disability or	0.753 (0.631 to 0.865)	>11,800	79.0	70.5	0.003*

death (based on mRS)					

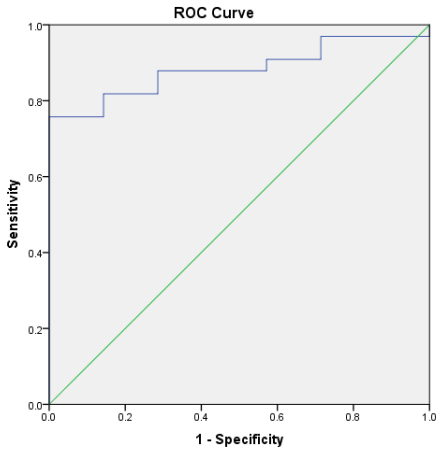
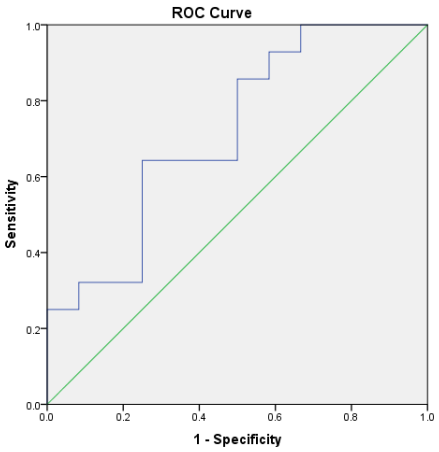
NIHSS scores	Modified Rankin Scale score
	

Figure 2: ROC analysis to determine the AUC of lipid tetrad index in predicting moderate to severe stroke (based on NIHSS) and moderate to severe disability or death (based on mRS)

4. DISCUSSION

The present study aimed to evaluate the association between lipid tetrad index, stroke severity (assessed using the NIHSS), and functional outcomes (measured using the mRS) among acute ischemic stroke patients. The study cohort had a mean age of 62.5 ± 10.8 years, with the majority of patients (90%) being over 40 years old. This aligns with prior epidemiological studies indicating that ischemic stroke incidence increases with age, primarily due to age-related vascular changes, including endothelial dysfunction and arterial stiffness (Feigin et al., 2021).(10) Furthermore, the predominance of male participants (65%) is consistent with previous research showing that men have a higher risk of ischemic stroke due to differences in hormonal protection and cardiovascular risk profiles (Abdu & Seyoum, 2022; Chung et al., 2023).(11, 12)

Among lifestyle factors, smoking was reported in 45% of patients, and alcohol consumption was noted in 35%. Smoking is a well-established independent risk factor for ischemic stroke, contributing to endothelial damage, platelet activation, and prothrombotic states (Shah & Cole, 2010).(13) Similarly, excessive alcohol consumption has been linked to hypertension, atrial fibrillation, and dyslipidaemia, all of which elevate stroke risk (Chung et al., 2023; Jiang et al., 2022).(14, 15) The high prevalence of hypertension (70%) and diabetes (55%) in this cohort further reinforces the role of these metabolic disorders in stroke pathogenesis, as both conditions contribute to atherosclerosis and microvascular dysfunction (Moghadam-Ahmadi et al., 2023).(16)

The lipid profile of the study population showed mean total cholesterol levels of 192.5 ± 28.3 mg/dL, serum triglycerides of 146.7 ± 32.4 mg/dL, HDL cholesterol of 42.3 ± 8.5 mg/dL, and LDL cholesterol of 118.6 ± 25.7 mg/dL. While total cholesterol and LDL cholesterol have been historically linked to atherosclerotic cardiovascular disease, their direct relationship with stroke remains controversial (Alloubani et al., 2021).(17) Some studies have suggested a paradoxical relationship wherein low cholesterol levels are associated with an increased risk of haemorrhagic stroke (Wang et al., 2013),(18) but in ischemic stroke, elevated LDL cholesterol contributes to plaque formation and rupture, leading to thromboembolism (Liang et al., 2022).(19)

In this study, LDL cholesterol showed a statistically significant correlation with NIHSS scores (rp=0.312, p=0.043), supporting its role in stroke severity. However, its correlation with mRS scores did not reach statistical significance (p=0.058), which may suggest that LDL cholesterol contributes more to acute stroke severity rather than long-term functional outcomes (Lui & Tan, 2020).(20) Conversely, HDL cholesterol demonstrated a weak negative correlation with both NIHSS and mRS scores, though not statistically significant. This aligns with evidence suggesting that HDL cholesterol plays a protective role by promoting reverse cholesterol transport and reducing inflammation (Madaudo et al., 2024).(21) Lipoprotein A was significantly correlated with stroke severity (rp=0.421, p=0.008) and functional outcomes (rp=0.351, p=0.022). This finding is in line with previous research indicating that elevated lipoprotein A levels are associated with an increased risk of ischemic stroke, particularly in individuals with prothrombotic and atherogenic profiles (Arora et al., 2019).(22) Lipoprotein A promotes atherosclerosis through its structural similarity to plasminogen, leading to impaired

fibrinolysis and increased thrombus formation (Rehberger Likozar et al., 2020).(23) The lipid tetrad index demonstrated the strongest correlation with both stroke severity (rp=0.506, p=0.002) and functional outcomes (rp=0.478, p=0.004). LTI, a composite index that integrates total cholesterol, triglycerides, lipoprotein A, and HDL cholesterol, has been previously suggested as a superior marker for cardiovascular risk assessment compared to individual lipid parameters (Morais et al., 2013).(8) This study supports its utility in stroke prognostication, as higher LTI values were associated with worse neurological impairment and functional disability.

ROC analysis revealed that LTI had a high predictive value for both stroke severity and functional outcomes. For moderate to severe stroke (NIHSS >12,500), the AUC was 0.782 (95% CI: 0.661–0.894), with a sensitivity of 82.5% and specificity of 74.5% (p<0.001). Similarly, for predicting moderate to severe disability or death (mRS >11,800), the AUC was 0.753 (95% CI: 0.631–0.865), with a sensitivity of 79.0% and specificity of 70.5% (p=0.003). These results highlight the potential role of LTI as a robust biomarker in clinical settings for early risk stratification in acute ischemic stroke patients. The findings of this study have important clinical implications. The significant association between LTI and stroke severity suggests that lipid profiling, particularly LTI assessment, should be considered in the initial evaluation of stroke patients. Identifying patients with elevated LTI could aid in risk stratification and guide more aggressive lipid-lowering strategies, such as statin therapy and lifestyle modifications. Additionally, the strong correlation between lipoprotein A and stroke outcomes underscores the need for targeted therapies addressing lipoprotein A levels. While conventional lipid-lowering agents have limited effects on lipoprotein A, emerging therapies such as antisense oligonucleotides and PCSK9 inhibitors show promise in reducing lipoprotein A-associated cardiovascular risks (Vinci et al., 2023).(24)

The present study has several limitations that should be acknowledged. Firstly, the study was conducted at a single tertiary care centre, which may introduce selection bias. Another limitation is the use of a single lipid profile measurement within 48 hours of stroke onset, which may not reflect long-term dyslipidaemia patterns or the impact of acute-phase responses on lipid levels. Furthermore, potential confounding factors such as dietary habits, physical activity, and genetic predisposition to dyslipidaemia were not accounted for, which could have influenced the results. Lastly, although the study established significant associations between lipid tetrad index, lipoprotein A, and stroke severity/outcomes, it was observational in nature and could not establish a causal relationship.

5. CONCLUSION

The present study highlights the significant association between lipid tetrad index, lipoprotein A, and stroke severity and functional outcomes in acute ischemic stroke patients. The findings suggest that higher LTI and lipoprotein A levels are correlated with increased stroke severity, as assessed by the NIHSS, and poorer functional outcomes, as measured by the mRS. Additionally, ROC analysis demonstrated the potential predictive value of LTI in identifying patients at risk of moderate to severe stroke and disability, underscoring its role as a promising biomarker for stroke prognosis.

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