**RESEARCH PAPER**

# Association between Serum Gamma Glutamyl Transferase (GGT) Levels and Acute Ischemic Stroke

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**Received:** 25th October 2026; **Revised:** 28th October 2026; **Accepted:** 3rd November 2026; **Available Online:** 7th November 2026

**ABSTRACT**

**Objectives:** The present study aimed to assess serum gamma-glutamyl transferase (GGT) levels in patients with acute ischemic stroke (AIS) and healthy controls and to evaluate the association between serum GGT levels and AIS.

**Methods:** This hospital-based, cross-sectional comparative study included 142 participants, comprising 71 patients with AIS and 71 healthy controls. Serum GGT activity was quantitatively estimated using the Szasz method. Univariable and multivariable Firth penalized logistic regression analyses were performed to evaluate the association between serum GGT levels and stroke. Receiver operating characteristic (ROC) curve analysis was additionally performed to identify an optimal GGT threshold based on the Youden index.

**Results:** Serum GGT levels were significantly higher in patients with AIS than in healthy controls. On multivariable analysis, higher serum GGT levels were independently associated with AIS, with an odds ratio of 1.55 ($p < 0.0001$). The multivariable model showed an area under the curve (AUC) of 0.901. For GGT alone, ROC analysis yielded an AUC of 0.817 (95% CI: 0.748–0.885; $p < 0.0001$). A GGT threshold of ≥66.00 U/L corresponded to a sensitivity of 64.79%, specificity of 91.55%, positive predictive value of 88.46%, negative predictive value of 72.22%, and accuracy of 78.17%.

**Conclusion:** Serum GGT levels were significantly elevated and independently associated with AIS. A GGT threshold of ≥66.00 U/L showed discriminatory potential in distinguishing patients with AIS from healthy controls; however, these findings require validation in larger prospective studies.

**Keywords:** biomarker, dyslipidemia, ischemia stroke, hypertension, risk assessment

**How to cite this article:** Sharma S, Kumar K, Kumawat R, Jakhar R., Association Between Serum Gamma Glutamyl Transferase (GGT) Levels and Acute Ischemic Stroke. Int J Drug Deliv Technol. 2026;16(90s): 1565-1571; DOI: 10.25258/ijddt.16.90s.158

## Introduction

Strokes occur when vascular disruption leads to an abrupt loss of neurological function. Marked by symptoms of brain impairment that endure for longer than 24 hours or result in mortality, stroke stands as the leading global cause of death as well as severe, chronic disability [1,2].

India accounts for 10.48% of global new cases, totaling 1.25 million strokes in 2021, against 12 million cases worldwide, with an incidence rate of 151.38 per lakh people [3].

Various markers have been explored for AIS, including TyG index [3], neuron-specific enolase (NSE), S100B, glial fibrillary acidic protein (GFAP) [4], ischemia-modified albumin (IMA), D-dimer, interleukin-6 (IL-6) [5], matrix metalloproteinase-9 (MMP-9), C-reactive protein (CRP), NfL, BNP/NT-proBNP, ICAM-1 [6], TNF-α, and von Willebrand factor (vWF) [7].

Considering its high mortality and disability, prognosis must be ascertained by the use of novel and simple markers, whereby the role of GGT has been emerging [8]. GGT, i.e., gamma-glutamyl transferase, is one of the enzymes that the liver produces and is involved in physiological processes [9-11].

It plays a role in redox signaling and defends against oxidative stress by helping maintain cellular glutathione levels. Its link to stroke risk has been the subject of ongoing research, and beyond stroke, it has also been associated with biliary obstruction, alcohol consumption, and cardiovascular risk — with several studies identifying GGT as a key predictor of stroke [12-15], However, this relationship remains inadequately explored, particularly in the Indian population.

The present study aimed to assess serum gamma-glutamyl transferase (GGT) levels in patients with acute ischemic stroke (AIS) and healthy controls and to evaluate the association between serum GGT levels and AIS. It also explored the association of serum GGT with established cerebrovascular risk factors among patients with AIS.

**Methods**

In our neurology department, a cross-sectional comparative 18-month study was conducted from July 2024 until December 2025, where consecutive acute ischemic stroke patients were enrolled.

Inclusion criteria were adult patients above 18 years, both males and females, hospitalized with acute stroke, with consent taken from themselves or from guardians. Patients with chronic liver/renal disease, endocrine/autoimmune disorders, relevant arterial surgery, GGT-altering drugs, or alcohol intake were excluded.

**Study participants:** The study population was categorized into Group A including inpatients admitted with confirmed acute stroke diagnosis, and Group B (controls) comprising participants without stroke attending the neurology outpatient department for unrelated complains. None of the controls had known cardiovascular disease.

Sample size was calculated using GGT data from Rathor, et al. [2], who reported significantly higher GGT levels in stroke cases versus controls (mean difference 17.82 U/L; pooled SD 20.25 U/L; Cohen's d = 0.88). At a two-sided alpha of 0.05, 95% power, and 1:1 allocation, this required at least 35 participants per group (70 total). To ensure adequate power, the present study enrolled 71 participants per group (142 total).

All eligible participants underwent clinical assessment for established cerebrovascular risk factors. Particular attention was given to diabetes mellitus, hypertension, hyperlipidaemia, smoking, cardiovascular disease, and peripheral vascular disease. Serum GGT levels were assessed in relation to these risk factors.

A non-contrast computed tomography (CT) scan of the brain/ MRI was performed within 24–72 hours of admission or stroke onset to confirm the infarct. A 5-mL random venous blood specimen was drawn from each participant. The serum was separated and subjected to quantitative estimation of gamma-glutamyl transferase (GGT). Enzymatic serum GGT activity was measured via the Szasz method using a reagent kit designed for quantitative serum or plasma GGT assessment. A serum GGT concentration exceeding 26 IU/L was considered abnormal.

**Statistical analysis**

All statistical analyses were executed R version 4.6.0. Comparison of groups was done through the Mann–Whitney U, chi-square, or Fisher–Freeman–Halton exact tests, as appropriate. Kruskal–Wallis testing compared GGT across infarct territories. Effect sizes and Hodges–Lehmann estimates were reported. Univariable and multivariable Firth logistic regression evaluated independent associations with stroke. ROC analysis assessed GGT discrimination and optimal cutoff using the Youden index. Among stroke cases, linear regression and Spearman correlation evaluated associations with clinical variables. Model discrimination, calibration, and performance were assessed using AUC, Nagelkerke $R^2$, Hosmer–Lemeshow testing, calibration measures, and Brier score. All statistical evaluations were two-sided, and results

were considered statistically significant when *p* was less than 0.05.

**Results**

The baseline characteristics of the stroke patients and controls are presented in Table 1. The mean age and gender were similar between the cases and controls, with P-values of 0.728 and 0.864, respectively. Body mass index was also comparable between cases and controls (30.70 vs. 31.20 kg/m², p=0.143).

**Table 1.** Comparison of Baseline characteristics of stroke patients and controls between study groups.

| Variable | Case (n=71) | Control (n=71) | Total | P value | Effect size |
|---|---|---|---|---|---|
| Age (years) | 67.00 (56.00–76.00) | 66.00 (56.00–76.00) | 66.50 (56.00–76.00) | 0.728* | r = 0.03 |
| Gender (female) | 28 (39.44%) | 29 (40.85%) | 57 (40.14%) | 0.864† | Phi coefficient = 0.014 |
| Body mass index (kg/m2) | 30.70 (29.40–32.40) | 31.20 (29.80–32.80) | 31.00 (29.60–32.77) | 0.143* | r = 0.12 |

** Mann-Whitney U test; † Pearson chi-square test.*

*Values are n (%) unless otherwise stated; continuous variables are median (IQR).*

Stroke patients had significantly elevated serum GGT than controls (71.83% vs. 28.17%; OR=6.50, p<0.0001) as shown in Table 2. Cases also had significantly higher serum GGT levels (76 vs. 21 U/L; p<0.0001). Smoking, diabetes, hypertension, dyslipidaemia, cardiovascular disease, and peripheral vascular disease were significantly more prevalent among stroke patients (all p≤0.045). Both groups had similar total cholesterol and triglyceride levels, but stroke patients had significantly higher HbA1c (p=0.0001).

**Table 2.** Comparison of Serum GGT, vascular risk factors, lipid profile and glycaemic control in stroke patients and controls (reference: controls).

| Variable | Case (n=71) | Control (n=71) | Total | Between-group effect (95% CI) | P value | Effect size |
|---|---|---|---|---|---|---|
| **Serum GGT** | | | | | | |
| Elevated serum GGT (>26 U/L) | 51 (71.83%) | 20 (28.17%) | 71 (50.00%) | Prop diff: 43.66% (95% CI: 27.58 to 56.58%) OR: 6.50 (95% CI: 3.13 to 13.51) | **<0.0001**† | Phi coefficient = 0.437 |
| Serum GGT (U/L) | 76.00 (23.00–94.50) | 21.00 (18.00–46.00) | 32.00 (20.00–77.75) | Hodges-Lehmann location shift: 42.00 (95% CI: 24.00 to 54.00) | **<0.0001*** | r = 0.55 |
| **Vascular risk factors** | | | | | | |
| Smoking | 33 (46.48%) | 17 (23.94%) | 50 (35.21%) | Prop diff: 22.54% (95% CI: 6.82 to 36.78%) OR: 2.76 (95% CI: 1.35 to 5.65) | **0.005**† | Phi coefficient = 0.236 |
| Diabetes mellitus | 33 (46.48%) | 16 (22.54%) | 49 (34.51%) | Prop diff: 23.94% (95% CI: 8.32 to 38.03%) OR: 2.99 (95% CI: 1.44 to 6.17) | **0.003**† | Phi coefficient = 0.252 |
| Hypertension | 37 (52.11%) | 18 (25.35%) | 55 (38.73%) | Prop diff: 26.76% (95% CI: 10.76 to 40.93%) OR: 3.20 (95% CI: 1.58 to 6.51) | **0.001**† | Phi coefficient = 0.275 |
| Dyslipidaemia | 21 (29.58%) | 11 (15.49%) | 32 (22.54%) | Prop diff: 14.08% (95% CI: 0.28 to 27.30%) OR: 2.29 (95% CI: 1.01 to 5.20) | **0.045**† | Phi coefficient = 0.169 |
| Cardiovascular disease | 9 (12.68%) | 1 (1.41%) | 10 (7.04%) | Prop diff: 11.27% (95% CI: 2.77 to 21.03%) OR: 10.16 (95% CI: 1.25 to 82.49) | **0.009**† | Phi coefficient = 0.220 |
| Peripheral vascular disease | 13 (18.31%) | 2 (2.82%) | 15 (10.56%) | Prop diff: 15.49% (95% CI: 5.47 to 26.23%) OR: 7.73 (95% CI: 1.68 to 35.68) | **0.003**† | Phi coefficient = 0.252 |
| **Lipid profile and glycaemic control** | | | | | | |
| Total cholesterol (mg/dL) | 160.00 (150.00–190.00) | 168.00 (150.00–180.00) | 164.00 (150.00–180.00) | Hodges-Lehmann location shift: 0.00 (95% CI: -10.00 to 10.00) | 0.947* | r = 0.01 |
| Triglycerides (mg/dL) | 120.00 (105.00–130.00) | 130.00 (110.00–140.00) | 120.00 (110.00–140.00) | Hodges-Lehmann location shift: -5.00 (95% CI: -10.00 to 0.00) | 0.237* | r = 0.10 |
| HbA1c (%) | 6.00 (5.50–9.00) | 5.50 (5.00–6.00) | 6.00 (5.00–8.00) | Hodges-Lehmann location shift: 1.00 (95% CI: 0.50 to 1.50) | **0.0001*** | r = 0.32 |

** Mann-Whitney U test; † Pearson chi-square test.*

*Values are n (%) unless otherwise stated; continuous variables are median (IQR).*

On univariable analysis, serum GGT was significantly associated with acute stroke, with each 10-unit increase associated with 49% higher odds of stroke (OR=1.49, 95% CI: 1.30–1.71; p<0.0001). Following adjustment via Firth penalized logistic regression, this association persisted with statistical significance and demonstrated a larger effect size (OR=1.55, p<0.0001). BMI, smoking, hypertension, and peripheral vascular disease were also independently associated with stroke. Diabetes, dyslipidaemia, and HbA1c were not independently significant in the multivariable model. The final model showed excellent discrimination (AUC 0.901, 95% CI 0.852–0.949) with a Nagelkerke $R^2$ of 0.612 (Table 3).

**Table 3.** Univariate and multivariate logistic regression (multivariable model: Firth penalized logistic regression (bias-reduced)): Association of serum GGT with acute stroke after adjustment for vascular risk factors: univariable and multivariable logistic regression. (N=142)

| Predictor | Univariate OR (95% CI) | Univariate P | Multivariate OR (95% CI) | Multivariate P |
|---|---|---|---|---|
| Serum GGT (per 10-unit change) | 1.49 (1.30–1.71) | <0.0001 | 1.55 (1.32–1.87) | <0.0001 |
| Age | 1.00 (0.98–1.03) | 0.769 | Not entered (univariate p≥0.2) | |
| Gender: Male (ref: Female) | 1.06 (0.54–2.07) | 0.864 | Not entered (univariate p≥0.2) | |
| Body mass index | 0.91 (0.81–1.02) | 0.110 | 0.85 (0.73–0.97) | 0.021 |
| Smoking: Yes (ref: No) | 2.76 (1.35–5.65) | 0.006 | 3.23 (1.20–9.39) | 0.020 |
| Diabetes mellitus: Yes (ref: No) | 2.99 (1.44–6.17) | 0.003 | 0.91 (0.14–5.32) | 0.917 |
| Hypertension: Yes (ref: No) | 3.20 (1.58–6.51) | 0.001 | 2.578 (1.001–6.953) | 0.049 |
| Dyslipidaemia: Yes (ref: No) | 2.29 (1.01–5.20) | 0.048 | 1.59 (0.52–4.91) | 0.410 |
| Peripheral vascular disease: Yes (ref: No) | 7.73 (1.68–35.68) | 0.009 | 11.34 (2.10–87.58) | 0.003 |
| Total cholesterol | 1.00 (0.99–1.01) | 0.847 | Not entered (univariate p≥0.2) | |
| Triglycerides | 0.99 (0.98–1.01) | 0.406 | Not entered (univariate p≥0.2) | |
| HbA1c | 1.37 (1.14–1.64) | 0.0006 | 1.48 (0.99–2.35) | 0.059 |

*Outcome modelled: acute stroke:Case; reference: Controls. Predictors with univariate p<0.20 were entered into a multivariable Firth penalized logistic regression; all 8 entered predictors were retained (142 complete cases, 71 events; ~8.9 events per parameter). Apparent model performance was AUC=0.901 (95% CI 0.852–0.949) and Nagelkerke $R^2$=0.612. Calibration showed no evidence of poor fit (Hosmer–Lemeshow p=0.280), with calibration intercept 0.00, slope 1.11 (95% CI 0.74–1.48), and Brier score 0.128. Because model development and performance assessment used the same sample, these estimates may be optimistic and require external validation.*

ROC analysis demonstrated that serum GGT significantly discriminated stroke patients from controls, with an AUC of 0.817 (95% CI: 0.748–0.885; p<0.0001). A cutoff of ≥66 U/L provided 64.79% sensitivity and 91.55% specificity. The PPV, NPV, and diagnostic accuracy were 88.46%, 72.22%, and 78.17%, respectively. The positive and negative likelihood ratios were 7.67 and 0.38, respectively (Figure 1).

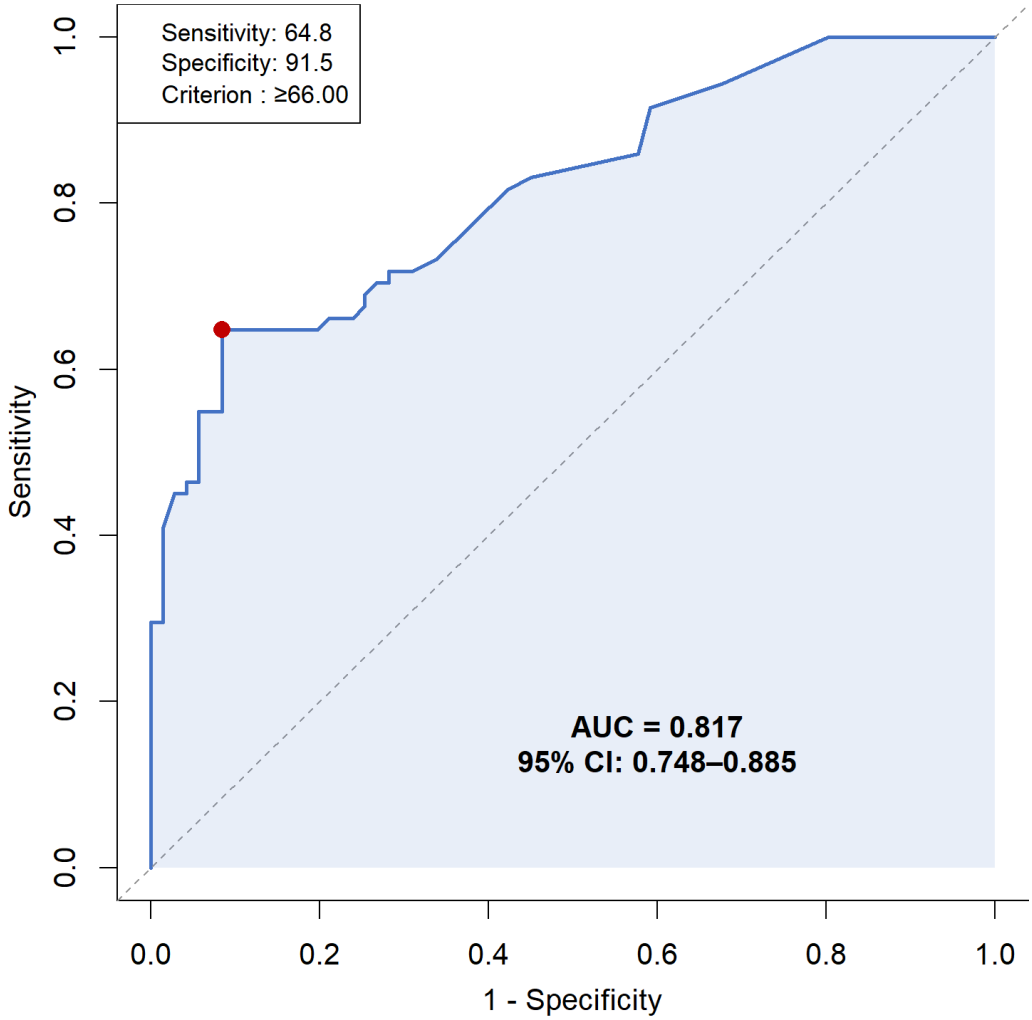


**Figure 1**. ROC curve: Serum GGT (U/L) predicting Study group.

**Discussion**

The study reports elevated serum GGT among stroke patients as compared to controls. Because serum GGT in our patients was measured 24 to 72 hours after stroke onset, a raised level may reflect a pre-existing characteristic of patients who go on to have a stroke, a response to the acute ischaemic event, or both; however, the cross-sectional nature of the study cannot separate these possibilities. Likewise, previous studies by Rathor, et al. [2], Mulakalapalli, et al. [1], Yaduvanshi, et al. [15], Amrutha, et al. [14], and Yan, et al. [8] also supported our findings, indicating increased stroke risk with higher GGT levels.

The likely mechanism is that acute ischemia of the brain causes hypoxia and oxidative stress, depleting glutathione (intracellularly) and triggering GGT release for providing defense against oxidative stress and supporting the metabolism of glutathione [14].

Evaluating these mechanisms is clinically meaningful, as serum GGT can actively drive atherogenesis, endothelial damage, and atherosclerotic plaque vulnerability through the promotion of low-density lipoprotein (LDL) oxidation - being involved in other chronic systemic diseases [16]. To circumvent this we

adjusted for confounding factors; however, GGT was still higher among stroke cases, with an odds ratio of 1.55 ($p<0.0001$). Likewise, Yan, et al. [8], after adjustment for multiple clinical and biochemical confounders, including smoking, diabetes, hypertension, lipid parameters, and liver enzymes, reported an independent association between higher GGT and stroke (adjusted OR=1.32, p=0.013). Similarly, Lee, et al. [12], reported an odds ratio of 1.3 for GGT-stroke association after multiple confounder adjustment (p=0.010).

Furthermore, ROC curve analysis was done in our study, which demonstrated that a specific GGT cut-off level of ≥66.00 U/L was significantly associated with stroke, demonstrating good discriminatory ability. This value was higher than those reported in previous studies such as Amrutha, et al. [14] used a cut-off of >40 U/L, which identified elevated GGT in 73.9% of moderate-to-severe and 92.9% of severe stroke cases. Similarly, Yan, et al. [8] identified a threshold with a cut-off range between 21.0 and 35.0 U/L where stroke risk sharply increased. The higher cut-off observed in our study may reflect differences in study populations, disease severity, and study design, while providing a potentially useful threshold for identifying patients at increased risk of acute stroke.

**Limitations**

The single-center, hospital-based cross-sectional design prevents establishing causal relationships and limits generalizability to broader sample populations. Moreover, the study did not assess serial GGT levels and long-term functional outcomes, requiring future prospective, multicentric cohort studies.

**Conclusion**

To conclude, serum GGT concentrations are markedly higher in acute stroke patients. High serum GGT serves as a strong, independent predictor of acute stroke, retaining significance after controlling for major traditional cardiovascular risk factors. ROC curve analysis established an optimal diagnostic threshold of ≥66.00 U/L, which yielded high specificity (91.55%) as well as good diagnostic discrimination (AUC: 0.817) for identifying stroke. Overall, serum GGT serves as a reliable, cost-effective, and accessible biochemical biomarker for acute stroke stratification in clinical practice, aiding early identification. Further prospective multicenter investigations are needed to monitor serial changes in GGT, confirm the diagnostic reliability of the proposed cutoff, and evaluate its prognostic relevance across stroke subtypes.

Acknowledgement: None

Conflicts of interest: None

Source of funding: None

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